

Methods for Treating Cancer

RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Appl. No. 63/615,064, filed on December 27, 2023 and U.S. Provisional Appl. No. 63/675,810, filed on July 26, 2024, which are hereby incorporated by reference in their entireties.

SEQUENCE LISTING

This application contains a Sequence Listing that has been submitted electronically as an XML file named "49366-0056WO3_ST26.SL.XML." The XML file, created on July 25, 2024, is 2,933 bytes in size. The material in the XML file is hereby incorporated by reference in its entirety.

FIELD

This disclosure provides compounds of Formula (I) and pharmaceutically acceptable salts thereof, that inhibit phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K) isoform alpha (PI3K α). These compounds are useful for treating a disease in which increased PI3K α activation contributes to the pathology, symptoms, and/or progression of the disease (e.g., cancer) in a subject.

BACKGROUND

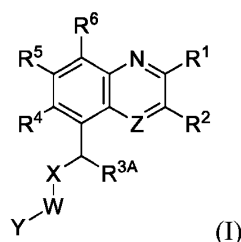
Phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K) isoform alpha (PI3K α), encoded by the *PIK3CA* gene is a part of the PI3K/AKT/TOR signaling network and is altered in several human cancers.

Activation of the PI3K pathway occurs in approximately 30–50% human cancers and contributes to resistance to various anti-cancer therapies. (See, Bauer, T.M. et al., Pharmacol. Ther. 2015, 146, 53–60.) However, development of PI3K inhibitors has been problematic for several reasons, in particular, inability to specifically inhibit signaling by mutant PI3K α while sparing wild-type PI3K α , and the related dose-limiting toxicities that prevent sustained PI3K pathway suppression. (See, Hanks et al., Cancer Discovery, April 2019;9: 482–491.) For example, alpelisib is a PI3K inhibitor that is equipotent against wild-type and mutant forms of PI3K α , which results in dose-limiting toxicities and hyperglycemia.

Thus, selectively targeting PI3K α represents an approach for the treatment of proliferative disorders such as cancer.

SUMMARY

5 Some embodiments provide a compound of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

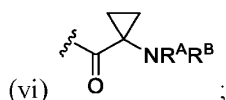
Z is N or CH;

10 R¹ is hydrogen, halogen, cyano, C3-C6 cycloalkyl, C1-C6 thioalkyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 alkoxyalkyl, 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl; or C1-C6 alkyl optionally substituted with (i) C3-C6 cycloalkyl or (ii) 4-10 membered heterocyclyl;

15 R² is C6-C10 aryl optionally substituted with 1-4 independently selected R^{2A}, 5-10 membered heteroaryl optionally substituted with 1-4 independently selected R^{2A}, 4-10 membered heterocyclyl optionally substituted with 1-4 independently selected R^{2A}, C4-C10 cycloalkyl optionally substituted with 1-4 independently selected R^{2A}, 4-10 membered heterocycloxy optionally substituted with 1-4 independently selected R^{2A}, 5-10 heteroaryloxy optionally substituted with 1-4 independently selected R^{2A}, C1-C6 alkoxyalkyl optionally substituted with –C(=O)NR^AR^C, or C1-C6 alkoxy optionally substituted with –C(=O)NR^AR^C, C4-C10 cycloalkyl, 4-10 membered heterocyclyl, 5-10 membered heteroaryl, or phenyl;

each R^{2A} is independently selected from:

- (i) halogen;
- (ii) cyano;
- 25 (iii) hydroxyl;
- (iv) -NR^AR^B;
- (v) -C(=O)NR^AR^B;



(vii) -NHC(=O)R^C;

(viii) -C(=O)OR^D;

(ix) -SO₂R^D;

5 (x) -NHSO₂R^D;

(xi) -SO₂NR^DR^E;

(xii) -NHC(=O)C1-C6 alkyl optionally substituted with NR^AR^B;

(xiii) C1-C6 haloalkyl;

(xiv) C1-C6 hydroxyalkyl;

10 (xv) 5-10 membered heteroaryl optionally substituted with 1-3 substituents independently selected from hydroxyl, cyano, halogen, -C(=O)NR^AR^B, -NR^AR^B, C1-C6 alkyl optionally substituted with hydroxyl; and 4-10 membered heterocyclyl optionally substituted with hydroxyl or C1-C6 alkyl;

(xvi) 4-10 membered heterocyclyl optionally substituted with 1-3 substituents
15 independently selected from hydroxyl, cyano, halogen, C1-C6 haloalkyl, -C(=O)C1-C6 alkyl, -SO₂(C1-C6 alkyl), -SO₂NR^DR^E, C1-C6 alkoxy, -C(=O)NR^AR^B, -NR^AR^B, -NHC(=O)C1-C6 alkyl optionally substituted with -NR^AR^B, and C1-C6 alkyl optionally substituted with C1-C6 alkoxy or hydroxyl;

(xvii) C1-C6 alkyl optionally substituted with 1-3 substituents independently selected from
20 hydroxyl, oxo, -NR^AR^B, -C(=O)NR^AR^B, C1-C6 alkoxy, and 4-10 membered heterocyclyl optionally substituted with hydroxyl, C1-C6 alkyl, aralkyl, heteroaralkyl, -C(=O)NR^AR^B, or -C(=O)C3-C6 cycloalkyl;

(xviii) C1-C6 alkoxy optionally substituted with -NR^AR^B or 4-10 membered heterocyclyl
optionally substituted with C1-C6 alkyl, aralkyl, heteroaralkyl, or -C(=O)C3-C6 cycloalkyl;

25 (xix) C3-C6 cycloalkyl optionally substituted with hydroxyl, -C(=O)NR^AR^B, -C(=N)OR^D, or 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl; and

(xx) 4-10 membered heterocycloxy optionally substituted with hydroxyl, cyano, halogen,
or C1-C6 alkyl optionally substituted with hydroxyl;

each R^A and R^B is independently selected from hydrogen, hydroxyl, C1-C6 alkoxy, C3-C6
30 cycloalkyl, C2-C6 alkenyl, and C1-C6 alkyl optionally substituted with hydroxyl or C1-C6 alkoxy,

or R^A and R^B together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclyl optionally substituted with 1-2 substituents independently selected from halogen, C1-C6 alkyl, and -C(=O)C1-C6 alkyl;

each R^C is independently selected from C3-C6 cycloalkyl, -C(=O)NHR^{Y1}, and a C1-C6 alkyl optionally substituted with -NR^AR^B or with 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl or with C1-C6 hydroxylalkyl;

each R^D and R^E is independently selected from hydrogen, hydroxyl, phenyl, C1-C6 alkoxy, and C1-C6 alkyl optionally substituted with oxo or -NR^AR^B;

each R^{3A} and R^{3B} is independently selected from hydrogen, C1-C6 alkyl, C1-C6 alkoxy, and C1-C6 haloalkyl, or R^{3A} and R^{3B}, together with the carbon and nitrogen atoms, respectively, to which they are attached together form a 4-8 membered heterocyclyl group;

R⁴ is hydrogen, halogen, C1-C6 alkyl, or acrylamido;

R⁵ is hydrogen, halogen, C1-C6 alkyl, cyano, -NR^{5A}R^{5B}, -NR^{5A}C(=O)R^{5B}, or -C(=O)NR^{5A}R^{5B};

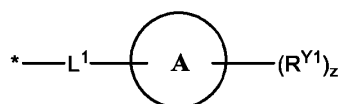
R^{5A} and R^{5B} are independently selected from hydrogen, C1-C6 alkyl, C2-C6 alkenyl, and C1-C6 hydroxyalkyl;

R⁶ is hydrogen, halogen, or C1-C6 alkyl;

X is a bond, CH₂, CH(CH₃), C(CH₃)₂, or ;

W is NR^{3B} or O;

Y is phenyl, naphthyl, or 5-10 membered heteroaryl, wherein the phenyl, naphthyl, and 5-10 membered heteroaryl are optionally and independently substituted with 1-3 independently



selected R^Y or , wherein * represents the connection of L¹ to the remainder of the compound of Formula (I);

each R^Y is independently selected from: halogen, cyano, hydroxyl, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkoxy, C1-C6 hydroxyalkyl, -(CH₂)_n-C(=O)R^F, -(CH₂)_n-NHC(=O)R^F, -(CH₂)_n-NHC(=O)OR^F, -C(=O)C(=O)NHR^F, -CO₂R^G, -(CH₂)_n-SO₂NR^HR^I, -(CH₂)_n-NHSO₂R^J, -(CH₂)_n-S(=O)(=NR^H)R^J, -(CH₂)_n-SO₂R^J, -(CH₂)_n-C(=O)NR^HR^I, -(CH₂)_n-C(=O)NR^HOR^I, and C1-C6 haloalkyl optionally substituted with hydroxyl;

each R^F is independently selected from: C3-C6 cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocyclyl optionally substituted with C1-C6 alkyl; and C1-C6 alkyl optionally substituted with hydroxyl or $-\text{SO}_2(\text{C1-C6 alkyl})$;

each R^G is independently selected from: hydrogen, C3-C6 cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocyclyl, and C1-C6 alkyl optionally substituted with hydroxyl or $-\text{SO}_2(\text{C1-C6 alkyl})$;

each R^H and R^I is independently selected from: hydrogen, C1-C6 alkoxy, C3-C6 cycloalkyl, C2-C6 alkenyl, $-(\text{CH}_2)_n-\text{C}(=\text{O})\text{NH}_2$, $-(\text{CH}_2)_n-\text{SO}_2\text{NH}_2$, $-(\text{CH}_2)_n-\text{SO}_2(\text{C1-C6 alkyl})$, C1-C6 alkyl optionally substituted with 1-2 substituents independently selected from hydroxyl, $-\text{SO}_2(\text{C1-C6 alkyl})$, C1-C6 alkoxy, 5-6 membered heteroaryl, C3-C6 cycloalkyl, and $-\text{C}(=\text{O})\text{NR}^{K1}\text{R}^{K2}$; or R^H and R^I together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclyl optionally substituted with 1-2 substituents independently selected from halogen, C1-C6 alkyl, and $-\text{C}(=\text{O})\text{C1-C6 alkyl}$;

R^J is C1-C6 alkyl, C3-C6 cycloalkyl, or C1-C6 alkoxy;

each R^{K1} and R^{K2} is independently hydrogen or C1-C6 alkyl;

Ring A is phenyl, 4-10 membered heteroaryl, 4-10 membered heterocyclyl, or C4-C10 cycloalkyl;

L^1 is a bond, C1-C6 alkoxy, $-(\text{CH}_2)_n-\text{NHC}(=\text{O})-$, $-\text{C}(=\text{O})\text{NH}-(\text{CH}_2)_n-$, $-\text{CO}_2-$, $-\text{SO}_2-$, $-\text{NHSO}_2-$, $-\text{SO}_2\text{NH}-$, $-\text{S}(=\text{O})(=\text{NR}^G)-$, $-\text{SO}_2(\text{C1-C6 alkylene})-$, $-\text{C}(=\text{O})\text{C}(=\text{O})\text{NH}-$, or C1-C6 alkylene optionally substituted with oxo;

each R^{Y1} is independently selected from: cyano, hydroxyl, halogen, $-\text{C}(=\text{O})\text{R}^F$, $-\text{NHC}(=\text{O})\text{R}^F$, $-\text{CO}_2\text{R}^G$, $-\text{SO}_2\text{NR}^H\text{R}^I$, $-\text{NHSO}_2\text{R}^J$, $-\text{S}(=\text{O})(=\text{NR}^H)\text{R}^J$, $-\text{SO}_2(\text{C1-C6 alkyl})$, $-\text{C}(=\text{O})\text{NR}^H\text{R}^I$, 4-6 membered heteroaryl, C1-C6 alkoxy optionally substituted with R^{Y2} , C1-C6 haloalkyl, C1-C6 alkyl optionally substituted with R^{Y2} , and 4-6 membered heterocyclyl optionally substituted with hydroxyl or C1-C6 alkyl;

R^{Y2} is hydroxyl, $-\text{NR}^H\text{R}^I$, $-\text{C}(=\text{O})\text{NR}^H\text{R}^I$, or $-\text{SO}_2\text{NR}^H\text{R}^I$;

n is 0, 1, or 2; and

z is 0, 1, 2, or 3.

Also provided herein is a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

Provided herein is a method for treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

Also provided herein is a method for treating cancer in a subject in need thereof, comprising
5 (a) determining that the cancer is associated with a dysregulation of a *PIK3CA* gene, a PI3K α protein, or expression or activity or level of any of the same; and (b) administering to the subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

Provided herein is a method of treating a PI3K α -associated disease in a subject, comprising
10 administering to a subject identified or diagnosed as having a PI3K α -associated disease a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

This disclosure also provides a method of treating a PI3K α -associated disease in a subject, comprising: determining that the cancer in the subject is a PI3K α -associated disease; and
15 administering to the subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

Further provided herein is a method of treating a PI3K α -associated cancer in a subject, comprising administering to a subject identified or diagnosed as having a PI3K α -associated cancer a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable
20 salt thereof, or a pharmaceutical composition as provided herein.

This disclosure also provides a method of treating a PI3K α -associated cancer in a subject, comprising: determining that the cancer in the subject is a PI3K α -associated cancer; and administering to the subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

Provided herein is a method of treating a subject, comprising administering a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein, to a subject having a clinical record that indicates that the subject has a dysregulation of a *PIK3CA* gene, a PI3K α protein, or expression or activity or level of any of the same.
25

This disclosure also provides a method for inhibiting PI3K α in a mammalian cell, comprising contacting the mammalian cell with an effective amount of a compound of Formula
30

(I), or a pharmaceutically acceptable salt thereof.

Other embodiments include those described in the Detailed Description and/or in the claims.

Additional Definitions

5 To facilitate understanding of the disclosure set forth herein, a number of additional terms are defined below. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well-known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in
10 the art to which this disclosure belongs. Each of the patents, applications, published applications, and other publications that are mentioned throughout the specification and the attached appendices are incorporated herein by reference in their entirety.

The term “about” when referring to a number or a numerical range means that the number or numerical range referred to is an approximation, for example, within experimental variability and/or statistical experimental error, and thus the number or numerical range may vary up to $\pm 10\%$
15 of the stated number or numerical range.

The term “acceptable” with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

20 The term “compound,” as used herein is meant to include all stereoisomers, geometric isomers, tautomers, and isotopically enriched variants of the structures depicted. Compounds herein identified by name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified.

It is understood that, in any compound described herein having one or more chiral centers,
25 if an absolute stereochemistry is not expressly indicated, then each center may independently be of R-configuration or S-configuration or a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, enantiomerically enriched, racemic mixture, diastereomerically pure, diastereomerically enriched, or a stereoisomeric mixture. In addition it is understood that, in any compound described herein having one or more double bond(s) generating geometrical
30 isomers that can be defined as E or Z, each double bond may independently be E or Z a mixture thereof.

The term "inhibit" or "inhibition of" means to reduce by a measurable amount, or to prevent entirely (e.g., 100% inhibition).

The phrase "therapeutically effective amount" means an amount of compound that, when administered to a subject in need of such treatment, is sufficient to (i) treat a PI3K α protein-associated disease, (ii) attenuate, ameliorate, or eliminate one or more symptoms of the particular disease, or (iii) delay the onset of one or more symptoms of the particular disease described herein.

The term "pharmaceutically acceptable salt" refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound.

As used herein, the term "subject" refer to any animal, including mammals such as primates (e.g., humans), mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, primates, and humans. In some embodiments, the subject is a human. In some embodiments, the subject has experienced and/or exhibited at least one symptom of the disease to be treated and/or prevented.

As used herein, terms "treat" or "treatment" refer to therapeutic or palliative measures. Beneficial or desired clinical results include, but are not limited to, alleviation, in whole or in part, of symptoms associated with a disease, diminishment of the extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state (e.g., one or more symptoms of the disease), and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

The term "halogen" refers to fluoro (F), chloro (Cl), bromo (Br), or iodo (I).

The term "oxo" refers to a divalent doubly bonded oxygen atom (i.e., "=O"). As used herein, oxo groups are attached to carbon atoms to form carbonyls.

The term "hydroxyl" refers to an -OH radical.

The term "cyano" refers to a -CN radical.

The term "alkyl" refers to a saturated acyclic hydrocarbon radical that may be a straight chain or branched chain, containing the indicated number of carbon atoms. For example, C₁₋₁₀ indicates that the group may have from 1 to 10 (inclusive) carbon atoms in it. Non-limiting examples include methyl, ethyl, *iso*-propyl, *tert*-butyl, *n*-hexyl. The term "saturated" as used in this context means only single bonds present between constituent carbon atoms and other available valences occupied by hydrogen and/or other substituents as defined herein.

The term “alkenyl” refers to an alkyl, in which one or more hydrogen atoms is/are removed such that the alkyl has one or more carbon-carbon double bonds.

The term “haloalkyl” refers to an alkyl, in which one or more hydrogen atoms is/are replaced with an independently selected halogen.

5 The term “alkoxy” refers to an -O-alkyl radical (e.g., -OCH₃).

The term “alkoxyalkyl” refers to an -alkyl-O-alkyl radical (e.g., -CH₂CH₂OCH₃).

The term “thioalkyl” refers to an -S-alkyl radical (e.g., -SCH₃) or an -alkyl-S-alkyl radical (e.g., -CH₂CH₂SCH₃).

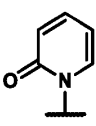
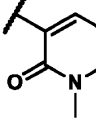
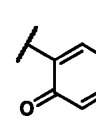
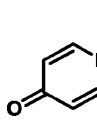
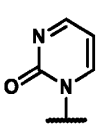
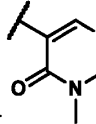
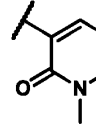
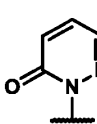
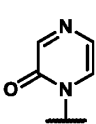
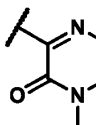
10 The term “hydroxyalkyl” refers to an alkyl, in which one or more hydrogen atoms is/are replaced with hydroxyl.

The term “aryl” refers to a 6-20 membered all carbon ring system wherein at least one ring in the system is aromatic (e.g., 6-carbon monocyclic, 10-carbon bicyclic, or 14-carbon tricyclic aromatic ring system). Examples of aryl groups include phenyl, naphthyl, tetrahydronaphthyl, 2,3-dihydro-1H-indene, and the like.

15 The term “cycloalkyl” as used herein refers to cyclic saturated hydrocarbon groups having, e.g., 3 to 20 ring carbons, preferably 3 to 16 ring carbons, and more preferably 3 to 12 ring carbons or 3-10 ring carbons or 3-6 ring carbons. Examples of cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Cycloalkyl may include multiple fused and/or bridged rings. Non-limiting examples of
20 fused/bridged cycloalkyl includes: bicyclo[1.1.0]butane, bicyclo[2.1.0]pentane, bicyclo[1.1.1]pentane, bicyclo[3.1.0]hexane, bicyclo[2.1.1]hexane, bicyclo[3.2.0]heptane, bicyclo[4.1.0]heptane, bicyclo[2.2.1]heptane, bicyclo[3.1.1]heptane, bicyclo[4.2.0]octane, bicyclo[3.2.1]octane, bicyclo[2.2.2]octane, and the like. Cycloalkyl also includes spirocyclic rings (e.g., spirocyclic bicycle wherein two rings are connected through just one atom). Non-limiting
25 examples of spirocyclic cycloalkyls include spiro[2.2]pentane, spiro[2.5]octane, spiro[3.5]nonane, spiro[3.5]nonane, spiro[3.5]nonane, spiro[4.4]nonane, spiro[2.6]nonane, spiro[4.5]decane, spiro[3.6]decane, spiro[5.5]undecane, and the like. The term “saturated” as used in this context means only single bonds present between constituent carbon atoms.

30 The term “heteroaryl”, as used herein, refers to a ring system having 5 to 20 ring atoms, such as 5, 6, 9, 10, or 14 ring atoms; wherein at least one ring in the system contains one or more heteroatoms independently selected from the group consisting of N, O, S, Si, and B, and at least

one ring in the system is aromatic (but does not have to be a ring which contains a heteroatom, e.g. tetrahydroisoquinoliny, e.g., tetrahydroquinoliny). Heteroaryl groups can include monocyclic, bridged, fused, and spiro ring systems, so long as one ring in the system is aromatic. Examples of heteroaryl include thienyl, pyridinyl, furyl, oxazolyl, oxadiazolyl, pyrrolyl, imidazolyl, triazolyl, thiodiazolyl, pyrazolyl, isoxazolyl, thiadiazolyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thiazolyl benzothienyl, benzoxadiazolyl, benzofuranyl, benzimidazolyl, benzotriazolyl, cinnoliny, indazolyl, indolyl, isoquinoliny, isothiazolyl, naphthyridinyl, purinyl, thienopyridinyl, pyrido[2,3-*d*]pyrimidinyl, pyrrolo[2,3-*b*]pyridinyl, quinazoliny, quinoliny, thieno[2,3-*c*]pyridinyl, pyrazolo[3,4-*b*]pyridinyl, pyrazolo[3,4-*c*]pyridinyl, pyrazolo[4,3-*c*]pyridine, pyrazolo[4,3-*b*]pyridinyl, tetrazolyl, chromane, 2,3-dihydrobenzo[*b*][1,4]dioxine, benzo[*d*][1,3]dioxole, 2,3-dihydrobenzofuran, tetrahydroquinoline, 2,3-dihydrobenzo[*b*][1,4]oxathiine, isoindoline, and others. In some embodiments, the heteroaryl is selected from thienyl, pyridinyl, furyl, pyrazolyl, imidazolyl, isoindoliny, pyranyl, pyrazinyl, and pyrimidinyl. For purposes of clarification, heteroaryl also includes aromatic lactams, aromatic cyclic ureas, or vinylogous analogs thereof, in which each ring nitrogen adjacent to a carbonyl is tertiary (i.e., all three valences are occupied by non-hydrogen substituents), such as one or more

of pyridone (e.g., , , , or ) , pyrimidone (e.g., , or ) , pyridazinone (e.g., , or ) , pyrazinone (e.g., ) , or ) , and imidazolone (e.g., ) , wherein each ring nitrogen adjacent to a carbonyl is tertiary (i.e., the oxo group (i.e., “=O”) herein is a constituent part of the heteroaryl ring).

The term “heterocyclyl” refers to a saturated or partially unsaturated ring systems with 3-16 ring atoms (e.g., 3-8 membered monocyclic, 5-12 membered bicyclic, or 10-14 membered tricyclic ring system) having at least one heteroatom selected from O, N, S, Si, and B, wherein one

or more ring atoms may be substituted by 1-3 oxo (forming, e.g., a lactam) and one or more N or S atoms may be substituted by 1-2 oxido (forming, e.g., an N-oxide, an S-oxide, or an S,S-dioxide), valence permitting. Heterocyclyl groups can also include one or two imino (=NH) groups, valence permitting. Heterocyclyl groups include monocyclic, bridged, fused, and spiro ring systems.

5 Examples of heterocyclyl groups include piperazinyl, pyrrolidinyl, dioxanyl, morpholinyl, tetrahydrofuranyl, tetrahydropyridyl, dihydropyrazinyl, dihydropyridyl, dihydropyrrolyl, dihydrofuranyl, dihydrothiophenyl, and the like. Heterocyclyl may include multiple fused and bridged rings. Non-limiting examples of fused/bridged heterocyclyl includes: 2-azabicyclo[1.1.0]butane, 2-azabicyclo[2.1.0]pentane, 2-azabicyclo[1.1.1]pentane, 3-azabicyclo[3.1.0]hexane, 5-azabicyclo[2.1.1]hexane, 3-azabicyclo[3.2.0]heptane, octahydrocyclopenta[c]pyrrole, 3-azabicyclo[4.1.0]heptane, 7-azabicyclo[2.2.1]heptane, 6-azabicyclo[3.1.1]heptane, 7-azabicyclo[4.2.0]octane, 2-azabicyclo[2.2.2]octane, 3-azabicyclo[3.2.1]octane, 2-oxabicyclo[1.1.0]butane, 2-oxabicyclo[2.1.0]pentane, 2-oxabicyclo[1.1.1]pentane, 3-oxabicyclo[3.1.0]hexane, 5-oxabicyclo[2.1.1]hexane, 3-oxabicyclo[3.2.0]heptane, 3-oxabicyclo[4.1.0]heptane, 7-oxabicyclo[2.2.1]heptane, 6-oxabicyclo[3.1.1]heptane, 7-oxabicyclo[4.2.0]octane, 2-oxabicyclo[2.2.2]octane, 3-oxabicyclo[3.2.1]octane, and the like. Heterocyclyl also includes spirocyclic rings (e.g., spirocyclic bicycle wherein two rings are connected through just one atom). Non-limiting examples of spirocyclic heterocyclyls include 2-azaspiro[2.2]pentane, 4-azaspiro[2.5]octane, 1-azaspiro[3.5]nonane, 2-azaspiro[3.5]nonane, 7-azaspiro[3.5]nonane, 2-azaspiro[4.4]nonane, 6-azaspiro[2.6]nonane, 1,7-diazaspiro[4.5]decane, 7-azaspiro[4.5]decane, 2,5-diazaspiro[3.6]decane, 3-azaspiro[5.5]undecane, 2-oxaspiro[2.2]pentane, 4-oxaspiro[2.5]octane, 1-oxaspiro[3.5]nonane, 2-oxaspiro[3.5]nonane, 7-oxaspiro[3.5]nonane, 2-oxaspiro[4.4]nonane, 6-oxaspiro[2.6]nonane, 1,7-dioxaspiro[4.5]decane, 2,5-dioxaspiro[3.6]decane, 1-oxaspiro[5.5]undecane, 3-oxaspiro[5.5]undecane, 3-oxa-9-azaspiro[5.5]undecane and the like.

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15
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An “aralkyl” refers to an aryl group, as defined herein, connected to the remainder of the molecule via a divalent C1-C6 alkyl group, as described herein. Non-limiting examples of an aralkyl group are benzyl, ethylphenyl, methylnaphthyl, and the like.

A “heteroaralkyl” refers to a heteroaryl group, as defined herein, connected to the remainder of the molecule via a divalent C1-C6 alkyl group, as described herein. Non-limiting examples of an aralkyl group are methylpyridyl, ethylpyrimidinyl, methylimidazolyl, and the like.

30

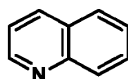
A “heterocycloxy” refers to an -O-heterocyclyl radical, wherein the heterocyclyl group is as defined herein.

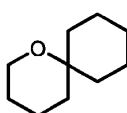
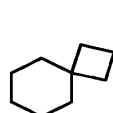
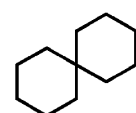
A “heteroaryloxy” refers to an -O-heteroaryl radical, wherein the heteroaryl group is as defined herein.

5 As used herein, examples of aromatic rings include: benzene, pyridine, pyrimidine, pyrazine, pyridazine, pyridone, pyrrole, pyrazole, oxazole, thioazole, isoxazole, isothiazole, and the like.

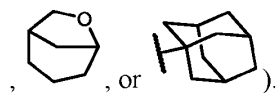
As used herein, when a ring is described as being “partially unsaturated”, it means said ring has one or more additional degrees of unsaturation (in addition to the degree of unsaturation attributed to the ring itself; e.g., one or more double or triple bonds between constituent ring atoms), provided that the ring is not aromatic. Examples of such rings include: cyclopentene, cyclohexene, cycloheptene, dihydropyridine, tetrahydropyridine, dihydropyrrole, dihydrofuran, dihydrothiophene, and the like.

For the avoidance of doubt, and unless otherwise specified, for rings and cyclic groups (e.g., aryl, heteroaryl, heterocyclyl, cycloalkyl, and the like described herein) containing a sufficient number of ring atoms to form bicyclic or higher order ring systems (e.g., tricyclic, polycyclic ring systems), it is understood that such rings and cyclic groups encompass those having fused rings, including those in which the points of fusion are located (i) on adjacent ring atoms

(e.g., [x.x.0] ring systems, in which 0 represents a zero atom bridge (e.g., )); (ii) a

20 single ring atom (spiro-fused ring systems) (e.g., , , or , or (iii)

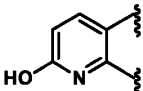
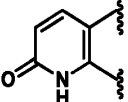
a contiguous array of ring atoms (bridged ring systems having all bridge lengths > 0) (e.g., ,



In addition, atoms making up the compounds of the present embodiments are intended to include all isotopic forms of such atoms. Isotopes, as used herein, include those atoms having the same atomic number but different mass numbers. By way of general example and without

limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include ^{13}C and ^{14}C .

In addition, the compounds generically or specifically disclosed herein are intended to include all tautomeric forms. Thus, by way of example, a compound containing the moiety:

5  encompasses the tautomeric form containing the moiety: . Similarly, a pyridinyl or pyrimidinyl moiety that is described to be optionally substituted with hydroxyl encompasses pyridone or pyrimidone tautomeric forms.

The compounds provided herein may encompass various stereochemical forms. The compounds also encompass enantiomers (e.g., R and S isomers), diastereomers, as well as mixtures of enantiomers (e.g., R and S isomers) including racemic mixtures and mixtures of diastereomers, as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in certain compounds. Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry (e.g., a “flat” structure) and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound. Likewise, unless otherwise indicated, when a disclosed compound is named or depicted by a structure that specifies the stereochemistry (e.g., a structure with “wedge” and/or “dashed” bonds) and has one or more chiral centers, it is understood to represent the indicated stereoisomer of the compound.

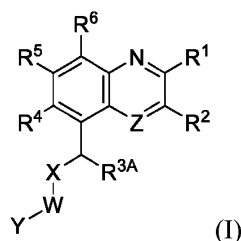
The details of one or more embodiments of this disclosure are set forth in the accompanying drawings and the description below. Other features and advantages of the present disclosure will be apparent from the description and drawings, and from the claims.

DETAILED DESCRIPTION

This disclosure provides compounds of Formula (I) and pharmaceutically acceptable salts thereof, that inhibit phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K) isoform alpha (PI3K α). These compounds are useful for treating a disease in which increased PI3K α activation contributes to the pathology, symptoms, and/or progression of the disease (e.g., cancer) in a subject.

Formulae (I) Compounds

Some embodiments provide a compound of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

5 Z is N or CH;

R¹ is hydrogen, halogen, cyano, C3-C6 cycloalkyl, C1-C6 thioalkyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 alkoxyalkyl, 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl; or C1-C6 alkyl optionally substituted with (i) C3-C6 cycloalkyl or (ii) 4-10 membered heterocyclyl;

10 R² is C6-C10 aryl optionally substituted with 1-4 independently selected R^{2A}, 5-10 membered heteroaryl optionally substituted with 1-4 independently selected R^{2A}, 4-10 membered heterocyclyl optionally substituted with 1-4 independently selected R^{2A}, C4-C10 cycloalkyl optionally substituted with 1-4 independently selected R^{2A}, 4-10 membered heterocycloxy optionally substituted with 1-4 independently selected R^{2A}, 5-10 heteroaryloxy optionally substituted with 1-4 independently selected R^{2A}, C1-C6 alkoxyalkyl optionally substituted with –C(=O)NR^AR^C, or C1-C6 alkoxy optionally substituted with –C(=O)NR^AR^C, C4-C10 cycloalkyl, 4-10 membered heterocyclyl, 5-10 membered heteroaryl, or phenyl;

each R^{2A} is independently selected from:

- 20 (i) halogen;
 (ii) cyano;
 (iii) hydroxyl;
 (iv) -NR^AR^B;
 (v) -C(=O)NR^AR^B;

25 (vi) ;

- (vii) -NHC(=O)R^C;
- (viii) -C(=O)OR^D;
- (ix) -SO₂R^D;
- (x) -NHSO₂R^D;
- 5 (xi) -SO₂NR^DR^E;
- (xii) -NHC(=O)C1-C6 alkyl optionally substituted with NR^AR^B;
- (xiii) C1-C6 haloalkyl;
- (xiv) C1-C6 hydroxyalkyl;
- (xv) 5-10 membered heteroaryl optionally substituted with 1-3 substituents independently
 10 selected from hydroxyl, cyano, halogen, -C(=O)NR^AR^B, -NR^AR^B, C1-C6 alkyl optionally substituted with hydroxyl; and 4-10 membered heterocyclyl optionally substituted with hydroxyl or C1-C6 alkyl;
- (xvi) 4-10 membered heterocyclyl optionally substituted with 1-3 substituents independently selected from hydroxyl, cyano, halogen, C1-C6 haloalkyl, -C(=O)C1-C6 alkyl, -
 15 SO₂(C1-C6 alkyl), -SO₂NR^DR^E, C1-C6 alkoxy, -C(=O)NR^AR^B, -NR^AR^B, -NHC(=O)C1-C6 alkyl optionally substituted with -NR^AR^B, and C1-C6 alkyl optionally substituted with C1-C6 alkoxy or hydroxyl;
- (xvii) C1-C6 alkyl optionally substituted with 1-3 substituents independently selected from hydroxyl, oxo, -NR^AR^B, -C(=O)NR^AR^B, C1-C6 alkoxy, and 4-10 membered heterocyclyl
 20 optionally substituted with hydroxyl, C1-C6 alkyl, aralkyl, heteroaralkyl, -C(=O)NR^AR^B, or -C(=O)C3-C6 cycloalkyl;
- (xviii) C1-C6 alkoxy optionally substituted with -NR^AR^B or 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl, aralkyl, heteroaralkyl, or -C(=O)C3-C6 cycloalkyl;
- (xix) C3-C6 cycloalkyl optionally substituted with hydroxyl, -C(=O)NR^AR^B, -C(=N)OR^D,
 25 or 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl; and
- (xx) 4-10 membered heterocycloxy optionally substituted with hydroxyl, cyano, halogen, or C1-C6 alkyl optionally substituted with hydroxyl;
- each R^A and R^B is independently selected from hydrogen, hydroxyl, C1-C6 alkoxy, C3-C6 cycloalkyl, C2-C6 alkenyl, and C1-C6 alkyl optionally substituted with hydroxyl or C1-C6 alkoxy,
 30 or R^A and R^B together with the nitrogen atom to which they are attached form a 4-10 membered

heterocyclyl optionally substituted with 1-2 substituents independently selected from halogen, C1-C6 alkyl, and $-C(=O)C1-C6$ alkyl;

each R^C is independently selected from C3-C6 cycloalkyl, $-C(=O)NHR^{Y1}$, and a C1-C6 alkyl optionally substituted with $-NR^A R^B$ or with 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl or with C1-C6 hydroxylalkyl;

each R^D and R^E is independently selected from hydrogen, hydroxyl, phenyl, C1-C6 alkoxy, and C1-C6 alkyl optionally substituted with oxo or $-NR^A R^B$;

each R^{3A} and R^{3B} is independently selected from hydrogen, C1-C6 alkyl, C1-C6 alkoxy, and C1-C6 haloalkyl, or R^{3A} and R^{3B} , together with the carbon and nitrogen atoms, respectively, to which they are attached together form a 4-8 membered heterocyclyl group;

R^4 is hydrogen, halogen, C1-C6 alkyl, or acrylamido;

R^5 is hydrogen, halogen, C1-C6 alkyl, cyano, $-NR^{5A} R^{5B}$, $-NR^{5A} C(=O)R^{5B}$, or $-C(=O)NR^{5A} R^{5B}$;

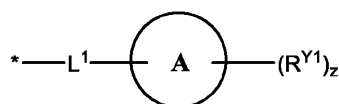
R^{5A} and R^{5B} are independently selected from hydrogen, C1-C6 alkyl, C2-C6 alkenyl, and C1-C6 hydroxyalkyl;

R^6 is hydrogen, halogen, or C1-C6 alkyl;

X is a bond, CH_2 , $CH(CH_3)$, $C(CH_3)_2$, or ;

W is NR^{3B} or O;

Y is phenyl, naphthyl, or 5-10 membered heteroaryl, wherein the phenyl, naphthyl, and 5-10 membered heteroaryl are optionally and independently substituted with 1-3 independently



selected R^Y or , wherein * represents the connection of L^1 to the remainder of the compound of Formula (I);

each R^Y is independently selected from: halogen, cyano, hydroxyl, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkoxy, C1-C6 hydroxyalkyl, $-(CH_2)_n-C(=O)R^F$, $-(CH_2)_n-NHC(=O)R^F$, $-(CH_2)_n-NHC(=O)OR^F$, $-C(=O)C(=O)NHR^F$, $-CO_2R^G$, $-(CH_2)_n-SO_2NR^H R^I$, $-(CH_2)_n-NHSO_2R^J$, $-(CH_2)_n-S(=O)(=NR^H)R^J$, $-(CH_2)_n-SO_2R^J$, $-(CH_2)_n-C(=O)NR^H R^I$, $-(CH_2)_n-C(=O)NR^H OR^I$, and C1-C6 haloalkyl optionally substituted with hydroxyl;

each R^F is independently selected from: C3-C6 cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocyclyl optionally substituted with C1-C6 alkyl; and C1-C6 alkyl optionally substituted with hydroxyl or $-\text{SO}_2(\text{C1-C6 alkyl})$;

each R^G is independently selected from: hydrogen, C3-C6 cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocyclyl, and C1-C6 alkyl optionally substituted with hydroxyl or $-\text{SO}_2(\text{C1-C6 alkyl})$;

each R^H and R^I is independently selected from: hydrogen, C1-C6 alkoxy, C3-C6 cycloalkyl, C2-C6 alkenyl, $-(\text{CH}_2)_n-\text{C}(=\text{O})\text{NH}_2$, $-(\text{CH}_2)_n-\text{SO}_2\text{NH}_2$, $-(\text{CH}_2)_n-\text{SO}_2(\text{C1-C6 alkyl})$, C1-C6 alkyl optionally substituted with 1-2 substituents independently selected from hydroxyl, $-\text{SO}_2(\text{C1-C6 alkyl})$, C1-C6 alkoxy, 5-6 membered heteroaryl, C3-C6 cycloalkyl, and $-\text{C}(=\text{O})\text{NR}^{K1}\text{R}^{K2}$; or R^H and R^I together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclyl optionally substituted with 1-2 substituents independently selected from halogen, C1-C6 alkyl, and $-\text{C}(=\text{O})\text{C1-C6 alkyl}$;

R^J is C1-C6 alkyl, C3-C6 cycloalkyl, or C1-C6 alkoxy;

each R^{K1} and R^{K2} is independently hydrogen or C1-C6 alkyl;

Ring A is phenyl, 4-10 membered heteroaryl, 4-10 membered heterocyclyl, or C4-C10 cycloalkyl;

L^1 is a bond, C1-C6 alkoxy, $-(\text{CH}_2)_n-\text{NHC}(=\text{O})-$, $-\text{C}(=\text{O})\text{NH}-(\text{CH}_2)_n-$, $-\text{CO}_2-$, $-\text{SO}_2-$, $-\text{NHSO}_2-$, $-\text{SO}_2\text{NH}-$, $-\text{S}(=\text{O})(=\text{NR}^G)-$, $-\text{SO}_2(\text{C1-C6 alkylene})-$, $-\text{C}(=\text{O})\text{C}(=\text{O})\text{NH}-$, or C1-C6 alkylene optionally substituted with oxo;

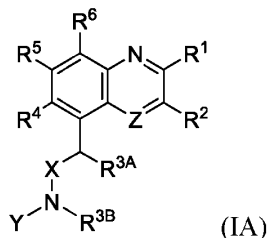
each R^{Y1} is independently selected from: cyano, hydroxyl, halogen, $-\text{C}(=\text{O})\text{R}^F$, $-\text{NHC}(=\text{O})\text{R}^F$, $-\text{CO}_2\text{R}^G$, $-\text{SO}_2\text{NR}^H\text{R}^I$, $-\text{NHSO}_2\text{R}^J$, $-\text{S}(=\text{O})(=\text{NR}^H)\text{R}^J$, $-\text{SO}_2(\text{C1-C6 alkyl})$, $-\text{C}(=\text{O})\text{NR}^H\text{R}^I$, 4-6 membered heteroaryl, C1-C6 alkoxy optionally substituted with R^{Y2} , C1-C6 haloalkyl, C1-C6 alkyl optionally substituted with R^{Y2} , and 4-6 membered heterocyclyl optionally substituted with hydroxyl or C1-C6 alkyl;

R^{Y2} is hydroxyl, $-\text{NR}^H\text{R}^I$, $-\text{C}(=\text{O})\text{NR}^H\text{R}^I$, or $-\text{SO}_2\text{NR}^H\text{R}^I$;

n is 0, 1, or 2; and

z is 0, 1, 2, or 3.

Some embodiments provide a compound of Formula (IA):



or a pharmaceutically acceptable salt thereof, wherein:

Z is N or CH;

5 R^1 is hydrogen, cyano, C3-C6 cycloalkyl, 4-10 membered heterocyclyl, C1-C6 alkyl optionally substituted with (i) C3-C6 cycloalkyl or (ii) 4-10 membered heterocyclyl, C1-C6 thioalkyl, C1-C6 haloalkyl, C1-C6 alkoxy, or C1-C6 alkoxyalkyl;

R^2 is phenyl optionally substituted with 1-4 independently selected R^{2A} , 5-10 membered heteroaryl optionally substituted with 1-4 independently selected R^{2A} , 4-10 membered heterocyclyl optionally substituted with 1-4 independently selected R^{2A} , 4-10 membered cycloalkyl optionally substituted with 1-4 independently selected R^{2A} , 4-10 membered heterocycloxy optionally substituted with 1-4 independently selected R^{2A} , 5-10 heteroaryloxy optionally substituted with 1-4 independently selected R^{2A} , C1-C6 alkoxyalkyl optionally substituted with $-C(=O)NR^A R^C$, or C1-C6 alkoxy optionally substituted with $-C(=O)NR^A R^C$,
15 4-10 membered cycloalkyl, 4-10 membered heterocyclyl, 5-10 membered heteroaryl, or phenyl;

each R^{2A} is independently selected from:

(i) halogen,

(ii) cyano,

(iii) hydroxyl,

20 (iv) $-NR^A R^B$,

(v) $-C(=O)NR^A R^B$,

(vi) ,

(vii) $-NHC(=O)R^C$,

(viii) $-C(=O)NR^D R^E$,

25 (ix) $-C(=O)OR^F$,

- (x) $-\text{SO}_2\text{R}^{\text{F}}$,
 (xi) $-\text{NHSO}_2\text{R}^{\text{F}}$,
 (xii) $-\text{SO}_2\text{NR}^{\text{F}}\text{R}^{\text{G}}$,
 (xiii) $-\text{NHC}(=\text{O})\text{C1-C6 alkyl}$ optionally substituted with $\text{NR}^{\text{A}}\text{R}^{\text{B}}$,
 5 (xiv) C1-C6 haloalkyl,
 (xv) C1-C6 hydroxyalkyl,
 (xvi) 5-10 membered heteroaryl optionally substituted with 1-3 substituents independently selected from C1-C6 alkyl and $-\text{NR}^{\text{A}}\text{R}^{\text{B}}$,
 (xvii) 4-10 membered heterocyclyl optionally substituted with 1-3 substituents
 10 independently selected from hydroxyl, C1-C6 haloalkyl, $-\text{C}(=\text{O})\text{C1-C6 alkyl}$, $-\text{SO}_2(\text{C1-C6 alkyl})$, $-\text{SO}_2\text{NR}^{\text{F}}\text{R}^{\text{G}}$, C1-C6 alkyl optionally substituted with C1-C6 alkoxy, $-\text{C}(=\text{O})\text{NR}^{\text{A}}\text{R}^{\text{B}}$, or $-\text{NHC}(=\text{O})\text{C1-C6 alkyl}$ optionally substituted with $-\text{NR}^{\text{A}}\text{R}^{\text{B}}$,
 (xviii) C1-C6 alkyl optionally substituted with 1-3 substituents independently selected from hydroxyl, oxo, $-\text{NR}^{\text{A}}\text{R}^{\text{B}}$, $-\text{C}(=\text{O})\text{NR}^{\text{A}}\text{R}^{\text{B}}$, C1-C6 alkoxy, and 4-10 membered heterocyclyl
 15 optionally substituted with hydroxyl, C1-C6 alkyl, aralkyl, heteroaralkyl, $-\text{C}(=\text{O})\text{NR}^{\text{A}}\text{R}^{\text{B}}$, or $-\text{C}(=\text{O})\text{C3-C6 cycloalkyl}$,
 (xix) C1-C6 alkoxy optionally substituted with $-\text{NR}^{\text{A}}\text{R}^{\text{B}}$ or 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl, aralkyl, heteroaralkyl, or $-\text{C}(=\text{O})\text{C3-C6 cycloalkyl}$, and
 (xx) C3-C6 cycloalkyl optionally substituted with 4-10 membered heterocyclyl optionally
 20 substituted with C1-C6 alkyl;
 each R^{A} and R^{B} is independently selected from hydrogen, hydroxyl, C1-C6 alkoxy, C3-C6 cycloalkyl, C2-C6 alkenyl, and C1-C6 alkyl optionally substituted with hydroxyl or C1-C6 alkoxy, or R^{A} and R^{B} together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclyl optionally substituted with 1-2 substituents independently selected from halogen, C1-
 25 C6 alkyl, and $-\text{C}(=\text{O})\text{C1-C6 alkyl}$;
 each R^{C} is independently selected from C3-C6 cycloalkyl, $-\text{C}(=\text{O})\text{NHR}^{\text{Y1}}$, or a C1-C6 alkyl optionally substituted with $-\text{NR}^{\text{A}}\text{R}^{\text{B}}$ or with 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl or with C1-C6 hydroxylalkyl;
 each R^{D} and R^{E} is independently selected from hydrogen, hydroxyl, C1-C6 alkyl, and C1-
 30 C6 alkoxy;

each R^{3A} and R^{3B} is independently selected from hydrogen, C1-C6 alkyl, C1-C6 alkoxy, and C1-C6 haloalkyl, or R^{3A} and R^{3B} , together with the carbon and nitrogen atoms, respectively, to which they are attached together form a 4-8 membered heterocyclcyl group;

R^4 is hydrogen, C1-C6 alkyl, or acrylamido;

5 R^5 is hydrogen, C1-C6 alkyl, cyano, $-NR^{5A}R^{5B}$, $-NR^{5A}C(=O)R^{5B}$, or $-C(=O)NR^{5A}R^{5B}$,

R^{5A} and R^{5B} are independently selected from hydrogen, C1-C6 alkyl, C2-C6 alkenyl, and C1-C6 hydroxyalkyl;

R^6 is hydrogen, halogen, or C1-C6 alkyl;

X is a bond, CH_2 , $CH(CH_3)$, $C(CH_3)_2$, or  ;

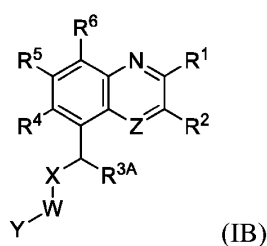
10 Y is phenyl optionally substituted with 1-3 independently selected R^Y , naphthyl optionally substituted with 1-3 independently selected R^Y , or 5-10 membered heteroaryl optionally substituted with 1-3 independently selected R^Y ;

each R^Y is independently selected from: halogen, cyano, hydroxyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy, C1-C6 hydroxyalkyl, $-NHC(=O)R^C$, $-C(=O)NHR^{Y1}$, $-CO_2R^A$,
15 $-SO_2NR^FR^G$, $-NHSO_2R^F$, $-S(=O)(=NR^F)R^G$, $-SO_2(C1-C6 \text{ alkyl})$, $-C(=O)NR^AR^B$, 5-6 membered heteroaryl, heteroaralkyl, and C1-C6 alkyl optionally substituted with $-CO_2R^A$ or 5-6 membered heteroaryl optionally substituted with R^{Y1} ;

R^{Y1} is $-SO_2(C1-C6 \text{ alkyl})$ or C1-C6 alkyl optionally substituted with oxo; and

20 each R^F and R^G is independently selected from hydrogen, phenyl, and C1-C6 alkyl optionally substituted with oxo or $-NR^AR^B$.

Some embodiments, provide a compound of Formula (IB):



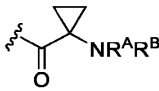
or a pharmaceutically acceptable salt thereof, wherein:

Z is N or CH;

R^1 is hydrogen, halogen, cyano, C3-C6 cycloalkyl, 4-10 membered heterocyclyl, C1-C6 alkyl optionally substituted with (i) C3-C6 cycloalkyl or (ii) 4-10 membered heterocyclyl, C1-C6 thioalkyl, C1-C6 haloalkyl, C1-C6 alkoxy, or C1-C6 alkoxyalkyl;

R^2 is phenyl optionally substituted with 1-4 independently selected R^{2A} , 5-10 membered heteroaryl optionally substituted with 1-4 independently selected R^{2A} , 4-10 membered heterocyclyl optionally substituted with 1-4 independently selected R^{2A} , 4-10 membered cycloalkyl optionally substituted with 1-4 independently selected R^{2A} , 4-10 membered heterocycloxy optionally substituted with 1-4 independently selected R^{2A} , 5-10 heteroaryloxy optionally substituted with 1-4 independently selected R^{2A} , C1-C6 alkoxyalkyl optionally substituted with $-C(=O)NR^A R^C$, or C1-C6 alkoxy optionally substituted with $-C(=O)NR^A R^C$, 4-10 membered cycloalkyl, 4-10 membered heterocyclyl, 5-10 membered heteroaryl, or phenyl;

each R^{2A} is independently selected from:

- (i) halogen,
- (ii) cyano,
- (iii) hydroxyl,
- (iv) $-NR^A R^B$,
- (v) $-C(=O)NR^A R^B$,
- (vi) ,
- (vii) $-NHC(=O)R^C$,
- (viii) $-C(=O)NR^D R^E$,
- (ix) $-C(=O)OR^F$,
- (x) $-SO_2 R^F$,
- (xi) $-NHSO_2 R^F$,
- (xii) $-SO_2 NR^F R^G$,
- (xiii) $-NHC(=O)C1-C6$ alkyl optionally substituted with $NR^A R^B$,
- (xiv) C1-C6 haloalkyl,
- (xv) C1-C6 hydroxyalkyl,
- (xvi) 5-10 membered heteroaryl optionally substituted with 1-3 substituents independently selected from C1-C6 alkyl and $-NR^A R^B$,

(xvii) 4-10 membered heterocyclyl optionally substituted with 1-3 substituents independently selected from hydroxyl, C1-C6 haloalkyl, $-C(=O)C1-C6$ alkyl, $-SO_2(C1-C6$ alkyl), $-SO_2NR^FR^G$, C1-C6 alkyl optionally substituted with C1-C6 alkoxy, $-C(=O)NR^AR^B$, or $-NHC(=O)C1-C6$ alkyl optionally substituted with $-NR^AR^B$,

5 (xviii) C1-C6 alkyl optionally substituted with 1-3 substituents independently selected from hydroxyl, oxo, $-NR^AR^B$, $-C(=O)NR^AR^B$, C1-C6 alkoxy, and 4-10 membered heterocyclyl optionally substituted with hydroxyl, C1-C6 alkyl, aralkyl, heteroaralkyl, $-C(=O)NR^AR^B$, or $-C(=O)C3-C6$ cycloalkyl,

(xix) C1-C6 alkoxy optionally substituted with $-NR^AR^B$ or 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl, aralkyl, heteroaralkyl, or $-C(=O)C3-C6$ cycloalkyl, and

(xx) C3-C6 cycloalkyl optionally substituted with 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl;

each R^A and R^B is independently selected from hydrogen, hydroxyl, C1-C6 alkoxy, C3-C6 cycloalkyl, C2-C6 alkenyl, and C1-C6 alkyl optionally substituted with hydroxyl or C1-C6 alkoxy, or R^A and R^B together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclyl optionally substituted with 1-2 substituents independently selected from halogen, C1-C6 alkyl, and $-C(=O)C1-C6$ alkyl;

each R^C is independently selected from C3-C6 cycloalkyl, $-C(=O)NHR^{Y1}$, or a C1-C6 alkyl optionally substituted with $-NR^AR^B$ or with 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl or with C1-C6 hydroxylalkyl;

each R^D and R^E is independently selected from hydrogen, hydroxyl, C1-C6 alkyl, and C1-C6 alkoxy;

each R^{3A} and R^{3B} is independently selected from hydrogen, C1-C6 alkyl, C1-C6 alkoxy, and C1-C6 haloalkyl, or R^{3A} and R^{3B} , together with the carbon and nitrogen atoms, respectively, to which they are attached together form a 4-8 membered heterocyclyl group;

R^4 is hydrogen, halogen, C1-C6 alkyl, or acrylamido;

R^5 is hydrogen, halogen, C1-C6 alkyl, cyano, $-NR^{5A}R^{5B}$, $-NR^{5A}C(=O)R^{5B}$, or $-C(=O)NR^{5A}R^{5B}$;

R^{5A} and R^{5B} are independently selected from hydrogen, C1-C6 alkyl, C2-C6 alkenyl, and C1-C6 hydroxyalkyl;

R^6 is hydrogen, halogen, or C1-C6 alkyl;

X is a bond, CH₂, CH(CH₃), C(CH₃)₂, or ;

W is NR^{3B} or O;

Y is phenyl optionally substituted with 1-3 independently selected R^Y, naphthyl optionally substituted with 1-3 independently selected R^Y, or 5-10 membered heteroaryl optionally substituted with 1-3 independently selected R^Y;

each R^Y is independently selected from: halogen, cyano, hydroxyl, C1-C6 haloalkyl optionally substituted with hydroxyl, C1-C6 alkoxy, C1-C6 haloalkoxy, C1-C6 hydroxyalkyl, -NHC(=O)R^C, -C(=O)NHR^{Y1}, -CO₂R^A, -SO₂NR^FR^G, -NHSO₂R^F, -S(=O)(=NR^F)R^G, -SO₂(C1-C6 alkyl), -C(=O)NR^AR^B, 4-6 membered heteroaryl, heteroaralkyl, 4-6 membered heterocyclyl optionally substituted with R^{Y1}, and C1-C6 alkyl optionally substituted with -CO₂R^A or 4-6 membered heteroaryl optionally substituted with R^{Y1};

R^{Y1} is -SO₂(C1-C6 alkyl) or C1-C6 alkyl optionally substituted with oxo; and

each R^F and R^G is independently selected from hydrogen, phenyl, and C1-C6 alkyl optionally substituted with oxo or -NR^AR^B.

In some embodiments, Z is CH.

In some embodiments, Z is N.

In some embodiments, R¹ is hydrogen.

In some embodiments, R¹ is halogen. In some embodiments, R¹ is I, Br, Cl, or F. In some embodiments, R¹ is Cl or F. In some embodiments, R¹ is F. In some embodiments, R¹ is Cl.

In some embodiments, R¹ is cyano.

In some embodiments, R¹ is C3-C6 cycloalkyl. In some embodiments, R¹ is cyclopropyl or cyclobutyl.

In some embodiments, R¹ is 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl. In some embodiments, R¹ is 4-10 membered heterocyclyl. In some embodiments, R¹ is 4-10 membered heterocyclyl substituted with C1-C6 alkyl.

In some embodiments, R¹ is 5-8 membered heterocyclyl.

In some embodiments, the heterocyclyl of R¹ is piperidinyl, piperazinyl, octahydrocyclopenta[c]pyranyl, octahydrocyclopenta[b]pyranyl, 2-oxabicyclo[2.1.1]hexanyl, 2-oxabicyclo[3.1.1]heptanyl, or morpholinyl. In some embodiments, the heterocyclyl of R¹ is octahydrocyclopenta[c]pyranyl. In some embodiments, the heterocyclyl of R¹ is

octahydrocyclopenta[b]pyranyl. In some embodiments, the heterocyclyl of R¹ is 2-oxabicyclo[2.1.1]hexanyl. In some embodiments, the heterocyclyl of R¹ is 2-oxabicyclo[3.1.1]heptanyl.

In some embodiments, R¹ is C1-C6 alkyl optionally substituted with (i) C3-C6 cycloalkyl or (ii) 4-10 membered heterocyclyl. In some embodiments, R¹ is C1-C6 alkyl substituted with (i) C3-C6 cycloalkyl or (ii) 4-10 membered heterocyclyl. In some embodiments, R¹ is C1-C3 alkyl substituted with (i) C3-C6 cycloalkyl or (ii) 4-10 membered heterocyclyl. In some embodiments, R¹ is C1-C6 alkyl substituted with C3-C6 cycloalkyl. In some embodiments, R¹ is C1-C6 alkyl substituted with 4-10 membered heterocyclyl. In some embodiments, R¹ is C1-C6 alkyl. In some embodiments, R¹ is methyl, ethyl, or isopropyl. In some embodiments, R¹ is methyl.

In some embodiments, R¹ is C1-C6 thioalkyl. In some embodiments, R¹ is C1-C3 thioalkyl. In some embodiments, R¹ is thiomethyl, thioethyl, or thiopropyl. In some embodiments, R¹ is methyl-thiomethyl, methyl-thioethyl, or ethyl-thiomethyl. In some embodiments, R¹ is thiomethyl.

In some embodiments, R¹ is C1-C6 haloalkyl. In some embodiments, R¹ is C1-C3 haloalkyl. In some embodiments, R¹ is C1-C3 fluoroalkyl. In some embodiments, R¹ is CF₃. In some embodiments, R¹ is CHF₂.

In some embodiments, R¹ is C1-C6 alkoxy. In some embodiments, R¹ is C1-C3 alkoxy. In some embodiments, R¹ is -OCH₃, -OCH₂CH₃, or -OCH₂CH₂CH₃. In some embodiments, R¹ is -OCH₃.

In some embodiments, R¹ is C1-C6 alkoxyalkyl. In some embodiments, R¹ is C1-C3 alkoxyalkyl. In some embodiments, R¹ is -CH₂OCH₃, -CH₂OCH₂CH₃, or -CH₂CH₂OCH₃. In some embodiments, R¹ is -CH₂OCH₃.

In some embodiments, R² is C6-C10 aryl optionally substituted with 1-4 independently selected R^{2A}. In some embodiments, R² is C6-C10 aryl substituted with 1 or 2 independently selected R^{2A}. In some embodiments, R² is C6-C10 aryl substituted with 1 R^{2A}. In some embodiments, R² is C6-C10 aryl substituted with 2 independently selected R^{2A}. In some embodiments, R² is C6-C10 aryl optionally substituted with 3 independently selected R^{2A}. In some embodiments, R² is C6-C10 aryl.

In some embodiments, R² is phenyl optionally substituted with 1-4 independently selected R^{2A}. In some embodiments, R² is phenyl substituted with 1 or 2 independently selected R^{2A}. In

some embodiments, R^2 is phenyl substituted with 1 R^{2A} . In some embodiments, R^2 is phenyl substituted with 2 independently selected R^{2A} . In some embodiments, R^2 is phenyl optionally substituted with 3 independently selected R^{2A} . In some embodiments, R^2 is phenyl.

5 In some embodiments, R^2 is 2,3-dihydro-1H-indenyl optionally substituted with 1-4 independently selected R^{2A} . In some embodiments, R^2 is 2,3-dihydro-1H-indenyl substituted with 1 or 2 independently selected R^{2A} . In some embodiments, R^2 is 2,3-dihydro-1H-indenyl substituted with 1 R^{2A} . In some embodiments, R^2 is 2,3-dihydro-1H-indenyl substituted with 2 independently selected R^{2A} . In some embodiments, R^2 is 2,3-dihydro-1H-indenyl optionally substituted with 3 independently selected R^{2A} . In some embodiments, R^2 is 2,3-dihydro-1H-
10 indenyl.

In some embodiments, R^2 is 5-10 membered heteroaryl optionally substituted with 1-4 independently selected R^{2A} . In some embodiments, R^2 is 5-10 membered heteroaryl substituted with 1 or 2 independently selected R^{2A} . In some embodiments, R^2 is 5-10 membered heteroaryl substituted with 1 R^{2A} . In some embodiments, R^2 is 5-10 membered heteroaryl substituted with 2
15 independently selected R^{2A} . In some embodiments, R^2 is 5-10 membered heteroaryl optionally substituted with 3 independently selected R^{2A} . In some embodiments, R^2 is 5-10 membered heteroaryl.

In some embodiments, R^2 is 6 membered heteroaryl optionally substituted with 1-4 independently selected R^{2A} . In some embodiments, R^2 is 6 membered heteroaryl substituted with
20 1 or 2 independently selected R^{2A} . In some embodiments, R^2 is 6 membered heteroaryl substituted with 1 R^{2A} . In some embodiments, R^2 is 6 membered heteroaryl substituted with 2 independently selected R^{2A} . In some embodiments, R^2 is 6 membered heteroaryl optionally substituted with 3 independently selected R^{2A} . In some embodiments, R^2 is 6 membered heteroaryl.

In some embodiments, R^2 is 9 membered heteroaryl optionally substituted with 1-4
25 independently selected R^{2A} . In some embodiments, R^2 is 9 membered heteroaryl substituted with 1 or 2 independently selected R^{2A} . In some embodiments, R^2 is 9 membered heteroaryl substituted with 1 R^{2A} . In some embodiments, R^2 is 9 membered heteroaryl substituted with 2 independently selected R^{2A} . In some embodiments, R^2 is 9 membered heteroaryl optionally substituted with 3 independently selected R^{2A} . In some embodiments, R^2 is 9 membered heteroaryl.

30 In some embodiments, the heteroaryl of R^2 is pyridinyl, pyrimidinyl, pyridazinyl, indole, indazole, azaindole, azaindazole, indoline, azaindoline, isoindoline, azaisoindoline,

benzimidazolyl, benzoxazolyl, benzothiazolyl, benzoisoxazolyl, benzisothiazolyl, quinolinyl, 6,7-dihydro-5H-cyclopenta[c]pyridinyl, 6,7-dihydro-5H-cyclopenta[b]pyridinyl, chromanyl, 3,4-dihydro-2H-112-quinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 6,7-dihydro-5H-cyclopenta[c]pyridinyl, 3,4-dihydro-2H-pyrano[2,3-b]pyridinyl, 3,4-dihydro-2H-pyrano[2,3-c]pyridinyl, 3,4-dihydro-2H-pyrano[3,2-b]pyridinyl, 7,8-dihydro-6H-pyrano[3,2-d]pyrimidinyl, 5,6,7,8-tetrahydroquinazolinyl, or isoquinolinyl. In some embodiments, the heteroaryl of R^2 is pyridinyl or pyrimidinyl. In some embodiments, the heteroaryl of R^2 is pyridinyl. In some embodiments, the heteroaryl of R^2 is indole, indazole, azaindole, azaindazole, indoline, azaindoline, isoindoline, or azaisoindoline. In some embodiments, the heteroaryl of R^2 is 6,7-dihydro-5H-cyclopenta[c]pyridinyl, 6,7-dihydro-5H-cyclopenta[b]pyridinyl, chromanyl, 3,4-dihydro-2H-112-quinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 6,7-dihydro-5H-cyclopenta[c]pyridinyl, 3,4-dihydro-2H-pyrano[2,3-b]pyridinyl, 3,4-dihydro-2H-pyrano[2,3-c]pyridinyl, 3,4-dihydro-2H-pyrano[3,2-b]pyridinyl, 7,8-dihydro-6H-pyrano[3,2-d]pyrimidinyl, or 5,6,7,8-tetrahydroquinazolinyl. In some embodiments, the heteroaryl of R^2 is 6,7-dihydro-5H-cyclopenta[c]pyridinyl. In some embodiments, the heteroaryl of R^2 is 6,7-dihydro-5H-cyclopenta[b]pyridinyl. In some embodiments, the heteroaryl of R^2 is chromanyl. In some embodiments, the heteroaryl of R^2 is 3,4-dihydro-2H-quinolinyl, 5,6,7,8-tetrahydroquinazolinyl, or 6,7-dihydro-5H-cyclopenta[c]pyridinyl. In some embodiments, the heteroaryl of R^2 is 3,4-dihydro-2H-112-quinolinyl. In some embodiments, the heteroaryl of R^2 is 5,6,7,8-tetrahydroquinazolinyl. In some embodiments, the heteroaryl of R^2 is 6,7-dihydro-5H-cyclopenta[c]pyridinyl. In some embodiments, the heteroaryl of R^2 is 4-dihydro-2H-pyrano[2,3-b]pyridinyl. In some embodiments, the heteroaryl of R^2 is 3,4-dihydro-2H-pyrano[2,3-c]pyridinyl, or 5,6,7,8-tetrahydroquinazolinyl. In some embodiments, the heteroaryl of R^2 is 3,4-dihydro-2H-pyrano[3,2-b]pyridinyl. In some embodiments, the heteroaryl of R^2 is 7,8-dihydro-6H-pyrano[3,2-d]pyrimidinyl. In some embodiments, the heteroaryl of R^2 is 5,6,7,8-tetrahydroquinazolinyl.

In some embodiments, R^2 is 5-10 membered heteroaryloxy optionally substituted with 1-4 independently selected R^{2A} . In some embodiments, R^2 is 5-10 membered heteroaryloxy substituted with 1 or 2 independently selected R^{2A} . In some embodiments, R^2 is 5-10 membered heteroaryloxy substituted with 1 R^{2A} . In some embodiments, R^2 is 5-10 membered heteroaryloxy substituted with 2 independently selected R^{2A} . In some embodiments, R^2 is 5-10 membered

heteroaryloxy optionally substituted with 3 independently selected R^{2A} . In some embodiments, R^2 is 5-10 membered heteroaryloxy.

In some embodiments, R^2 is 6 membered heteroaryloxy optionally substituted with 1-4 independently selected R^{2A} . In some embodiments, R^2 is 6 membered heteroaryloxy substituted with 1 or 2 independently selected R^{2A} . In some embodiments, R^2 is 6 membered heteroaryloxy substituted with 1 R^{2A} . In some embodiments, R^2 is 6 membered heteroaryloxy substituted with 2 independently selected R^{2A} . In some embodiments, R^2 is 6 membered heteroaryloxy optionally substituted with 3 independently selected R^{2A} . In some embodiments, R^2 is 6 membered heteroaryloxy.

In some embodiments, R^2 is 4-10 membered heterocyclyl optionally substituted with 1-4 independently selected R^{2A} . In some embodiments, R^2 is 4-10 membered heterocyclyl substituted with 1 or 2 independently selected R^{2A} . In some embodiments, R^2 is 4-10 membered heterocyclyl substituted with 1 R^{2A} . In some embodiments, R^2 is 4-10 membered heterocyclyl substituted with 2 independently selected R^{2A} . In some embodiments, R^2 is 4-10 membered heterocyclyl optionally substituted with 3 independently selected R^{2A} . In some embodiments, R^2 is 4-10 membered heterocyclyl.

In some embodiments, R^2 is 4-10 membered bicyclic ether optionally substituted with 1 or 2 independently selected R^{2A} . In some embodiments, R^2 is 4-10 membered bridging bicyclic ether optionally substituted with 1 or 2 independently selected R^{2A} . In some embodiments, R^2 is 4-10 membered fused bicyclic ether optionally substituted with 1 or 2 independently selected R^{2A} . In some embodiments, R^2 is 4-10 membered spirocyclic ether optionally substituted with 1 or 2 independently selected R^{2A} . In some embodiments, R^2 is an unsubstituted 4-10 membered bridging bicyclic ether. In some embodiments, R^2 is an unsubstituted 4-10 membered fused bicyclic ether. In some embodiments, R^2 is an unsubstituted 4-10 membered spirocyclic ether. In some embodiments, R^2 is 4-10 membered bridging bicyclic ether substituted with 1 or 2 independently selected R^{2A} . In some embodiments, R^2 is 4-10 membered fused bicyclic ether substituted with 1 or 2 independently selected R^{2A} . In some embodiments, R^2 is 4-10 membered spirocyclic ether substituted with 1 or 2 independently selected R^{2A} . In some embodiments, R^2 is 5-8 membered heterocyclyl optionally substituted with 1-4 independently selected R^{2A} . In some embodiments, R^2 is 5-8 membered heterocyclyl substituted with 1 or 2 independently selected R^{2A} . In some embodiments, R^2 is 5-8 membered heterocyclyl substituted with 1 R^{2A} . In some

embodiments, R^2 is 5-8 membered heterocyclyl substituted with 2 independently selected R^{2A} . In some embodiments, R^2 is 5-8 membered heterocyclyl optionally substituted with 3 independently selected R^{2A} . In some embodiments, R^2 is 5-8 membered heterocyclyl.

In some embodiments, the heterocyclyl of R^2 is piperidiny, piperaziny, 5 octahydrocyclopenta[c]pyranyl, octahydrocyclopenta[b]pyranyl, 2-oxabicyclo[2.1.1]hexanyl, 2-oxabicyclo[3.1.1]heptanyl, or morpholiny. In some embodiments, the heterocyclyl of R^2 is octahydrocyclopenta[c]pyranyl. In some embodiments, the heterocyclyl of R^2 is octahydrocyclopenta[b]pyranyl. In some embodiments, the heterocyclyl of R^2 is 2-oxabicyclo[2.1.1]hexanyl. In some embodiments, the heterocyclyl of R^2 is 2-oxabicyclo[3.1.1]heptanyl. In some embodiments, R^2 is 4-10 membered heterocycloxy 10 optionally substituted with 1-4 independently selected R^{2A} . In some embodiments, R^2 is 4-10 membered heterocycloxy substituted with 1 or 2 independently selected R^{2A} . In some embodiments, R^2 is 4-10 membered heterocycloxy substituted with 1 R^{2A} . In some embodiments, R^2 is 4-10 membered heterocycloxy substituted with 2 independently selected R^{2A} . In some embodiments, R^2 is 4-10 membered heterocycloxy optionally substituted with 3 15 independently selected R^{2A} . In some embodiments, R^2 is 4-10 membered heterocycloxy.

In some embodiments, R^2 is 5-8 membered heterocycloxy optionally substituted with 1-4 independently selected R^{2A} . In some embodiments, R^2 is 5-8 membered heterocycloxy substituted with 1 or 2 independently selected R^{2A} . In some embodiments, R^2 is 5-8 membered 20 heterocycloxy substituted with 1 R^{2A} . In some embodiments, R^2 is 5-8 membered heterocycloxy substituted with 2 independently selected R^{2A} . In some embodiments, R^2 is 5-8 membered heterocycloxy optionally substituted with 3 independently selected R^{2A} . In some embodiments, R^2 is 5-8 membered heterocycloxy.

In some embodiments, R^2 is C4-C10 cycloalkyl optionally substituted with 1-4 25 independently selected R^{2A} . In some embodiments, R^2 is C4-C10 cycloalkyl substituted with 1 or 2 independently selected R^{2A} . In some embodiments, R^2 is C4-C10 cycloalkyl substituted with 1 R^{2A} . In some embodiments, R^2 is C4-C10 cycloalkyl substituted with 2 independently selected R^{2A} . In some embodiments, R^2 is C4-C10 cycloalkyl optionally substituted with 3 independently selected R^{2A} . In some embodiments, R^2 is C4-C10 cycloalkyl.

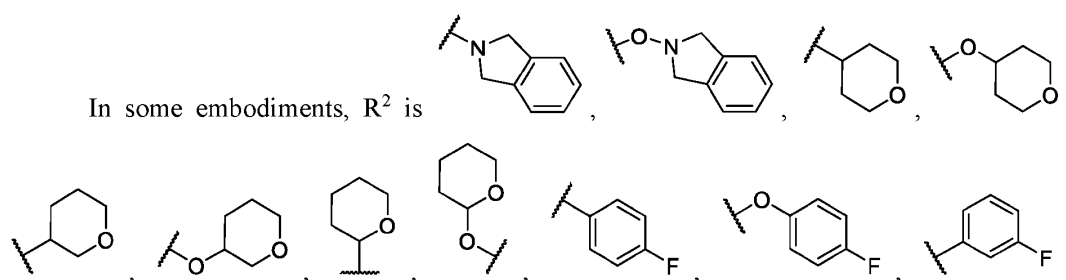
30 In some embodiments, R^2 is C5-C7 cycloalkyl optionally substituted with 1-4 independently selected R^{2A} . In some embodiments, R^2 is C5-C7 cycloalkyl substituted with 1 or

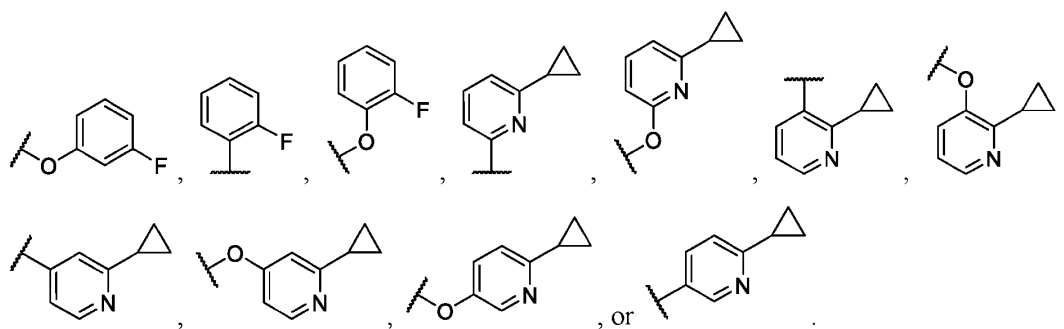
2 independently selected R^{2A} . In some embodiments, R^2 is C5-C7 cycloalkyl substituted with 1 R^{2A} . In some embodiments, R^2 is C5-C7 cycloalkyl substituted with 2 independently selected R^{2A} . In some embodiments, R^2 is C5-C7 cycloalkyl optionally substituted with 3 independently selected R^{2A} . In some embodiments, R^2 is C5-C7 cycloalkyl.

5 In some embodiments, the cycloalkyl of R^2 is cyclopentyl, [1.1.1]bicyclopentyl, octahydro-1H-indenyl, bicyclo[2.1.1]hexanyl, bicyclo[3.1.0]hexanyl, spiro[2.4]heptanyl, or cyclohexyl. In some embodiments, the cycloalkyl of R^2 is octahydro-1H-indenyl. In some embodiments, the cycloalkyl of R^2 is bicyclo[2.1.1]hexanyl. In some embodiments, the cycloalkyl of R^2 is bicyclo[3.1.0]hexanyl.

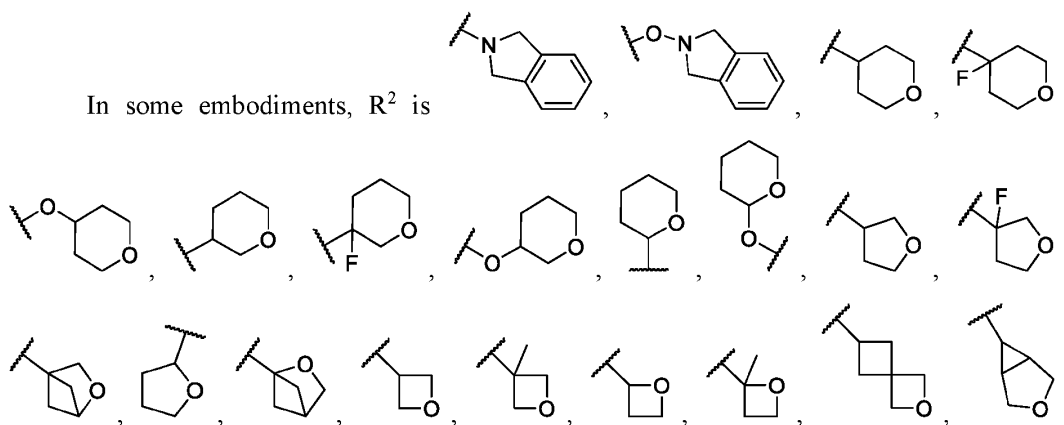
10 In some embodiments, R^2 is C1-C6 alkoxy optionally substituted with $-C(=O)NR^A R^C$, C4-C10 cycloalkyl, or phenyl. In some embodiments, R^2 is C1-C6 alkoxy substituted with $-C(=O)NR^A R^C$, C4-C10 cycloalkyl, or phenyl. In some embodiments, R^2 is C1-C6 alkoxy substituted with $-C(=O)NR^A R^C$. In some embodiments, R^2 is C1-C6 alkoxy substituted with C4-C10 cycloalkyl. In some embodiments, R^2 is C1-C6 alkoxy substituted with C4-C6 cycloalkyl. In some embodiments, R^2 is C1-C6 alkoxy substituted with phenyl. In some embodiments, R^2 is C1-C6 alkoxy. In some embodiments, R^2 is C1-C3 alkoxy. In some embodiments, R^2 is $-OCH_3$ or $-OCH_2CH_3$.

In some embodiments, R^2 is C1-C6 alkoxyalkyl optionally substituted with $-C(=O)NR^A R^C$. In some embodiments, R^2 is C1-C6 alkoxyalkyl substituted with $-C(=O)NR^A R^C$.
 20 In some embodiments, R^2 is C3-C6 alkoxyalkyl substituted with $-C(=O)NR^A R^C$. In some embodiments, R^2 is C1-C6 alkoxyalkyl. In some embodiments, R^2 is $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, or $-CH_2CH_2OCH_3$. In some embodiments, R^2 is $-CH_2OCH_3$.

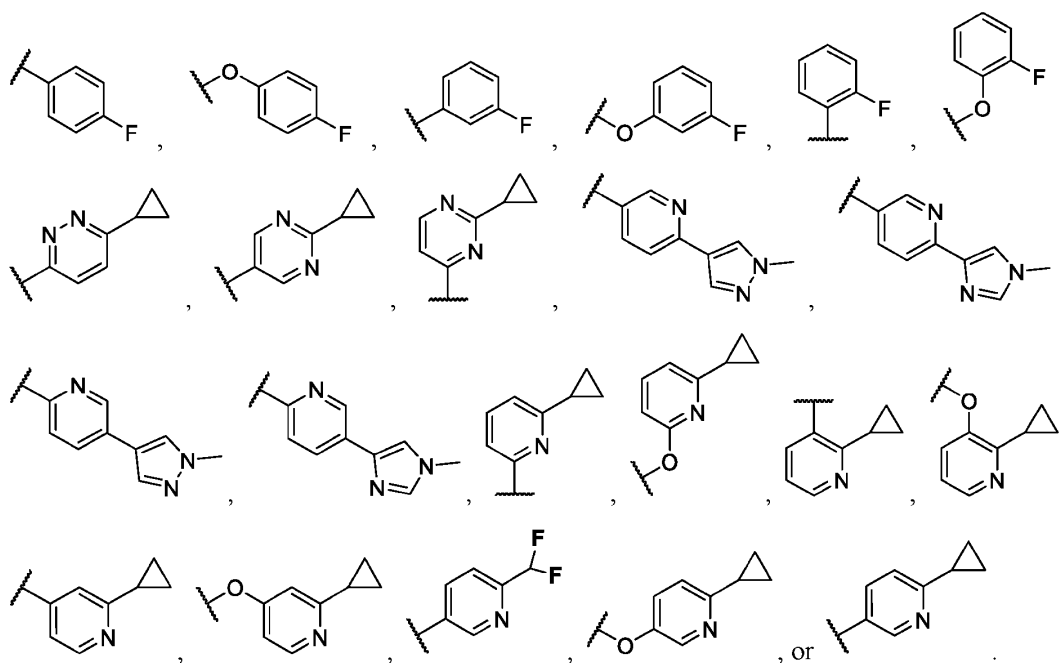




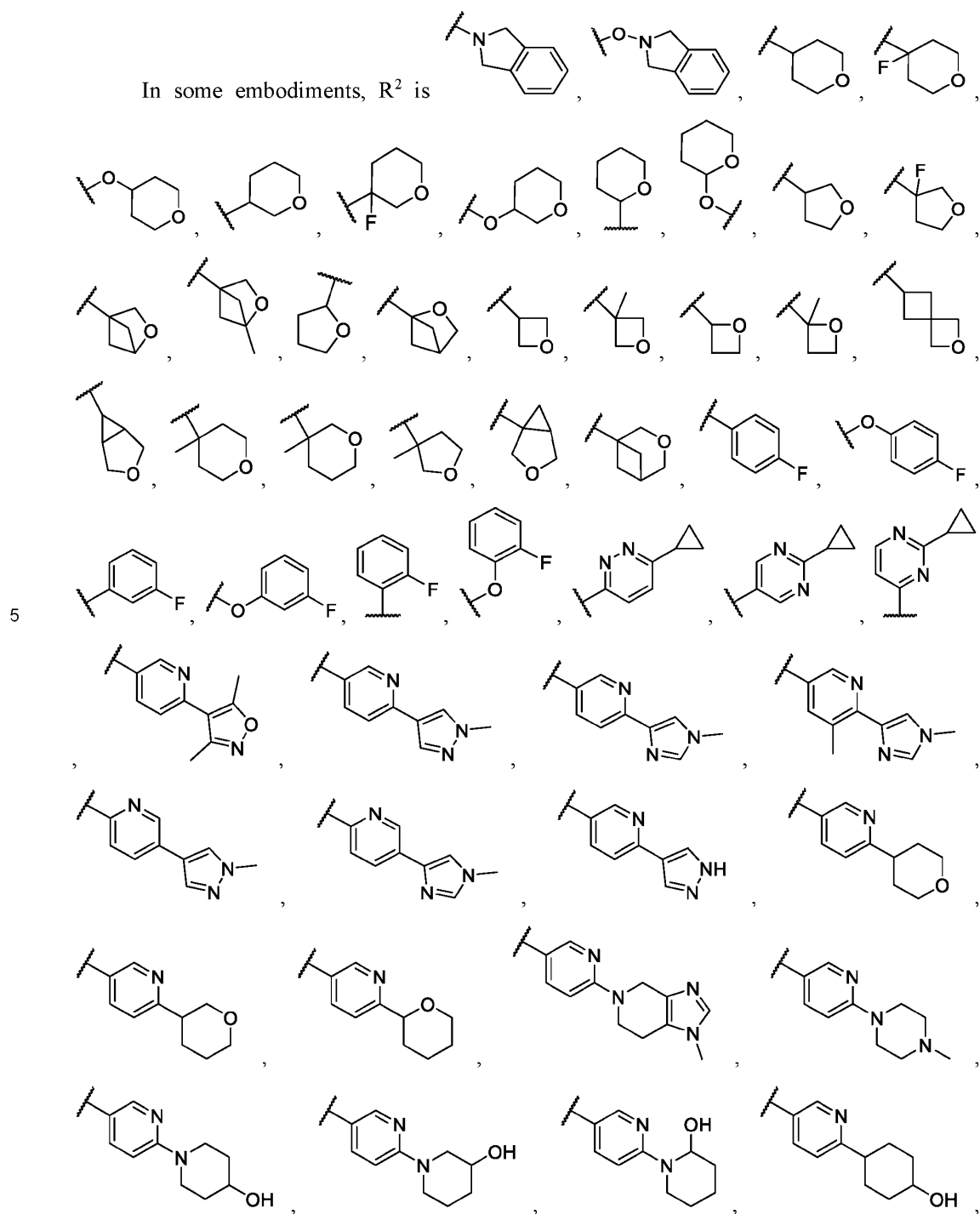
In some embodiments, R^2 is

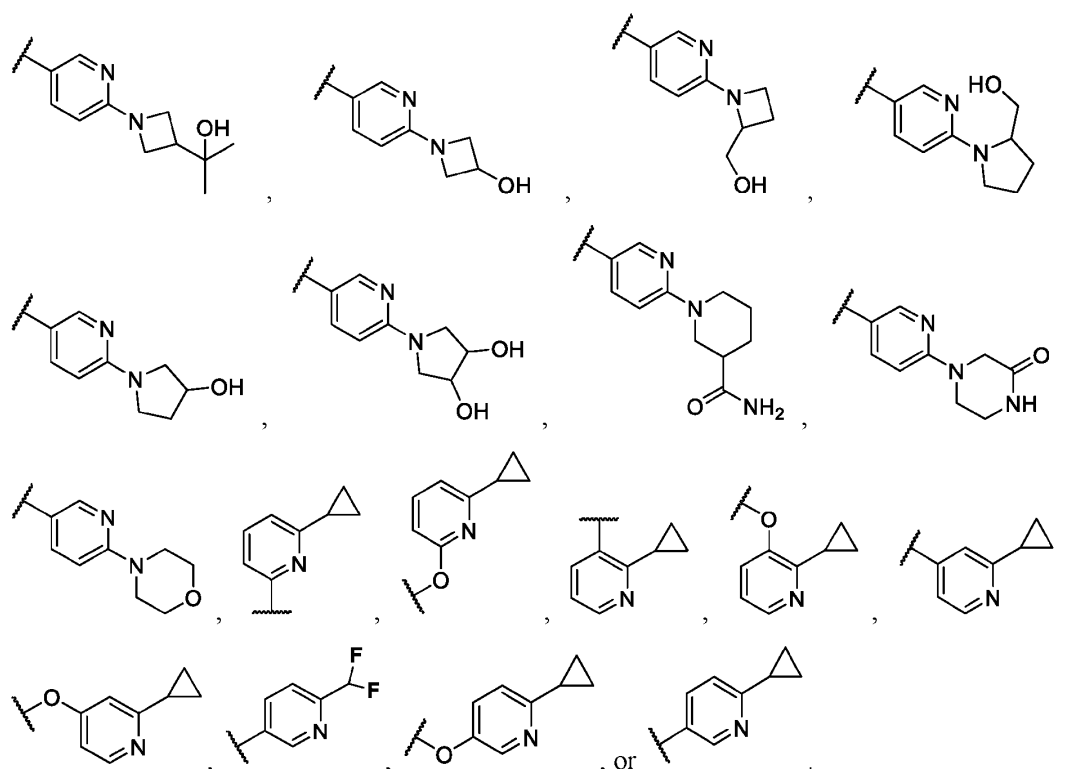


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In some embodiments, R² is





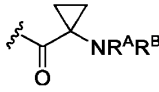
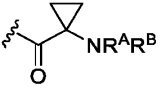
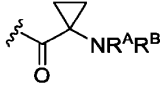
5 In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently halogen. In some embodiments, 1, 2, or 3 of R^{2A} are independently fluoro or chloro. In some embodiments, 1 or 2 of R^{2A} are independently fluoro or chloro. In some embodiments, 1 R^{2A} is fluoro or chloro.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently cyano. In some embodiments, 1 or 2 of R^{2A} are cyano. In some embodiments, 1 R^{2A} is cyano.

10 In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently hydroxyl. In some embodiments, 1 or 2 of R^{2A} are hydroxyl. In some embodiments, 1 R^{2A} is hydroxyl.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently $-NR^A R^B$. In some embodiments, 1 or 2 of R^{2A} are independently $-NR^A R^B$. In some embodiments, 1 R^{2A} is $-NR^A R^B$.

15 In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently $-C(=O)NR^A R^B$. In some embodiments, 1 or 2 of R^{2A} are independently $-C(=O)NR^A R^B$. In some embodiments, 1 R^{2A} is $-C(=O)NR^A R^B$.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently . In some
embodiments, 1 or 2 of R^{2A} are independently . In some embodiments, 1 R^{2A} is
.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently -NHC(=O)R^C . In some
5 embodiments, 1 or 2 of R^{2A} are independently -NHC(=O)R^C . In some embodiments, 1, 2, 3, or 4
of R^{2A} are independently -C(=O)OR^D . In some embodiments, 1 or 2 of R^{2A} are independently -C(=O)OR^D . In some embodiments, 1 R^{2A} is -C(=O)OR^D .

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently $\text{-SO}_2\text{R}^D$. In some
embodiments, 1 or 2 of R^{2A} are independently $\text{-SO}_2\text{R}^D$. In some embodiments, 1 R^{2A} is $\text{-SO}_2\text{R}^D$.

10 In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently $\text{-NHSO}_2\text{R}^D$. In some
embodiments, 1 or 2 of R^{2A} are independently $\text{-NHSO}_2\text{R}^D$. In some embodiments, 1 R^{2A} is
 $\text{-NHSO}_2\text{R}^D$.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently $\text{-SO}_2\text{NR}^D\text{R}^E$. In some
embodiments, 1 or 2 of R^{2A} are independently $\text{-SO}_2\text{NR}^D\text{R}^E$. In some embodiments, 1 R^{2A} is
15 $\text{-SO}_2\text{NR}^D\text{R}^E$.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently $\text{-NHC(=O)C1-C6 alkyl}$
optionally substituted with NR^AR^B . In some embodiments, 1, 2, or 3 of R^{2A} are independently
 $\text{-NHC(=O)C1-C6 alkyl}$ substituted with NR^AR^B . In some embodiments, 1, 2, or 3 of R^{2A} are
independently $\text{-NHC(=O)C1-C6 alkyl}$. In some embodiments, 1 or 2 of R^{2A} are independently
20 $\text{-NHC(=O)C1-C6 alkyl}$ optionally substituted with NR^AR^B . In some embodiments, 1 or 2
of R^{2A} are independently $\text{-NHC(=O)C1-C6 alkyl}$ substituted with NR^AR^B . In some embodiments, 1 or 2
of R^{2A} are independently $\text{-NHC(=O)C1-C6 alkyl}$. In some embodiments, 1 R^{2A} is $\text{-NHC(=O)C1-C6 alkyl}$
optionally substituted with NR^AR^B .

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently C1-C6 haloalkyl. In some
25 embodiments, 1 or 2 of R^{2A} are independently C1-C3 haloalkyl. In some embodiments, 1 or 2 of
 R^{2A} are trifluoromethyl. In some embodiments, 1 R^{2A} is C1-C6 haloalkyl.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently C1-C6 hydroxyalkyl. In some embodiments, 1 or 2 of R^{2A} are independently C1-C3 hydroxyalkyl. In some embodiments, 1 R^{2A} is C1-C3 hydroxyalkyl.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently 5-10 membered heteroaryl optionally substituted with 1-3 substituents independently selected from hydroxyl, cyano, halogen, $-C(=O)NR^{AB}$, $-NR^{AB}$, C1-C6 alkyl optionally substituted with hydroxyl; and 4-10 membered heterocyclyl optionally substituted with hydroxyl or C1-C6 alkyl. In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently 5-10 membered heteroaryl substituted with 1-3 substituents independently selected from hydroxyl, cyano, C1-C6 alkyl, halogen, $-C(=O)NR^{AB}$, $-NR^{AB}$, and 4-10 membered heterocyclyl optionally substituted with hydroxyl or C1-C6 alkyl. In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently 5-10 membered heteroaryl. In some embodiments, 1 R^{2A} is 5-10 membered heteroaryl optionally substituted with 1-3 substituents independently selected from hydroxyl, cyano, halogen, $-C(=O)NR^{AB}$, $-NR^{AB}$, C1-C6 alkyl optionally substituted with hydroxyl; and 4-10 membered heterocyclyl optionally substituted with hydroxyl or C1-C6 alkyl.

In some embodiments, 1 of R^{2A} is 5-6 membered heteroaryl optionally substituted with 1-3 substituents independently selected from hydroxyl, cyano, C1-C6 alkyl, halogen, $-C(=O)NR^{AB}$, $-NR^{AB}$, and 4-10 membered heterocyclyl optionally substituted with hydroxyl or C1-C6 alkyl. In some embodiments, 1 of R^{2A} is 5-6 membered heteroaryl substituted with 1-3 substituents independently selected from hydroxyl, cyano, C1-C6 alkyl, halogen, $-C(=O)NR^{AB}$, $-NR^{AB}$, and 4-10 membered heterocyclyl optionally substituted with hydroxyl or C1-C6 alkyl. In some embodiments, 1 of R^{2A} is 5-6 membered heteroaryl.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently 4-10 membered heterocyclyl optionally substituted with 1-3 substituents independently selected from hydroxyl, cyano, halogen, C1-C6 haloalkyl, $-C(=O)C1-C6$ alkyl, $-SO_2(C1-C6$ alkyl), $-SO_2NR^{DE}$, C1-C6 alkoxy, $-C(=O)NR^{AB}$, $-NR^{AB}$, $-NHC(=O)C1-C6$ alkyl optionally substituted with $-NR^{AB}$, and C1-C6 alkyl optionally substituted with C1-C6 alkoxy or hydroxyl. In some embodiments, 1 of R^{2A} is 4-10 membered heterocyclyl optionally substituted with 1-3 substituents independently selected from hydroxyl, cyano, halogen, C1-C6 haloalkyl, $-C(=O)C1-C6$ alkyl, $-SO_2(C1-C6$ alkyl), $-SO_2NR^{DE}$, C1-C6 alkoxy, $-C(=O)NR^{AB}$, $-NR^{AB}$, $-NHC(=O)C1-C6$ alkyl optionally substituted with $-NR^{AB}$, and C1-C6 alkyl optionally substituted with C1-C6 alkoxy or hydroxyl.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently 4-10 membered heterocyclyl substituted with 1-3 substituents independently selected from hydroxyl, cyano, halogen, C1-C6 haloalkyl, $-C(=O)C1-C6$ alkyl, $-SO_2(C1-C6$ alkyl), $-SO_2NR^{DR^E}$, C1-C6 alkoxy, $-C(=O)NR^A R^B$, $-NR^A R^B$, $-NHC(=O)C1-C6$ alkyl, and C1-C6 alkyl. In some embodiments, 1 of R^{2A} is 4-10 membered heterocyclyl substituted with 1-3 substituents independently selected from hydroxyl, cyano, halogen, C1-C6 haloalkyl, $-C(=O)C1-C6$ alkyl, $-SO_2(C1-C6$ alkyl), $-SO_2NR^{DR^E}$, C1-C6 alkoxy, $-C(=O)NR^A R^B$, $-NR^A R^B$, $-NHC(=O)C1-C6$ alkyl, and C1-C6 alkyl.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently 4-10 membered heterocyclyl substituted with 1-3 substituents independently selected from hydroxyl, cyano, halogen, C1-C6 haloalkyl, $-C(=O)C1-C6$ alkyl, $-SO_2(C1-C6$ alkyl), $-SO_2NR^{DR^E}$, C1-C6 alkoxy, $-C(=O)NR^A R^B$, $-NR^A R^B$, $-NHC(=O)C1-C6$ alkyl optionally substituted with $-NR^A R^B$, and C1-C6 alkyl substituted with C1-C6 alkoxy or hydroxyl. In some embodiments, 1 of R^{2A} is 4-10 membered heterocyclyl substituted with 1-3 substituents independently selected from hydroxyl, cyano, halogen, C1-C6 haloalkyl, $-C(=O)C1-C6$ alkyl, $-SO_2(C1-C6$ alkyl), $-SO_2NR^{DR^E}$, C1-C6 alkoxy, $-C(=O)NR^A R^B$, $-NR^A R^B$, $-NHC(=O)C1-C6$ alkyl substituted with $-NR^A R^B$, and C1-C6 alkyl substituted with C1-C6 alkoxy or hydroxyl.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently 4-10 membered heterocyclyl substituted with 1 substituent independently selected from hydroxyl, cyano, C1-C6 haloalkyl, $-C(=O)C1-C6$ alkyl, $-SO_2(C1-C6$ alkyl), $-SO_2NR^{DR^E}$, C1-C6 alkyl, $-C(=O)NR^A R^B$, $-NR^A R^B$, or $-NHC(=O)C1-C6$ alkyl. In some embodiments, 1 of R^{2A} is 4-10 membered heterocyclyl substituted with 1 substituent independently selected from hydroxyl, cyano, C1-C6 haloalkyl, $-C(=O)C1-C6$ alkyl, $-SO_2(C1-C6$ alkyl), $-SO_2NR^{DR^E}$, C1-C6 alkyl, $-C(=O)NR^A R^B$, $-NR^A R^B$, or $-NHC(=O)C1-C6$ alkyl.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently 4-10 membered heterocyclyl. In some embodiments, 1 of R^{2A} is 4-10 membered heterocyclyl.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently C1-C6 alkyl optionally substituted with 1-3 substituents independently selected from hydroxyl, oxo, $-NR^A R^B$, $-C(=O)NR^A R^B$, C3-C10 cycloalkyl, and 4-10 membered heterocyclyl optionally substituted with hydroxyl, C1-C6 alkyl, aralkyl, heteroaralkyl, $-C(=O)NR^A R^B$, or $-C(=O)C3-C6$ cycloalkyl. In some embodiments, 1 or 2 of R^{2A} are independently C1-C6 alkyl optionally substituted with 1-3 substituents independently selected from hydroxyl, oxo, $-NR^A R^B$,

-C(=O)NR^AR^B, C3-C10 cycloalkyl, and 4-10 membered heterocyclyl optionally substituted with hydroxyl, C1-C6 alkyl, aralkyl, heteroaralkyl, -C(=O)NR^AR^B, or -C(=O)C3-C6 cycloalkyl. In some embodiments, 1 R^{2A} is C1-C6 alkyl optionally substituted with 1-3 substituents independently selected from hydroxyl, oxo, -NR^AR^B,
 5 -C(=O)NR^AR^B, C3-C10 cycloalkyl, and 4-10 membered heterocyclyl optionally substituted with hydroxyl, C1-C6 alkyl, aralkyl, heteroaralkyl, -C(=O)NR^AR^B, or -C(=O)C3-C6 cycloalkyl.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently C1-C6 alkyl substituted with 1-3 substituents independently selected from hydroxyl, oxo, -NR^AR^B, -C(=O)NR^AR^B, C3-C10 cycloalkyl, and 4-10 membered heterocyclyl optionally substituted with hydroxyl, C1-C6 alkyl,
 10 aralkyl, heteroaralkyl, -C(=O)NR^AR^B, or -C(=O)C3-C6 cycloalkyl.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently C1-C6 alkyl substituted with 1-3 substituents independently selected from hydroxyl, oxo, -NR^AR^B, -C(=O)NR^AR^B, C3-C10 cycloalkyl, and 4-10 membered heterocyclyl substituted with hydroxyl, C1-C6 alkyl, aralkyl, heteroaralkyl, -C(=O)NR^AR^B, or -C(=O)C3-C6 cycloalkyl.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently C1-C6 alkyl substituted with 1-3 substituents independently selected from hydroxyl, oxo, -NR^AR^B, -C(=O)NR^AR^B, C3-C10 cycloalkyl, and 4-10 membered heterocyclyl.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently C1-C6 alkyl. In some embodiments, 1, 2, or 3 of R^{2A} are independently C1-C3 alkyl. In some embodiments, 1, 2, or 3 of R^{2A} are methyl. In some embodiments, 1 or 2 of R^{2A} are independently C1-C6 alkyl. In some
 20 embodiments, 1 or 2 of R^{2A} are independently C1-C3 alkyl. In some embodiments, 1 or 2 of R^{2A} are methyl.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently C1-C6 alkoxy optionally substituted with -NR^AR^B or 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl, aralkyl, heteroaralkyl, or -C(=O)C3-C6 cycloalkyl. In some embodiments, 1 or 2 of R^{2A} are independently C1-C6 alkoxy optionally substituted with -NR^AR^B or 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl, aralkyl, heteroaralkyl, or -C(=O)C3-C6 cycloalkyl. In some
 25 embodiments, 1 R^{2A} is C1-C6 alkoxy optionally substituted with -NR^AR^B or 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl, aralkyl, heteroaralkyl, or -C(=O)C3-C6 cycloalkyl.
 30 cycloalkyl.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently C1-C6 alkoxy substituted with $-NR^A R^B$ or 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl, aralkyl, heteroaralkyl, or $-C(=O)C3-C6$ cycloalkyl.

5 In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently C1-C6 alkoxy substituted with $-NR^A R^B$ or 4-10 membered heterocyclyl substituted with C1-C6 alkyl, aralkyl, heteroaralkyl, or $-C(=O)C3-C6$ cycloalkyl.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently C1-C6 alkoxy substituted with $-NR^A R^B$ or 4-10 membered heterocyclyl.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently C1-C6 alkoxy.

10 In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently C3-C6 cycloalkyl optionally substituted with hydroxyl, $-C(=O)NR^A R^B$, $-C(=N)OR^D$, or 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl. In some embodiments, 1 or 2 of R^{2A} are independently C3-C6 cycloalkyl optionally substituted with hydroxyl, $-C(=O)NR^A R^B$, $-C(=N)OR^D$, or 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl. In some embodiments, 1 R^{2A} is C3-C6
15 cycloalkyl optionally substituted with hydroxyl, $-C(=O)NR^A R^B$, $-C(=N)OR^D$, or 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently C3-C6 cycloalkyl substituted with hydroxyl, $-C(=O)NR^A R^B$, $-C(=N)OR^D$, or 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl.

20 In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently C3-C6 cycloalkyl substituted with hydroxyl, $-C(=O)NR^A R^B$, $-C(=N)OR^D$, or 4-10 membered heterocyclyl substituted with C1-C6 alkyl.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently C3-C6 cycloalkyl substituted with hydroxyl, $-C(=O)NR^A R^B$, $-C(=N)OR^D$, or 4-10 membered heterocyclyl.

25 In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently C3-C6 cycloalkyl. In some embodiments, 1 or 2 of R^{2A} are independently C3-C6 cycloalkyl.

In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently 4-10 membered heterocyclyloxy optionally substituted with hydroxyl, cyano, halogen, or C1-C6 alkyl optionally substituted with hydroxyl. In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently 4-10
30 membered heterocyclyloxy. In some embodiments, 1, 2, 3, or 4 of R^{2A} are independently 4-10 membered heterocyclyloxy substituted with hydroxyl, cyano, halogen, or C1-C6 alkyl optionally

substituted with hydroxyl. In some embodiments, 1 or 2 of R^{2A} are independently 4-10 membered heterocycloxy optionally substituted with hydroxyl, cyano, halogen, or C1-C6 alkyl optionally substituted with hydroxyl. In some embodiments, 1 R^{2A} is 4-10 membered heterocycloxy optionally substituted with hydroxyl, cyano, halogen, or C1-C6 alkyl optionally substituted with hydroxyl.

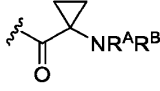
In some embodiments, R^2 is substituted with 1 R^{2A} . In some embodiments, R^2 is substituted with 2 independently selected R^{2A} . In some embodiments, R^2 is substituted with 3 independently selected R^{2A} . In some embodiments, R^2 is substituted with 4 independently selected R^{2A} .

In some embodiments, R^2 is piperidinyl substituted with 1-2 independently selected R^{2A} . In some embodiments, R^2 is piperidinyl substituted with 2-4 independently selected R^{2A} . In some embodiments, R^2 is morpholinyl substituted with 2-4 independently selected R^{2A} . In some embodiments, R^2 is morpholinyl. In some embodiments, R^2 is piperazinyl substituted with 1-2 independently selected R^{2A} .

In some embodiments, R^2 is phenyl substituted with 1-2 independently selected R^{2A} . In some embodiments, R^2 is pyridinyl substituted with 1-2 independently selected R^{2A} .

In some embodiments, R^2 is indolyl substituted with 1-2 independently selected R^{2A} . In some embodiments, R^2 is indazolyl substituted with 1-2 independently selected R^{2A} . In some embodiments, R^2 is 7-azaindolyl substituted with 1-2 independently selected R^{2A} . In some embodiments, R^2 is 7-azaindazolyl substituted with 1-2 independently selected R^{2A} . In some embodiments, R^2 is 1,2-dihydro-3H-indazol-3-one substituted with 1-2 independently selected R^{2A} . In some embodiments, R^2 is isoindolinyl substituted with 1-2 independently selected R^{2A} . In some embodiments, R^2 is isoindolinyl. In some embodiments, R^2 is 2-indolinone substituted with 1-2 independently selected R^{2A} . In some embodiments, R^2 is benzimidazolyl substituted with 1-2 independently selected R^{2A} . In some embodiments, R^2 is imidazopyridinyl substituted with 1-2 independently selected R^{2A} . In some embodiments, R^2 is 1,3-dihydro-2H-benzo[d]imidazol-2-onyl substituted with 1-2 independently selected R^{2A} . In some embodiments, R^2 is [1,2,4]triazolo[1,5-a]pyridine substituted with 1-2 independently selected R^{2A} .

In some embodiments, one R^{2A} is C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 hydroxyalkyl, cyano, or hydroxyl, and the other R^{2A} are independently selected from C1-C6 haloalkyl, C1-C6

hydroxyalkyl, cyano, hydroxyl, halogen, $-NR^A R^B$, $-C(=O)NR^A R^B$, , $-NHC(=O)R^C$,

-C(=O)OR^D, -SO₂R^D, -NHSO₂R^D, -SO₂NR^{DR^E}, -NHC(=O)C1-C6 alkyl optionally substituted with NR^{AR^B}, 5-10 membered heteroaryl optionally substituted with 1-3 substituents independently selected from C1-C6 alkyl and -NR^{AR^B}, 4-10 membered heterocyclyl optionally substituted with 1-3 substituents independently selected from hydroxyl, C1-C6 haloalkyl, -C(=O)C1-C6 alkyl, -SO₂(C1-C6 alkyl), -SO₂NR^{DR^E}, C1-C6 alkyl optionally substituted with C1-C6 alkoxy, -C(=O)NR^{AR^B}, or -NHC(=O)C1-C6 alkyl optionally substituted with -NR^{AR^B}, C1-C6 alkyl optionally substituted with 1-3 substituents independently selected from hydroxyl, oxo, -NR^{AR^B}, -C(=O)NR^{AR^B}, C1-C6 alkoxy, and 4-10 membered heterocyclyl optionally substituted with hydroxyl, C1-C6 alkyl, aralkyl, heteroaralkyl, -C(=O)NR^{AR^B}, or -C(=O)C3-C6 cycloalkyl, C1-C6 alkoxy optionally substituted with -NR^{AR^B} or 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl, aralkyl, heteroaralkyl, or -C(=O)C3-C6 cycloalkyl, and C3-C6 cycloalkyl optionally substituted with 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl.

In some embodiments, each R^{2A} is independently selected from halogen, methyl, ethyl, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)NH₂, -C(=O)NHCH₃, -C(=O)N(CH₃)₂, -C(=O)NHOH, -SO₂NH₂, -SO₂NHCH₃, -SO₂N(CH₃)₂, cyclopropyl, cyclobutyl, trifluoromethyl, 2,2,2-trifluoroethyl, and acetyl.

In some embodiments, 1, 2, or 3 R^{2A} are independently selected from halogen, methyl, ethyl, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)NH₂, -C(=O)NHCH₃, -C(=O)N(CH₃)₂, -C(=O)NHOH, -SO₂NH₂, -SO₂NHCH₃, -SO₂N(CH₃)₂, cyclopropyl, cyclobutyl, trifluoromethyl, 2,2,2-trifluoroethyl, and acetyl.

In some embodiments, 1 or 2 R^{2A} are independently selected from halogen, methyl, ethyl, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)NH₂, -C(=O)NHCH₃, -C(=O)N(CH₃)₂, -C(=O)NHOH, -SO₂NH₂, -SO₂NHCH₃, -SO₂N(CH₃)₂, cyclopropyl, cyclobutyl, trifluoromethyl, 2,2,2-trifluoroethyl, and acetyl.

In some embodiments, each R^{2A} is independently selected from:

- (i) halogen;
- (ii) C3-C6 cycloalkyl optionally substituted with hydroxyl, -C(=O)NR^{AR^B}, or -C(=N)OR^D;
- (iii) methyl;
- (iv) C1-C2 haloalkyl;

(v) 4-6 membered heterocyclyl optionally substituted with 1-3 substituents independently selected from halogen, hydroxyl, $-C(=O)NR^A R^B$, $-C(=O)C1-C6$ alkyl, $-NR^A R^B$, and C1-C6 alkyl optionally substituted with hydroxyl; and

(vi) 5-6 membered heteroaryl optionally substituted with halogen, cyano, C1-C6 alkyl optionally substituted with hydroxyl, hydroxyl, $-C(=O)NR^A R^B$, $-NR^A R^B$, or 4-10 membered heterocyclyl optionally substituted with hydroxyl or C1-C6 alkyl.

In some embodiments, 1 or 2 R^{2A} are independently selected from:

(i) halogen;

(ii) C3-C6 cycloalkyl optionally substituted with hydroxyl, $-C(=O)NR^A R^B$, or $-C(=N)OR^D$;

(iii) methyl;

(iv) C1-C2 haloalkyl;

(v) 4-6 membered heterocyclyl optionally substituted with 1-3 substituents independently selected from halogen, hydroxyl, $-C(=O)NR^A R^B$, $-C(=O)C1-C6$ alkyl, $-NR^A R^B$, and C1-C6 alkyl optionally substituted with hydroxyl; and

(vi) 5-6 membered heteroaryl optionally substituted with halogen, cyano, C1-C6 alkyl optionally substituted with hydroxyl, hydroxyl, $-C(=O)NR^A R^B$, $-NR^A R^B$, or 4-10 membered heterocyclyl optionally substituted with hydroxyl or C1-C6 alkyl.

In some embodiments, 1 R^{2A} is:

(i) halogen;

(ii) C3-C6 cycloalkyl optionally substituted with hydroxyl, $-C(=O)NR^A R^B$, or $-C(=N)OR^D$;

(iii) methyl;

(iv) C1-C2 haloalkyl;

(v) 4-6 membered heterocyclyl optionally substituted with 1-3 substituents independently selected from halogen, hydroxyl, $-C(=O)NR^A R^B$, $-C(=O)C1-C6$ alkyl, $-NR^A R^B$, and C1-C6 alkyl optionally substituted with hydroxyl; or

(vi) 5-6 membered heteroaryl optionally substituted with halogen, cyano, C1-C6 alkyl optionally substituted with hydroxyl, hydroxyl, $-C(=O)NR^A R^B$, $-NR^A R^B$, or 4-10 membered heterocyclyl optionally substituted with hydroxyl or C1-C6 alkyl.

In some embodiments, X is a bond.

In some embodiments, X is CH₂.

In some embodiments, X is CH(CH₃).

In some embodiments, X is C(CH₃)₂.

In some embodiments, X is .

5 In some embodiments, W is O.

In some embodiments, R^{3A} is hydrogen.

In some embodiments, R^{3A} is C1-C6 alkyl. In some embodiments, R^{3A} is methyl or ethyl.

In some embodiments, R^{3A} is methyl.

In some embodiments, R^{3A} is C1-C6 alkoxy. In some embodiments, R^{3A} is C1-C3 alkoxy.

10 In some embodiments, R^{3A} is -OCH₃, -OCH₂CH₃, or -OCH₂CH₂CH₃. In some embodiments, R^{3A} is -OCH₃.

In some embodiments, R^{3A} is C1-C6 haloalkyl. In some embodiments, R^{3A} is C1-C3 haloalkyl. In some embodiments, R^{3A} is C1-C3 fluoroalkyl. In some embodiments, R^{3A} is CF₃. In some embodiments, R^{3A} is CHF₂.

15 In some embodiments, W is NR^{3B}.

In some embodiments, one of R^{3A} and R^{3B} is hydrogen and the other of R^{3A} and R^{3B} is C1-C6 alkyl. In some embodiments, one of R^{3A} and R^{3B} is hydrogen and the other of R^{3A} and R^{3B} is methyl. In some embodiments, each of R^{3A} and R^{3B} is hydrogen. In some embodiments, each of R^{3A} and R^{3B} is an independently selected C1-C6 alkyl. In some embodiments, each of R^{3A} and R^{3B} is methyl.

20 In some embodiments, one of R^{3A} and R^{3B} is hydrogen and the other of R^{3A} and R^{3B} is C1-C6 alkoxy. In some embodiments, one of R^{3A} and R^{3B} is C1-C6 alkyl and the other of R^{3A} and R^{3B} is C1-C6 alkoxy. In some embodiments, R^{3A} is C1-C6 alkoxy. In some embodiments, R^{3A} is C1-C3 alkoxy. In some embodiments, R^{3A} is -OCH₃, -OCH₂CH₃, or -OCH₂CH₂CH₃. In some embodiments, R^{3A} is -OCH₃.

25 In some embodiments, one of R^{3A} and R^{3B} is hydrogen and the other of R^{3A} and R^{3B} is C1-C6 haloalkyl. In some embodiments, one of R^{3A} and R^{3B} is C1-C6 alkyl and the other of R^{3A} and R^{3B} is C1-C6 haloalkyl. In some embodiments, R^{3A} is C1-C6 haloalkyl. In some embodiments, R^{3A} is C1-C3 haloalkyl. In some embodiments, R^{3A} is C1-C3 fluoroalkyl. In some embodiments, R^{3A} is CF₃. In some embodiments, R^{3A} is CHF₂.

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In some embodiments, R^{3A} and R^{3B} , together with the carbon and nitrogen atoms, respectively, to which they are attached together form a 4-8 membered heterocyclyl group. In some embodiments, R^{3A} and R^{3B} , together with the carbon and nitrogen atoms, respectively, to which they are attached together form a 5-6 membered heterocyclyl group.

5 In some embodiments, Y is phenyl, naphthyl, or 5-10 membered heteroaryl, wherein the phenyl, naphthyl, and 5-10 membered heteroaryl are optionally and independently substituted with 1-3 independently selected R^Y .

In some embodiments, Y is phenyl optionally substituted with R^Y , naphthyl substituted with R^Y , or 5-10 membered heteroaryl substituted with R^Y .

10 In some embodiments, Y is phenyl optionally substituted with 1-3 independently selected R^Y . In some embodiments, Y is phenyl substituted with 1 or 2 independently selected R^Y . In some embodiments, Y is phenyl substituted with 1 R^Y . In some embodiments, Y is phenyl substituted with 2 independently selected R^Y . In some embodiments, Y is phenyl optionally substituted with 3 independently selected R^Y . In some embodiments, Y is phenyl.

15 In some embodiments, Y is naphthyl optionally substituted with 1-3 independently selected R^Y . In some embodiments, Y is naphthyl substituted with 1 or 2 independently selected R^Y . In some embodiments, Y is naphthyl substituted with 1 R^Y . In some embodiments, Y is naphthyl substituted with 2 independently selected R^Y . In some embodiments, Y is naphthyl optionally substituted with 3 independently selected R^Y . In some embodiments, Y is naphthyl.

20 In some embodiments, Y is 5-10 membered heteroaryl optionally substituted with 1-3 independently selected R^Y . In some embodiments, Y is 5-10 membered heteroaryl substituted with 1 or 2 independently selected R^Y . In some embodiments, Y is 5-10 membered heteroaryl substituted with 1 R^Y . In some embodiments, Y is 5-10 membered heteroaryl substituted with 2 independently selected R^Y . In some embodiments, Y is 5-10 membered heteroaryl optionally substituted with 3 independently selected R^Y . In some embodiments, Y is 5-10 membered heteroaryl.

25 In some embodiments, Y is 6 membered heteroaryl optionally substituted with 1-3 independently selected R^Y . In some embodiments, Y is 6 membered heteroaryl substituted with 1 or 2 independently selected R^Y . In some embodiments, Y is 6 membered heteroaryl substituted with 1 R^Y . In some embodiments, Y is 6 membered heteroaryl substituted with 2 independently selected R^Y . In some embodiments, Y is 6 membered heteroaryl optionally substituted with 3

independently selected R^Y . In some embodiments, Y is 6 membered heteroaryl. In some embodiments, the 6 membered heteroaryl of Y is pyridyl (e.g., 3-pyridyl).

In some embodiments, Y is 9 membered heteroaryl optionally substituted with 1-3 independently selected R^Y . In some embodiments, Y is 9 membered heteroaryl substituted with 1 or 2 independently selected R^Y . In some embodiments, Y is 9 membered heteroaryl substituted with 1 R^Y . In some embodiments, Y is 9 membered heteroaryl substituted with 2 independently selected R^Y . In some embodiments, Y is 9 membered heteroaryl optionally substituted with 3 independently selected R^Y . In some embodiments, Y is 9 membered heteroaryl.

In some embodiments, 1, 2, or 3 of R^Y is independently halogen. In some embodiments, 1, 2, or 3 of R^Y is independently chloro or fluoro. In some embodiments, 1 or 2 of R^Y is independently chloro or fluoro.

In some embodiments, 1, 2, or 3 of R^Y is hydroxyl. In some embodiments, 1 or 2 of R^Y is hydroxyl.

In some embodiments, 1, 2, or 3 of R^Y is cyano. In some embodiments, 1 or 2 of R^Y is cyano.

In some embodiments, 1, 2, or 3 of R^Y is independently C1-C6 alkyl. In some embodiments, 1 or 2 of R^Y is independently C1-C6 alkyl. In some embodiments, 1 or 2 of R^Y is independently C1-C3 alkyl.

In some embodiments, 1, 2, or 3 of R^Y is independently unsubstituted C1-C6 haloalkyl. In some embodiments, 1 or 2 of R^Y is independently unsubstituted C1-C3 haloalkyl. In some embodiments, 1 or 2 of R^Y is trifluoromethyl.

In some embodiments, 1, 2, or 3 of R^Y is independently C1-C6 haloalkyl substituted with hydroxyl. In some embodiments, 1 or 2 of R^Y is independently C1-C3 haloalkyl substituted with hydroxyl.

In some embodiments, 1, 2, or 3 of R^Y is independently C1-C6 alkoxy. In some embodiments, 1 or 2 of R^Y is independently C1-C3 alkoxy. In some embodiments, 1 or 2 of R^Y is methoxy.

In some embodiments, 1, 2, or 3 of R^Y is independently C1-C6 haloalkoxy. In some embodiments, 1 or 2 of R^Y is independently C1-C3 haloalkoxy. In some embodiments, 1 or 2 of R^Y is trifluoromethoxy.

In some embodiments, 1, 2, or 3 of R^Y is independently C1-C6 hydroxyalkyl. In some embodiments, 1 or 2 of R^Y is independently C1-C3 hydroxyalkyl. In some embodiments, 1 or 2 of R^Y is independently mono-hydroxyl C1-C3 alkyl. In some embodiments, 1 or 2 of R^Y is independently di-hydroxyl C2-C3 alkyl.

5 In some embodiments, 1, 2, or 3 of R^Y is independently $-(CH_2)_n-C(=O)R^F$, where n is 1 or 2. In some embodiments, 1 of R^Y is independently $-(CH_2)_n-C(=O)R^F$, where n is 1.

In some embodiments, 1, 2, or 3 of R^Y is independently $-C(=O)R^F$. In some embodiments, 1 or 2 of R^Y is independently $-C(=O)R^F$. In some embodiments, 1 of R^Y is $-C(=O)R^F$. In some embodiments, Y is substituted with 1 R^Y , and R^Y is $-C(=O)R^F$.

10 In some embodiments, 1, 2, or 3 of R^Y is independently $-(CH_2)_n-NHC(=O)R^F$, where n is 1 or 2. In some embodiments, 1 of R^Y is independently $-(CH_2)_n-NHC(=O)R^F$, where n is 1.

In some embodiments, 1, 2, or 3 of R^Y is independently $-NHC(=O)R^F$. In some embodiments, 1 or 2 of R^Y is independently $-NHC(=O)R^F$. In some embodiments, 1 of R^Y is $-NHC(=O)R^F$. In some embodiments, Y is substituted with 1 R^Y , and R^Y is $-NHC(=O)R^F$.

15 In some embodiments, 1, 2, or 3 of R^Y is independently $-C(=O)C(=O)NHR^F$. In some embodiments, 1 or 2 of R^Y is independently $-C(=O)C(=O)NHR^F$. In some embodiments, 1 of R^Y is $-C(=O)C(=O)NHR^F$. In some embodiments, Y is substituted with 1 R^Y , and R^Y is $-C(=O)C(=O)NHR^F$.

In some embodiments, 1, 2, or 3 of R^Y is independently $-CO_2R^G$. In some embodiments, 20 1 or 2 of R^Y is independently $-CO_2R^G$. In some embodiments, 1 of R^Y is $-CO_2R^G$. In some embodiments, Y is substituted with 1 R^Y , and R^Y is $-CO_2R^G$. In some embodiments, Y is substituted with 1 R^Y , and R^Y is $-CO_2H$.

In some embodiments, 1, 2, or 3 of R^Y is independently $-(CH_2)_n-SO_2NR^H R^I$, where n is 1 or 2. In some embodiments, 1 of R^Y is independently $-(CH_2)_n-SO_2NR^H R^I$, where n is 1.

25 In some embodiments, 1, 2, or 3 of R^Y is independently $-SO_2NR^H R^I$. In some embodiments, 1 or 2 of R^Y is independently $-SO_2NR^H R^I$. In some embodiments, 1 of R^Y is $-SO_2NR^H R^I$. In some embodiments, Y is substituted with 1 R^Y , and R^Y is $-SO_2NR^H R^I$.

In some embodiments, 1, 2, or 3 of R^Y is independently $-(CH_2)_n-NHSO_2R^J$, where n is 1 or 2. In some embodiments, 1 of R^Y is independently $-(CH_2)_n-NHSO_2R^J$, where n is 1.

In some embodiments, 1, 2, or 3 of R^Y is independently $-NHSO_2R^J$. In some embodiments, 1 or 2 of R^Y is independently $-NHSO_2R^J$. In some embodiments, 1 of R^Y is $-NHSO_2R^J$. In some embodiments, Y is substituted with 1 R^Y , and R^Y is $-NHSO_2R^J$.

In some embodiments, 1, 2, or 3 of R^Y is independently $-(CH_2)_n-S(=O)(=NR^H)R^J$, where n is 1 or 2. In some embodiments, 1 of R^Y is independently $-(CH_2)_n-S(=O)(=NR^H)R^J$, where n is 1.

In some embodiments, 1, 2, or 3 of R^Y is independently $-S(=O)(=NR^H)R^J$. In some embodiments, 1 or 2 of R^Y is independently $-S(=O)(=NR^H)R^J$. In some embodiments, 1 of R^Y is $-S(=O)(=NR^H)R^J$. In some embodiments, Y is substituted with 1 R^Y , and R^Y is $-S(=O)(=NR^H)R^J$.

In some embodiments, 1, 2, or 3 of R^Y is independently $-(CH_2)_n-SO_2R^J$, where n is 1 or 2. In some embodiments, 1 of R^Y is independently $-(CH_2)_n-SO_2R^J$, where n is 1.

In some embodiments, 1, 2, or 3 of R^Y is independently $-SO_2R^J$. In some embodiments, 1 or 2 of R^Y is independently $-SO_2R^J$. In some embodiments, 1 of R^Y is $-SO_2R^J$. In some embodiments, 1, 2, or 3 of R^Y is independently $-SO_2(C1-C6 \text{ alkyl})$. In some embodiments, 1 or 2 of R^Y is $-SO_2CH_3$. In some embodiments, 1 of R^Y is $-SO_2CH_3$. In some embodiments, Y is substituted with 1 R^Y , and R^Y is $-SO_2CH_3$.

In some embodiments, 1, 2, or 3 of R^Y is independently $-(CH_2)_n-C(=O)NR^H R^I$, where n is 1 or 2. In some embodiments, 1 of R^Y is independently $-(CH_2)_n-C(=O)NR^H R^I$, where n is 1.

In some embodiments, 1, 2, or 3 of R^Y is independently $-C(=O)NR^H R^I$. In some embodiments, 1 or 2 of R^Y is independently $-C(=O)NR^H R^I$. In some embodiments, 1 of R^Y is $-C(=O)NR^H R^I$. In some embodiments, Y is substituted with 1 R^Y , and R^Y is $-C(=O)NR^H R^I$.

In some embodiments, 1, 2, or 3 of R^Y is independently $-(CH_2)_n-C(=O)NR^H OR^I$, where n is 1 or 2. In some embodiments, 1 of R^Y is independently $-(CH_2)_n-C(=O)NR^H OR^I$, where n is 1.

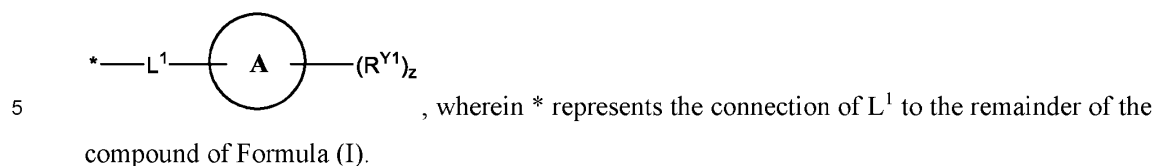
In some embodiments, 1, 2, or 3 of R^Y is independently $-(CH_2)_n-C(=O)NR^H OR^I$. In some embodiments, 1 or 2 of R^Y is independently $-(CH_2)_n-C(=O)NR^H OR^I$. In some embodiments, 1 of R^Y is $-(CH_2)_n-C(=O)NR^H OR^I$. In some embodiments, Y is substituted with 1 R^Y , and R^Y is $-(CH_2)_n-C(=O)NR^H OR^I$.

In some embodiments, each R^Y is independently selected from: halogen, $-CO_2H$, $-SO_2NH_2$, $-SO_2CH_3$, $-C(=O)NH_2$, $-C(=O)NHR^H$, $-(CH_2)_n-C(=O)NHOR^I$, and $-(CH_2)_n-S(=O)(=NH)R^J$.

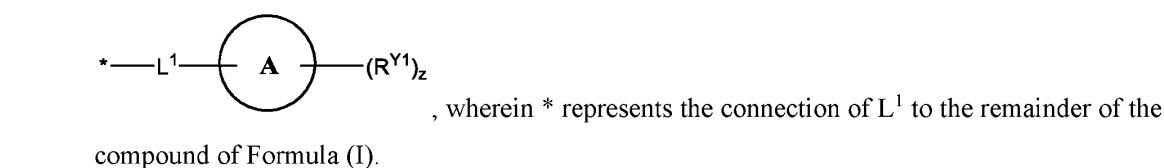
In some embodiments, 1 or 2 R^Y is independently selected from: halogen, $-CO_2H$, $-SO_2NH_2$, $-SO_2CH_3$, $-C(=O)NH_2$, $-C(=O)NHR^H$, $-(CH_2)_n-C(=O)NHOR^I$, and $-(CH_2)_n-S(=O)(=NH)R^J$.

In some embodiments, 1 R^Y is halogen, $-\text{CO}_2\text{H}$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{CH}_3$, $-\text{C}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{O})\text{NHR}^H$, $-(\text{CH}_2)_n-\text{C}(=\text{O})\text{NHOR}^I$, or $-(\text{CH}_2)_n-\text{S}(=\text{O})(=\text{NH})\text{R}^J$.

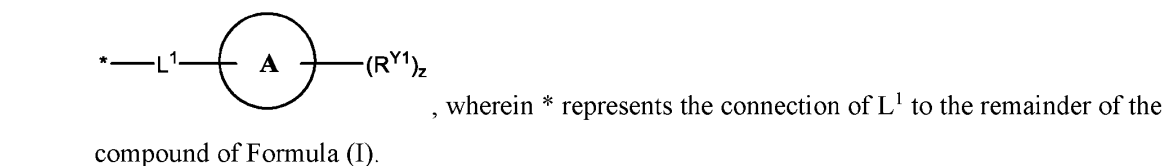
In some embodiments, Y is phenyl, naphthyl, or 5-10 membered heteroaryl, wherein the phenyl, naphthyl, and 5-10 membered heteroaryl are optionally and independently substituted with



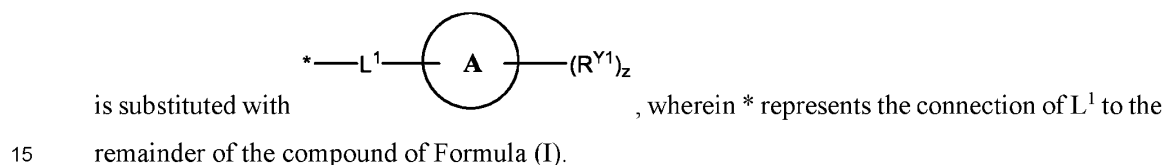
In some embodiments, Y is phenyl and the phenyl is substituted with



In some embodiments, Y is naphthyl and the naphthyl is substituted with



In some embodiments, Y is 5-10 membered heteroaryl and the 5-10 membered heteroaryl



In some embodiments, Ring A is phenyl.

In some embodiments, Ring A is 4-10 membered heteroaryl. In some embodiments, Ring A is 9-10 membered heteroaryl. In some embodiments, Ring A is 4-6 membered heteroaryl.

20 In some embodiments, Ring A is 4-10 membered heterocyclyl. In some embodiments, Ring A is 9-10 membered heterocyclyl. In some embodiments, Ring A is 4-6 membered heterocyclyl.

In some embodiments, Ring A is C4-C10 cycloalkyl. In some embodiments, Ring A is C9-C10 cycloalkyl. In some embodiments, Ring A is C4-C6 cycloalkyl.

In some embodiments, L^1 is a bond.

In some embodiments, L^1 is C1-C6 alkoxylenes.

In some embodiments, L^1 is $-(CH_2)_n-NHC(=O)-$.

In some embodiments, L^1 is $-C(=O)NH-(CH_2)_n-$.

In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2.

In some embodiments, n is 3.

5 In some embodiments, L^1 is $-CO_2-$.

In some embodiments, L^1 is $-SO_2-$.

In some embodiments, L^1 is $-NHSO_2-$.

In some embodiments, L^1 is $-SO_2NH-$.

In some embodiments, L^1 is $-S(=O)(=NR^G)-$.

10 In some embodiments, L^1 is $-SO_2(C1-C6 \text{ alkylene})-$.

In some embodiments, L^1 is $-C(=O)C(=O)NH-$.

In some embodiments, L^1 is C1-C6 alkylene optionally substituted with oxo. In some embodiments, L^1 is unsubstituted C1-C6 alkylene. In some embodiments, L^1 is C1-C6 alkylene substituted with oxo.

15 In some embodiments, z is 0. In some embodiments, z is 1. In some embodiments, z is 2.

In some embodiments, z is 3.

In some embodiments, 1, 2, or 3 of R^{Y1} is independently halogen. In some embodiments, 1, 2, or 3 of R^{Y1} is independently chloro or fluoro. In some embodiments, 1 or 2 of R^{Y1} is independently chloro or fluoro.

20 In some embodiments, 1, 2, or 3 of R^{Y1} is hydroxyl. In some embodiments, 1 or 2 of R^{Y1} is hydroxyl.

In some embodiments, 1, 2, or 3 of R^{Y1} is cyano. In some embodiments, 1 or 2 of R^{Y1} is cyano.

25 In some embodiments, 1, 2, or 3 of R^{Y1} is independently C1-C6 alkyl. In some embodiments, 1 or 2 of R^{Y1} is independently C1-C6 alkyl. In some embodiments, 1 or 2 of R^{Y1} is independently C1-C3 alkyl.

In some embodiments, 1, 2, or 3 of R^{Y1} is independently C1-C6 alkyl substituted with R^{Y2} . In some embodiments, 1 or 2 of R^{Y1} is independently C1-C6 alkyl substituted with R^{Y2} . In some embodiments, 1 or 2 of R^{Y1} is independently C1-C3 alkyl substituted with R^{Y2} .

In some embodiments, 1, 2, or 3 of R^{Y1} is independently unsubstituted C1-C6 haloalkyl. In some embodiments, 1 or 2 of R^{Y1} is independently unsubstituted C1-C3 haloalkyl. In some embodiments, 1 or 2 of R^{Y1} is trifluoromethyl.

In some embodiments, 1, 2, or 3 of R^{Y1} is independently C1-C6 alkoxy substituted with R^{Y2} . In some embodiments, 1 or 2 of R^{Y1} is independently C1-C3 alkoxy substituted with R^{Y2} . In some embodiments, 1 or 2 of R^{Y1} is methoxy substituted with R^{Y2} .

In some embodiments, R^{Y2} is hydroxyl.

In some embodiments, R^{Y2} is $-NR^H R^I$.

In some embodiments, R^{Y2} is $-C(=O)NR^H R^I$.

10 In some embodiments, R^{Y2} is $-SO_2NR^H R^I$.

In some embodiments, 1, 2, or 3 of R^{Y1} is independently C1-C6 alkoxy. In some embodiments, 1 or 2 of R^{Y1} is independently C1-C3 alkoxy. In some embodiments, 1 or 2 of R^{Y1} is methoxy.

In some embodiments, 1, 2, or 3 of R^{Y1} is independently $-C(=O)R^F$. In some embodiments, 15 1 or 2 of R^{Y1} is independently $-C(=O)R^F$. In some embodiments, 1 of R^{Y1} is $-C(=O)R^F$. In some embodiments, Ring A is substituted with 1 R^{Y1} , and R^{Y1} is $-C(=O)R^F$.

In some embodiments, 1, 2, or 3 of R^{Y1} is independently $-NHC(=O)R^F$. In some embodiments, 1 or 2 of R^{Y1} is independently $-NHC(=O)R^F$. In some embodiments, 1 of R^{Y1} is $-NHC(=O)R^F$. In some embodiments, Ring A is substituted with 1 R^{Y1} , and R^{Y1} is $-NHC(=O)R^F$.

20 In some embodiments, 1, 2, or 3 of R^{Y1} is independently $-CO_2R^G$. In some embodiments, 1 or 2 of R^{Y1} is independently $-CO_2R^G$. In some embodiments, 1 of R^{Y1} is $-CO_2R^G$. In some embodiments, Y is substituted with 1 R^{Y1} , and R^{Y1} is $-CO_2R^G$. In some embodiments, Ring A is substituted with 1 R^{Y1} , and R^{Y1} is $-CO_2H$.

In some embodiments, 1, 2, or 3 of R^{Y1} is independently $-SO_2NR^H R^I$. In some 25 embodiments, 1 or 2 of R^{Y1} is independently $-SO_2NR^H R^I$. In some embodiments, 1 of R^{Y1} is $-SO_2NR^H R^I$. In some embodiments, Ring A is substituted with 1 R^{Y1} , and R^{Y1} is $-SO_2NR^H R^I$.

In some embodiments, 1, 2, or 3 of R^{Y1} is independently $-NHSO_2R^J$. In some embodiments, 1 or 2 of R^{Y1} is independently $-NHSO_2R^J$. In some embodiments, 1 of R^{Y1} is $-NHSO_2R^J$. In some embodiments, Ring A is substituted with 1 R^{Y1} , and R^{Y1} is $-NHSO_2R^J$.

30 In some embodiments, 1, 2, or 3 of R^{Y1} is independently $-S(=O)(=NR^H)R^J$. In some embodiments, 1 or 2 of R^{Y1} is independently $-S(=O)(=NR^H)R^J$. In some embodiments, 1 of R^{Y1}

is $-S(=O)(=NR^H)R^J$. In some embodiments, Ring A is substituted with 1 R^{Y1} , and R^{Y1} is $-S(=O)(=NR^H)R^J$.

In some embodiments, 1, 2, or 3 of R^{Y1} is independently $-SO_2(C1-C6 \text{ alkyl})$. In some embodiments, 1 or 2 of R^{Y1} is $-SO_2CH_3$. In some embodiments, 1 of R^Y is $-SO_2CH_3$. In some
5 embodiments, Ring A is substituted with 1 R^{Y1} , and R^{Y1} is $-SO_2CH_3$.

In some embodiments, 1, 2, or 3 of R^{Y1} is independently $-C(=O)NR^HR^I$. In some embodiments, 1 or 2 of R^{Y1} is independently $-C(=O)NR^HR^I$. In some embodiments, 1 of R^{Y1} is $-C(=O)NR^HR^I$. In some embodiments, Ring A is substituted with 1 R^{Y1} , and R^{Y1} is $-C(=O)NR^HR^I$.

In some embodiments, 1, 2, or 3 of R^{Y1} is independently 4-6 membered heteroaryl. In some
10 embodiments, 1 of R^{Y1} is 4-6 membered heteroaryl. In some embodiments, Ring A is substituted with 1 R^{Y1} , and R^{Y1} is 4-6 membered heteroaryl.

In some embodiments, 1, 2, or 3 of R^{Y1} is independently 5-6 membered heteroaryl. In some embodiments, 1 of R^{Y1} is 5-6 membered heteroaryl. In some embodiments, Ring A is substituted with 1 R^{Y1} , and R^{Y1} is 5-6 membered heteroaryl.

In some embodiments, 1, 2, or 3 of R^{Y1} is independently 4-6 membered heterocyclyl optionally substituted with hydroxyl or C1-C6 alkyl. In some embodiments, 1, 2, or 3 of R^{Y1} is independently 4-6 membered heterocyclyl substituted with hydroxyl or C1-C6 alkyl. In some
15 embodiments, 1, 2, or 3 of R^{Y1} is independently 4-6 membered heterocyclyl.

In some embodiments, each R^{Y1} is independently selected from: hydroxyl, cyano, $-SO_2NH_2$, $-C(=O)R^F$, $-C(=O)NH_2$, C1-C3 alkoxy optionally substituted with hydroxyl, and C1-C3 alkyl optionally substituted with hydroxyl.
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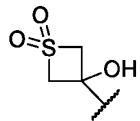
In some embodiments, 1 or 2 R^{Y1} is independently selected from: hydroxyl, cyano, $-SO_2NH_2$, $-C(=O)R^F$, $-C(=O)NH_2$, C1-C3 alkoxy optionally substituted with hydroxyl, and C1-C3 alkyl optionally substituted with hydroxyl.

In some embodiments, 1 R^{Y1} is hydroxyl, cyano, $-SO_2NH_2$, $-C(=O)R^F$, $-C(=O)NH_2$, C1-C3 alkoxy optionally substituted with hydroxyl, and C1-C3 alkyl optionally substituted with hydroxyl.
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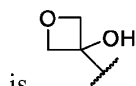
In some embodiments, 1, 2, or 3 of R^Y is independently heteroaralkyl. In some embodiments, 1 of R^Y is independently heteroaralkyl.

In some embodiments, 1, 2, or 3 of R^Y is independently 4-6 membered heterocyclyl optionally substituted with R^{Y1} . In some embodiments, 1 of R^Y is 4-6 membered heterocyclyl. In
30 some embodiments, 1 of R^Y is 4-6 membered heterocyclyl substituted with R^{Y1} . In some

embodiments, Y is substituted with 1 R^Y, and R^Y is 4-6 membered heterocyclyl substituted with

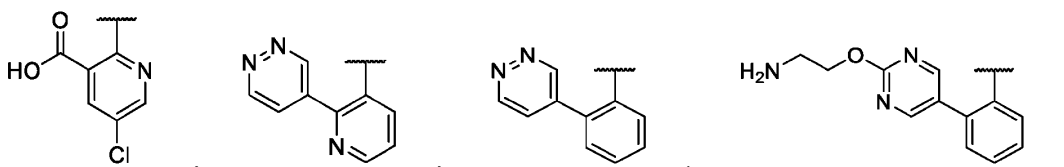
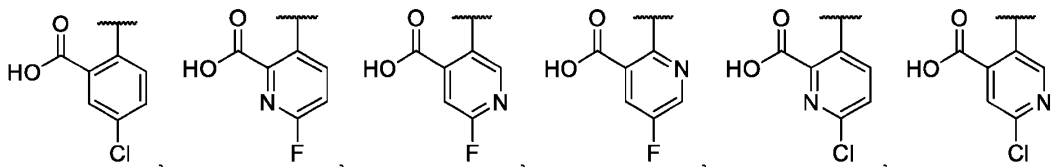
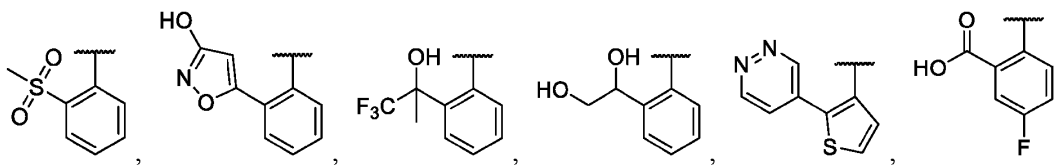
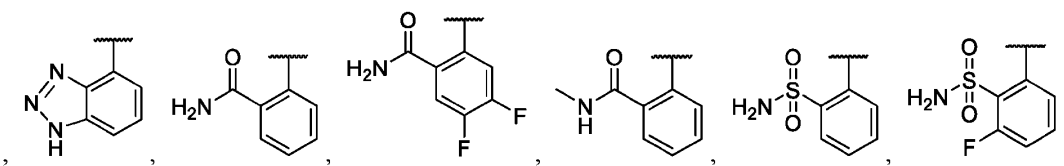
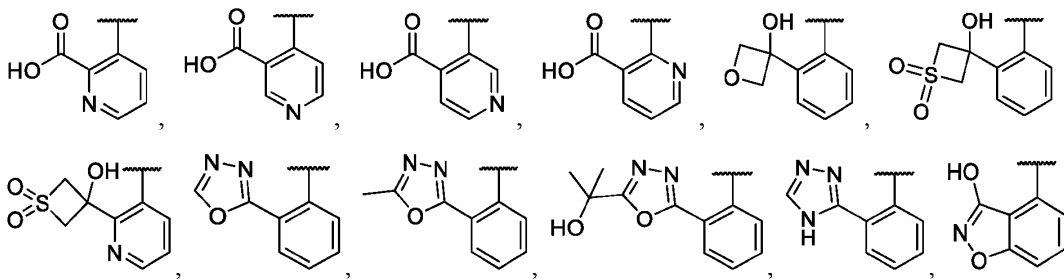
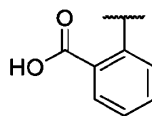


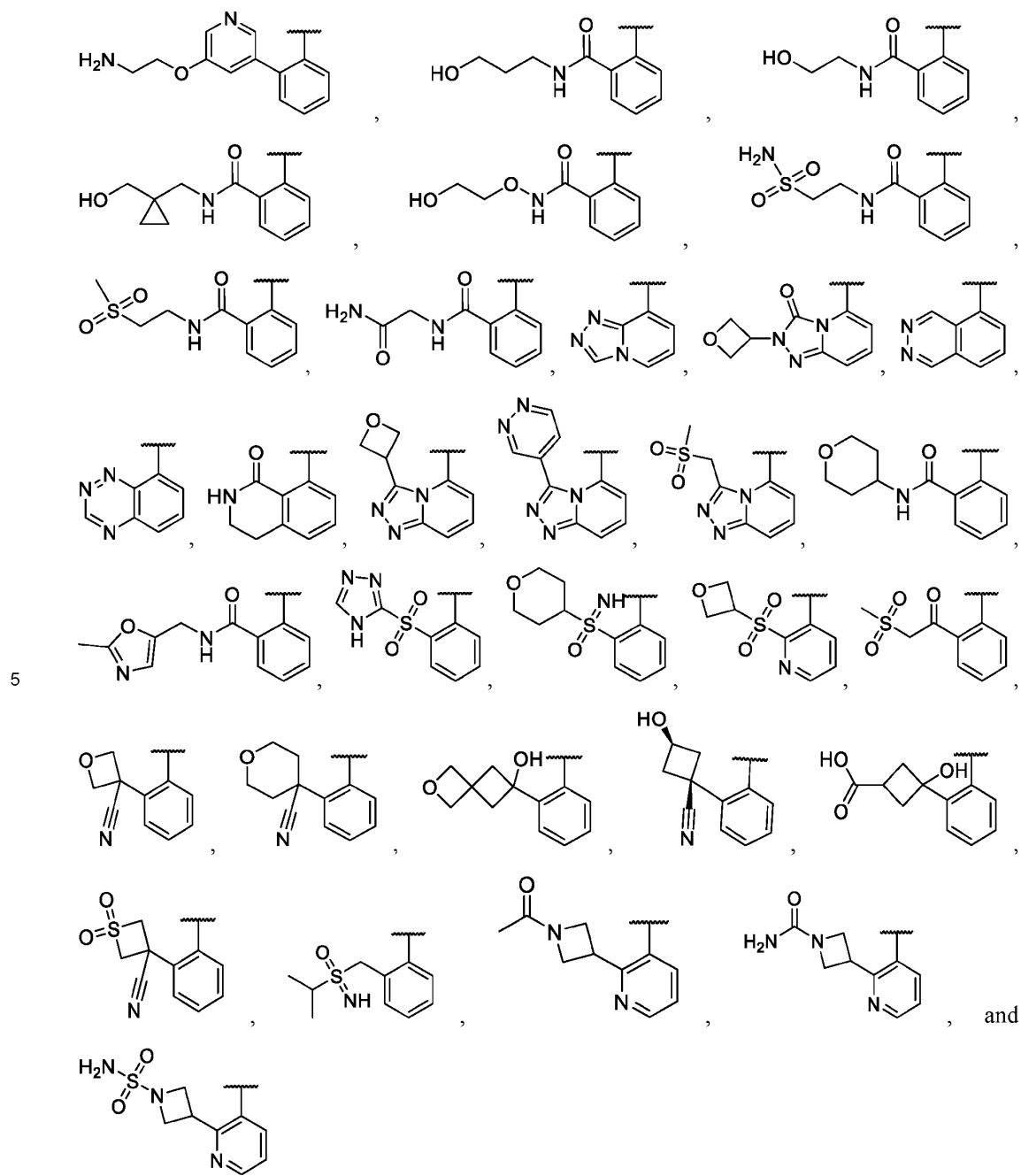
R^{Y1} , where R^{Y1} is hydroxyl. In some embodiments, R^Y is . In some embodiments, R^Y



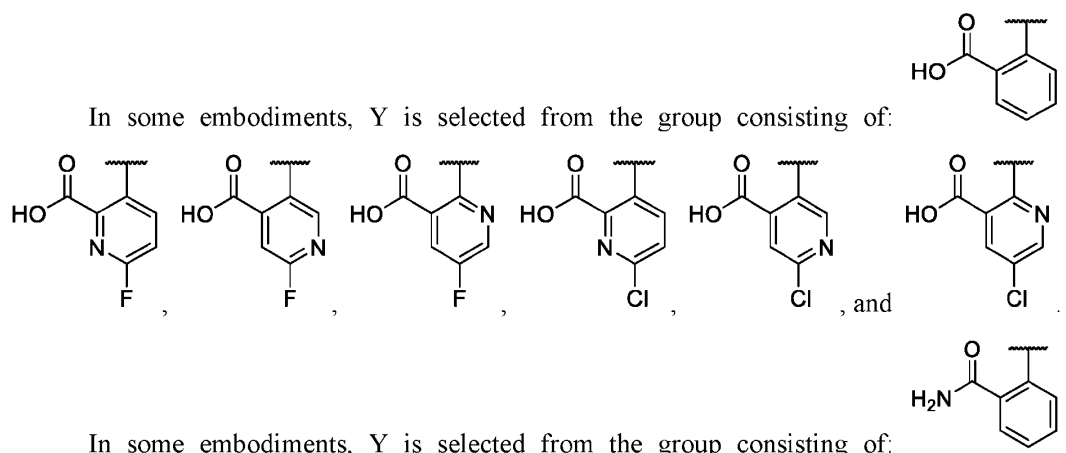
is

In some embodiments, Y is selected from the group consisting of:

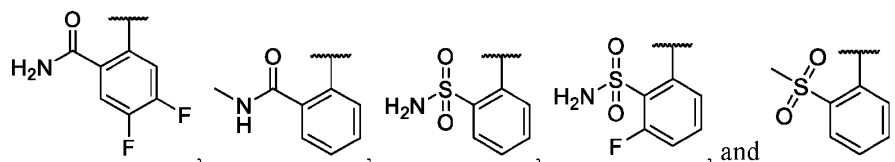




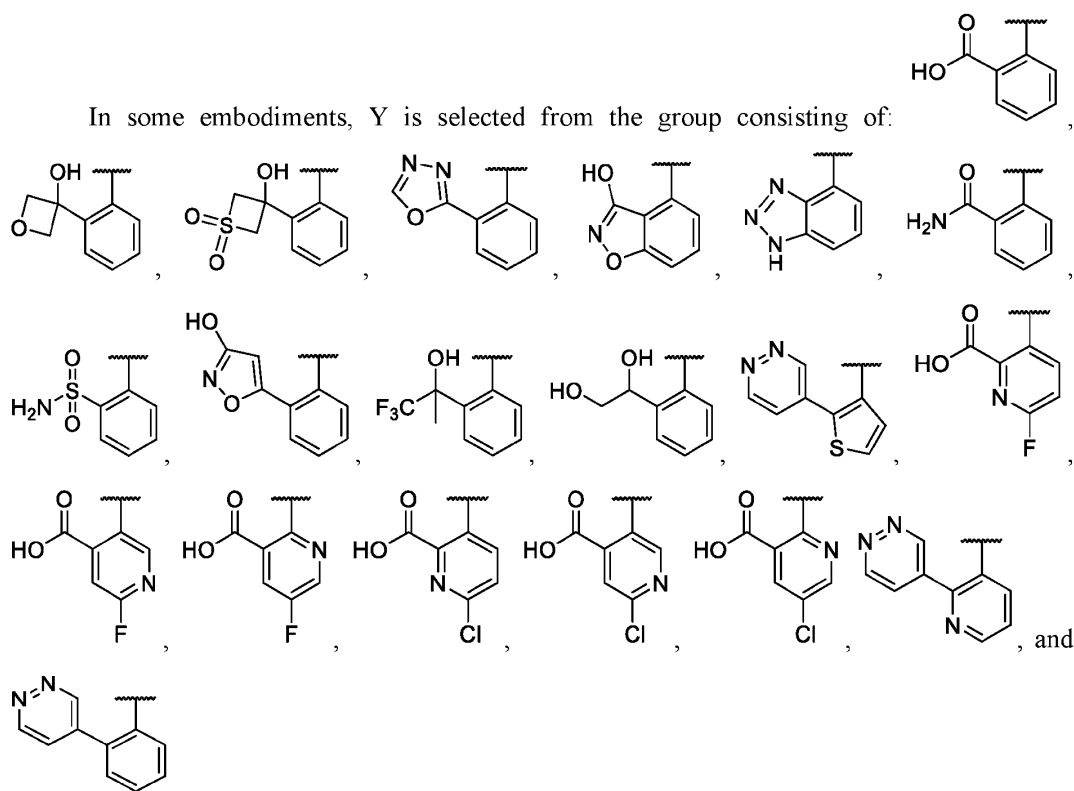
In some embodiments, Y is selected from the group consisting of:



In some embodiments, Y is selected from the group consisting of:



In some embodiments, Y is selected from the group consisting of:



In some embodiments, 1, 2, or 3 of R^Y is independently C1-C6 alkyl optionally substituted with $-\text{CO}_2R^A$ or 5-6 membered heteroaryl optionally substituted with R^{Y1} . In some embodiments, 1, 2, or 3 of R^Y is independently C1-C6 alkyl substituted with $-\text{CO}_2R^A$ or 5-6 membered heteroaryl optionally substituted with R^{Y1} . In some embodiments, 1, 2, or 3 of R^Y is independently C1-C6 alkyl substituted with $-\text{CO}_2R^A$ or 5-6 membered heteroaryl substituted with R^{Y1} . In some
 5 embodiments, 1, 2, or 3 of R^Y is independently C1-C6 alkyl substituted with $-\text{CO}_2R^A$ or 5-6 membered heteroaryl. In some embodiments, Y is substituted with 1 R^Y , and R^Y is C1-C6 alkyl substituted with $-\text{CO}_2R^A$. In some embodiments, Y is substituted with 1 R^Y , and R^Y is C1-C6 alkyl substituted with $-\text{CO}_2\text{H}$.

10 In some embodiments, 1 or 2 of R^Y is independently C1-C6 alkyl optionally substituted with $-\text{CO}_2R^A$ or 5-6 membered heteroaryl optionally substituted with R^{Y1} . In some embodiments, 1 or 2 of R^Y is independently C1-C6 alkyl substituted with $-\text{CO}_2R^A$ or 5-6 membered heteroaryl optionally substituted with R^{Y1} . In some embodiments, 1 or 2 of R^Y is independently C1-C6 alkyl substituted with $-\text{CO}_2R^A$ or 5-6 membered heteroaryl substituted with R^{Y1} . In some embodiments,
 15 1 or 2 of R^Y is independently C1-C6 alkyl substituted with $-\text{CO}_2R^A$ or 5-6 membered heteroaryl.

In some embodiments, 1 or 2 of R^Y is independently C1-C6 alkyl substituted with $-\text{CO}_2R^A$. In some embodiments, 1 or 2 of R^Y is independently C1-C6 alkyl substituted 5-6 membered heteroaryl optionally substituted with R^{Y1} . In some embodiments, 1 or 2 of R^Y is independently C1-C6 alkyl substituted with 5-6 membered heteroaryl substituted with R^{Y1} . In some
 20 embodiments, 1 or 2 of R^Y is independently C1-C6 alkyl substituted with 5-6 membered heteroaryl.

In some embodiments, 1, 2, or 3 of R^Y is independently C1-C6 alkyl. In some embodiments, 1 or 2 of R^Y is independently C1-C3 alkyl. In some embodiments, 1, 2, or 3 of R^Y is methyl. In some embodiments, R^{Y1} is $-\text{SO}_2(\text{C1-C6 alkyl})$. In some embodiments, R^{Y1} is $-\text{SO}_2\text{CH}_3$.
 25

In some embodiments, R^{Y1} is C1-C6 alkyl optionally substituted with oxo. In some embodiments, R^{Y1} is C1-C6 alkyl substituted with oxo. In some embodiments, R^{Y1} is acetyl, 1-oxoethyl, or 1-oxopropyl. In some embodiments, R^{Y1} is C1-C6 alkyl. In some embodiments, R^{Y1} is methyl. In some embodiments, R^4 is hydrogen.

30 In some embodiments, R^4 is halogen. In some embodiments, R^4 is fluoro or chloro. In some embodiments, R^4 is fluoro. In some embodiments, R^4 is chloro.

In some embodiments, R^4 is C1-C6 alkyl. In some embodiments, R^4 is methyl or ethyl. In some embodiments, R^4 is methyl.

In some embodiments, R^4 is acrylamido.

In some embodiments, R^5 is hydrogen. In some embodiments, R^5 is C1-C6 alkyl. In some
5 embodiments, R^5 is methyl or ethyl. In some embodiments, R^5 is methyl.

In some embodiments, R^5 is halogen. In some embodiments, R^5 is fluoro or chloro. In some
embodiments, R^5 is fluoro. In some embodiments, R^5 is chloro.

In some embodiments, R^5 is cyano.

In some embodiments, R^5 is $-NR^{5A}R^{5B}$.

10 In some embodiments, R^5 is $-NR^{5A}C(=O)R^{5B}$.

In some embodiments, R^5 is $-C(=O)NR^{5A}R^{5B}$.

In some embodiments, one of R^{5A} and R^{5B} is hydrogen and the other of R^{5A} and R^{5B} is C1-
C6 alkyl, C2-C6 alkenyl, or C1-C6 hydroxyalkyl. In some embodiments, one of R^{5A} and R^{5B} is
C1-C6 alkyl and the other of R^{5A} and R^{5B} is C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 hydroxyalkyl.
15 In some embodiments, each of R^{5A} and R^{5B} is hydrogen. In some embodiments, each of R^{5A} and
 R^{5B} is an independently selected C1-C6 alkyl. In some embodiments, each of R^{5A} and R^{5B} is
methyl. In some embodiments, the C1-C6 hydroxyalkyl of R^{5A} and R^{5B} is hydroxymethyl, 1-
hydroxyethyl, 2-hydroxyethyl, dihydroxypropyl or dihydroxybutyl.

In some embodiments, R^5 is acrylamido.

20 In some embodiments, R^6 is hydrogen.

In some embodiments, R^6 is halogen. In some embodiments, R^6 is fluoro. In some
embodiments, R^6 is chloro.

In some embodiments, R^6 is C1-C6 alkyl. In some embodiments, R^6 is methyl.

In some embodiments, each of R^A and R^B are independently selected from hydrogen,
25 hydroxyl, C1-C6 alkoxy, C3-C6 cycloalkyl, C2-C6 alkenyl, and C1-C6 alkyl optionally
substituted with hydroxyl or C1-C6 alkoxy.

In some embodiments, one of R^A and R^B is hydrogen and the other of R^A and R^B is
hydroxyl, C1-C6 alkoxy, C3-C6 cycloalkyl, C2-C6 alkenyl, or C1-C6 alkyl optionally substituted
with hydroxyl or C1-C6 alkoxy.

In some embodiments, one of R^A and R^B is hydrogen and the other of R^A and R^B is hydroxyl, C1-C6 alkoxy, C3-C6 cycloalkyl, C2-C6 alkenyl, or C1-C6 alkyl substituted with hydroxyl or C1-C6 alkoxy.

5 In some embodiments, one of R^A and R^B is hydrogen and the other of R^A and R^B is hydroxyl, C1-C6 alkoxy, C3-C6 cycloalkyl, C2-C6 alkenyl, or C1-C6 alkyl.

In some embodiments, one of R^A and R^B is hydrogen and the other of R^A and R^B is hydroxyl. In some embodiments, one of R^A and R^B is hydrogen and the other of R^A and R^B is C1-C6 alkoxy. In some embodiments, one of R^A and R^B is hydrogen and the other of R^A and R^B is C3-C6 cycloalkyl. In some embodiments, one of R^A and R^B is hydrogen and the other of R^A and R^B is C2-C6 alkenyl. In some embodiments, one of R^A and R^B is hydrogen and the other of R^A and R^B is C1-C6 alkyl optionally substituted with hydroxyl or C1-C6 alkoxy. In some
10 embodiments, one of R^A and R^B is hydrogen and the other of R^A and R^B is C1-C6 alkyl substituted with hydroxyl. In some embodiments, one of R^A and R^B is hydrogen and the other of R^A and R^B is C1-C6 alkyl substituted with C1-C6 alkoxy.

15 In some embodiments, one of R^A and R^B is hydrogen and the other of R^A and R^B is C1-C6 alkyl. In some embodiments, each of R^A and R^B are hydrogen. In some embodiments, each of R^A and R^B are an independently selected C1-C6 alkyl optionally substituted with hydroxyl or C1-C6 alkoxy. In some embodiments, each of R^A and R^B are an independently selected C1-C6 alkyl. In some embodiments, each of R^A and R^B are methyl.

20 In some embodiments, R^A and R^B together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclcyl optionally substituted with 1-2 substituents independently selected from halogen, C1-C6 alkyl, hydroxyl, and $-C(=O)C1-C6$ alkyl.

In some embodiments, R^A and R^B together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclcyl substituted with 1-2 substituents independently
25 selected from halogen, C1-C6 alkyl, hydroxyl, and $-C(=O)C1-C6$ alkyl.

In some embodiments, R^A and R^B together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclcyl substituted with halogen, C1-C6 alkyl, hydroxyl, or $-C(=O)C1-C6$ alkyl. In some embodiments, R^A and R^B together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclcyl substituted with 1-2 substituents
30 independently selected from fluoro, hydroxyl, methyl, and acetyl.

In some embodiments, R^A and R^B together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclyl. In some embodiments, R^A and R^B together with the nitrogen atom to which they are attached form a 4-6 membered heterocyclyl.

5 In some embodiments, each R^C is independently selected from C3-C6 cycloalkyl, $-C(=O)NHR^{Y1}$, and a C1-C6 alkyl substituted with $-NR^A R^B$ or with 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl or with C1-C6 hydroxylalkyl. In some embodiments, each R^C is independently C3-C6 cycloalkyl, $-C(=O)NHR^{Y1}$, or a C1-C6 alkyl substituted with $-NR^A R^B$ or with 4-10 membered heterocyclyl substituted with C1-C6 alkyl or with C1-C6 hydroxylalkyl. In some embodiments, each R^C is independently C3-C6 cycloalkyl, $-C(=O)NHR^{Y1}$, or a C1-C6
10 alkyl substituted with $-NR^A R^B$ or with 4-10 membered heterocyclyl. In some embodiments, each R^C is independently C3-C6 cycloalkyl, $-C(=O)NHR^{Y1}$, or a C1-C6 alkyl.

In some embodiments, each R^C is independently C3-C6 cycloalkyl. In some embodiments, each R^C is independently $-C(=O)NHR^{Y1}$. In some embodiments, each R^C is independently C1-C6 alkyl optionally substituted with $-NR^A R^B$ or with 4-10 membered heterocyclyl optionally
15 substituted with C1-C6 alkyl or with C1-C6 hydroxylalkyl. In some embodiments, each R^C is independently C1-C6 alkyl substituted with $-NR^A R^B$ or with 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl or with C1-C6 hydroxylalkyl.

In some embodiments, each R^D is independently selected from hydrogen, hydroxyl, phenyl, C1-C6 alkoxy, and C1-C6 alkyl optionally substituted with oxo or $-NR^A R^B$.

20 In some embodiments, R^D is hydrogen.

In some embodiments, R^D is hydroxyl.

In some embodiments, R^D is phenyl.

In some embodiments, R^D is C1-C6 alkoxy.

In some embodiments, R^D is C1-C6 alkyl optionally substituted with oxo or $-NR^A R^B$. In
25 some embodiments, R^D is unsubstituted C1-C6 alkyl. In some embodiments, R^D is C1-C6 alkyl substituted with oxo or $-NR^A R^B$. In some embodiments, R^D is C1-C6 alkyl substituted with $-NR^A R^B$.

In some embodiments, each R^E is independently selected from hydrogen, hydroxyl, phenyl, C1-C6 alkoxy, and C1-C6 alkyl optionally substituted with oxo or $-NR^A R^B$.

30 In some embodiments, R^E is hydrogen.

In some embodiments, R^E is hydroxyl.

In some embodiments, R^E is phenyl.

In some embodiments, R^E is C1-C6 alkoxy.

In some embodiments, R^E is C1-C6 alkyl optionally substituted with oxo or $-NR^A R^B$. In some embodiments, R^E is unsubstituted C1-C6 alkyl. In some embodiments, R^E is C1-C6 alkyl substituted with oxo or $-NR^A R^B$. In some embodiments, R^E is C1-C6 alkyl substituted with $-NR^A R^B$.

In some embodiments, one of R^D and R^E is hydrogen and the other of R^D and R^E is hydroxyl, C1-C6 alkyl, or C1-C6 alkoxy. In some embodiments, one of R^D and R^E is hydrogen and the other of R^D and R^E is hydroxyl. In some embodiments, one of R^D and R^E is hydrogen and the other of R^D and R^E is C1-C6 alkyl. In some embodiments, one of R^D and R^E is hydrogen and the other of R^D and R^E is C1-C6 alkoxy. In some embodiments, one of R^D and R^E is hydrogen and the other of R^D and R^E is hydroxyl, methyl, or methoxy. In some embodiments, each of R^D and R^E is hydrogen. In some embodiments, each of R^D and R^E is an independently selected C1-C6 alkyl. In some embodiments, each of R^D and R^E is methyl.

In some embodiments, each R^F is independently selected from: C3-C6 cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocyclyl, and C1-C6 alkyl optionally substituted with hydroxyl or $-SO_2(C1-C6\text{ alkyl})$.

In some embodiments, R^F is C3-C6 cycloalkyl.

In some embodiments, R^F is 5-6 membered heteroaryl.

In some embodiments, R^F is 4-6 membered heterocyclyl optionally substituted with C1-C6 alkyl. In some embodiments, R^F is 4-6 membered heterocyclyl. In some embodiments, R^F is 4-6 membered heterocyclyl substituted with C1-C6 alkyl.

In some embodiments, R^F is C1-C6 alkyl optionally substituted with hydroxyl or $-SO_2(C1-C6\text{ alkyl})$. In some embodiments, R^F is unsubstituted C1-C6 alkyl. In some embodiments, R^F is C1-C6 alkyl substituted with hydroxyl or $-SO_2(C1-C6\text{ alkyl})$. In some embodiments, R^F is C1-C6 alkyl substituted with hydroxyl. In some embodiments, R^F is C1-C6 alkyl substituted with $-SO_2(C1-C6\text{ alkyl})$.

In some embodiments, each R^G is independently selected from: hydrogen, C3-C6 cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocyclyl, and C1-C6 alkyl optionally substituted with hydroxyl or $-SO_2(C1-C6\text{ alkyl})$.

In some embodiments, R^G is hydrogen.

In some embodiments, R^G is C3-C6 cycloalkyl.

In some embodiments, R^G is 5-6 membered heteroaryl.

In some embodiments, R^G is 4-6 membered heterocyclyl.

In some embodiments, R^G is C1-C6 alkyl optionally substituted with hydroxyl or $-\text{SO}_2(\text{C1-C6 alkyl})$. In some embodiments, R^G is unsubstituted C1-C6 alkyl. In some embodiments, R^G is C1-C6 alkyl substituted with hydroxyl or $-\text{SO}_2(\text{C1-C6 alkyl})$. In some embodiments, R^G is C1-C6 alkyl substituted with hydroxyl. In some embodiments, R^G is C1-C6 alkyl substituted with $-\text{SO}_2(\text{C1-C6 alkyl})$.

In some embodiments, each R^H and R^I is independently selected from: hydrogen, C1-C6 alkoxy, C3-C6 cycloalkyl, C2-C6 alkenyl, $-(\text{CH}_2)_n-\text{C}(=\text{O})\text{NH}_2$, $-(\text{CH}_2)_n-\text{SO}_2\text{NH}_2$, $-(\text{CH}_2)_n-\text{SO}_2(\text{C1-C6 alkyl})$, C1-C6 alkyl optionally substituted with 1-2 substituents independently selected from hydroxyl, $-\text{SO}_2(\text{C1-C6 alkyl})$, C1-C6 alkoxy, 5-6 membered heteroaryl, C3-C6 cycloalkyl, and $-\text{C}(=\text{O})\text{NR}^{\text{K1}}\text{R}^{\text{K2}}$.

In some embodiments, R^H is hydrogen.

In some embodiments, R^H is C1-C6 alkoxy.

In some embodiments, R^H is C3-C6 cycloalkyl.

In some embodiments, R^H is C2-C6 alkenyl.

In some embodiments, R^H is $-(\text{CH}_2)_n-\text{C}(=\text{O})\text{NH}_2$.

In some embodiments, R^H is $-(\text{CH}_2)_n-\text{SO}_2\text{NH}_2$.

In some embodiments, R^H is $-(\text{CH}_2)_n-\text{SO}_2(\text{C1-C6 alkyl})$.

In some embodiments, R^H is C1-C6 alkyl optionally substituted with 1-2 substituents independently selected from hydroxyl, $-\text{SO}_2(\text{C1-C6 alkyl})$, C1-C6 alkoxy, 5-6 membered heteroaryl, C3-C6 cycloalkyl, and $-\text{C}(=\text{O})\text{NR}^{\text{K1}}\text{R}^{\text{K2}}$. In some embodiments, R^H is unsubstituted C1-C6 alkyl. In some embodiments, R^H is C1-C6 alkyl substituted with hydroxyl or $-\text{SO}_2(\text{C1-C6 alkyl})$. In some embodiments, R^H is C1-C6 alkyl substituted with hydroxyl. In some embodiments, R^H is C1-C6 alkyl substituted with $-\text{SO}_2(\text{C1-C6 alkyl})$. In some embodiments, R^H is C1-C6 alkyl substituted with C1-C6 alkoxy. In some embodiments, R^H is C1-C6 alkyl substituted with 5-6 membered heteroaryl. In some embodiments, R^H is C1-C6 alkyl substituted with C3-C6 cycloalkyl. In some embodiments, R^H is C1-C6 alkyl substituted with $-\text{C}(=\text{O})\text{NR}^{\text{K1}}\text{R}^{\text{K2}}$.

In some embodiments, both R^{K1} and R^{K2} are hydrogen.

In some embodiments, both R^{K1} and R^{K2} are C1-C6 alkyl.

In some embodiments, one of R^{K1} and R^{K2} is hydrogen and the other of R^{K1} and R^{K2} is C1-C6 alkyl.

In some embodiments, R^I is hydrogen.

In some embodiments, R^I is C1-C6 alkoxy.

5 In some embodiments, R^I is C3-C6 cycloalkyl.

In some embodiments, R^I is C2-C6 alkenyl.

In some embodiments, R^I is $-(CH_2)_n-C(=O)NH_2$.

In some embodiments, R^I is $-(CH_2)_n-SO_2NH_2$.

In some embodiments, R^I is $-(CH_2)_n-SO_2(C1-C6 \text{ alkyl})$.

10 In some embodiments, R^I is C1-C6 alkyl optionally substituted with 1-2 substituents independently selected from hydroxyl, $-SO_2(C1-C6 \text{ alkyl})$, C1-C6 alkoxy, 5-6 membered heteroaryl, C3-C6 cycloalkyl, and $-C(=O)NR^{K1}R^{K2}$. In some embodiments, R^I is unsubstituted C1-C6 alkyl. In some embodiments, R^I is C1-C6 alkyl substituted with hydroxyl or $-SO_2(C1-C6 \text{ alkyl})$. In some embodiments, R^I is C1-C6 alkyl substituted with hydroxyl. In some embodiments, 15 R^I is C1-C6 alkyl substituted with $-SO_2(C1-C6 \text{ alkyl})$. In some embodiments, R^I is C1-C6 alkyl substituted with C1-C6 alkoxy. In some embodiments, R^I is C1-C6 alkyl substituted with 5-6 membered heteroaryl. In some embodiments, R^I is C1-C6 alkyl substituted with C3-C6 cycloalkyl. In some embodiments, R^I is C1-C6 alkyl substituted with $-C(=O)NR^{K1}R^{K2}$.

20 In some embodiments, one of R^H and R^I is hydrogen and the other of R^H and R^I is phenyl or C1-C6 alkyl optionally substituted with oxo or $-NR^A R^B$. In some embodiments, one of R^H and R^I is hydrogen and the other of R^H and R^I is phenyl or C1-C6 alkyl substituted with oxo or $-NR^A R^B$. In some embodiments, one of R^H and R^I is hydrogen and the other of R^H and R^I is phenyl or C1-C6 alkyl. In some embodiments, one of R^H and R^I is hydrogen and the other of R^H and R^I 25 is phenyl. In some embodiments, one of R^H and R^I is hydrogen and the other of R^H and R^I is C1-C6 alkyl optionally substituted with oxo or $-NR^A R^B$. In some embodiments, one of R^H and R^I is hydrogen and the other of R^H and R^I is C1-C6 alkyl substituted with oxo or $-NR^A R^B$. In some embodiments, each of R^H and R^I is hydrogen. In some embodiments, each of R^H and R^I is an independently selected C1-C6 alkyl. In some embodiments, each of R^H and R^I is methyl.

30 In some embodiments, each of R^H and R^I is hydrogen.

In some embodiments, one of R^H and R^I is hydrogen and the other of R^H and R^I is C1-C6 alkoxy, C3-C6 cycloalkyl, or C2-C6 alkenyl.

In some embodiments, one of R^H and R^I is hydrogen and the other of R^H and R^I is C1-C6 alkyl optionally substituted with hydroxyl, $-\text{SO}_2(\text{C1-C6 alkyl})$, or C1-C6 alkoxy.

5 In some embodiments, one of R^H and R^I is hydrogen and the other of R^H and R^I is $-(\text{CH}_2)_n-\text{C}(=\text{O})\text{NH}_2$, $-(\text{CH}_2)_n-\text{SO}_2\text{NH}_2$, or $-(\text{CH}_2)_n-\text{SO}_2(\text{C1-C6 alkyl})$.

In some embodiments, R^H and R^I together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclyl optionally substituted with 1-2 substituents independently selected from halogen, C1-C6 alkyl, and $-\text{C}(=\text{O})\text{C1-C6 alkyl}$. In some embodiments, R^H and R^I together with the nitrogen atom to which they are attached form an unsubstituted 4-10 membered heterocyclyl. In some embodiments, R^H and R^I together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclyl substituted with 1-2 substituents independently selected from halogen, C1-C6 alkyl, and $-\text{C}(=\text{O})\text{C1-C6 alkyl}$. In some embodiments, R^H and R^I together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclyl substituted with 1 substituent independently selected from halogen, C1-C6 alkyl, and $-\text{C}(=\text{O})\text{C1-C6 alkyl}$. In some embodiments, R^H and R^I together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclyl substituted with 2 substituents independently selected from halogen, C1-C6 alkyl, and $-\text{C}(=\text{O})\text{C1-C6 alkyl}$.

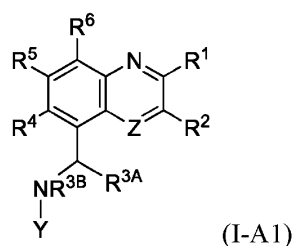
In some embodiments, R^J is C1-C6 alkyl, C3-C6 cycloalkyl, or C1-C6 alkoxy.

20 In some embodiments, R^J is C1-C6 alkyl. In some embodiments, R^J is C1-C3 alkyl.

In some embodiments, R^J is C3-C6 cycloalkyl.

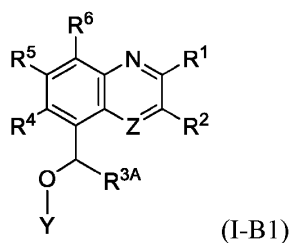
In some embodiments, R^J is C1-C6 alkoxy.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A1):



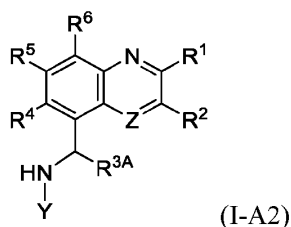
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-B1):



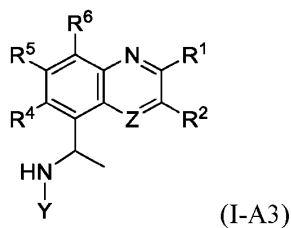
or a pharmaceutically acceptable salt thereof.

5 In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A2):



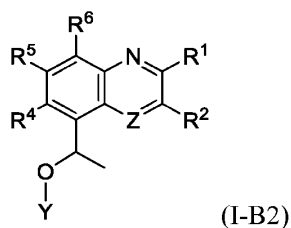
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A3):



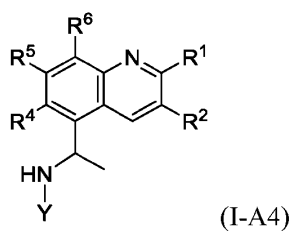
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-B2):



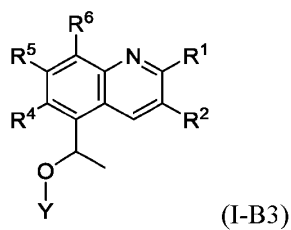
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A5):



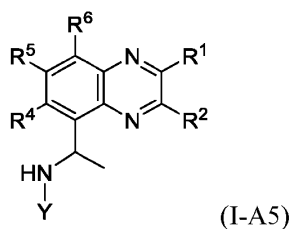
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-B3):



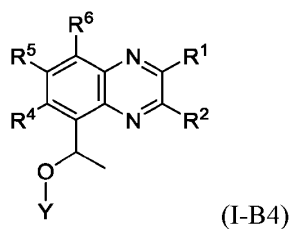
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A5):



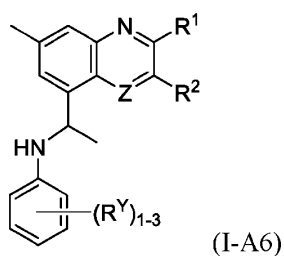
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-B4):



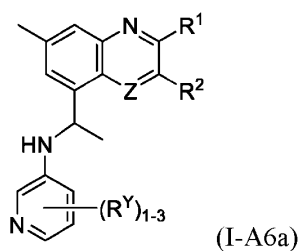
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A6):



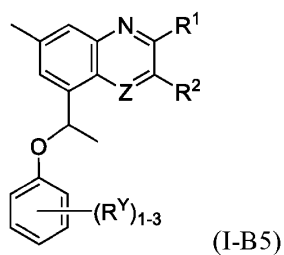
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A6a):



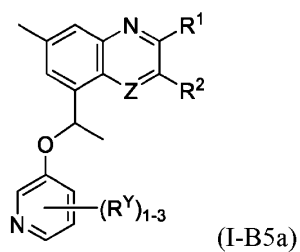
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-B5):



or a pharmaceutically acceptable salt thereof.

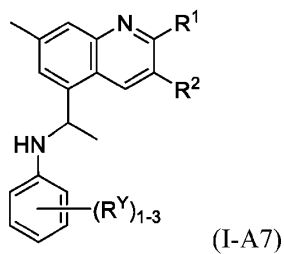
In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-B5a):



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or a pharmaceutically acceptable salt thereof.

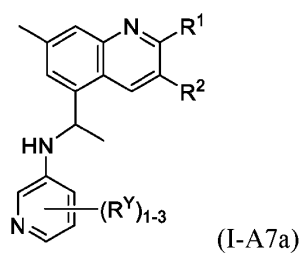
In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A7):



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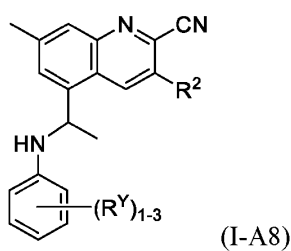
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A7a):



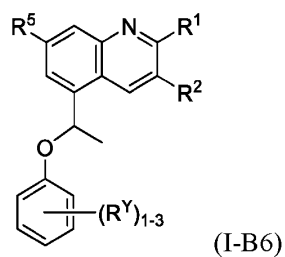
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A8):



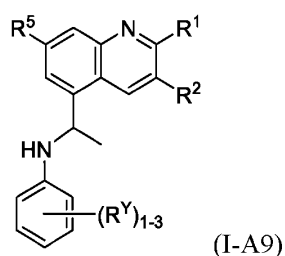
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-B6):



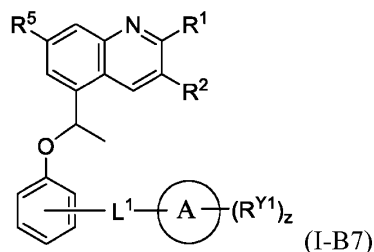
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A9):



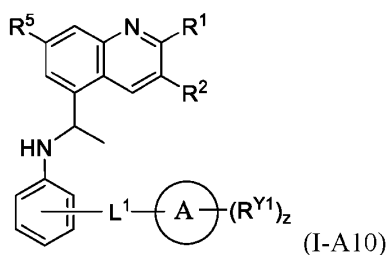
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-B7):



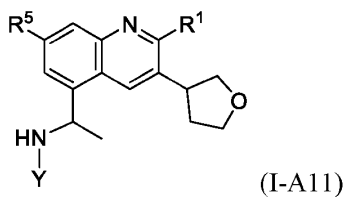
5 or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A10):



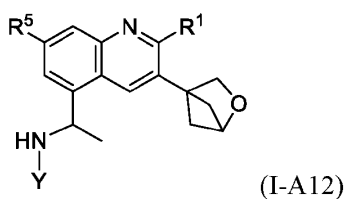
or a pharmaceutically acceptable salt thereof.

10 In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A11):



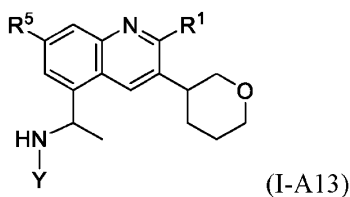
or a pharmaceutically acceptable salt thereof.

15 In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A12):



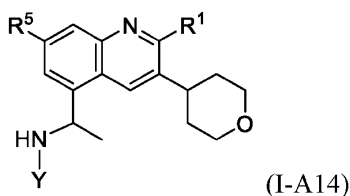
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A13):



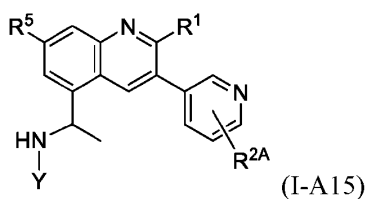
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A14):



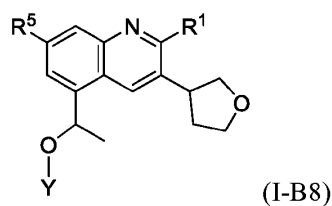
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A15):



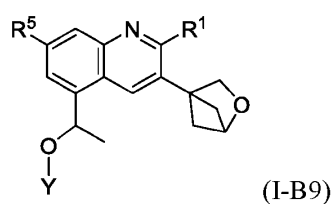
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-B8):



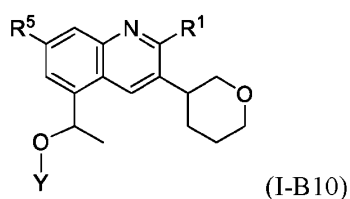
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-B9):



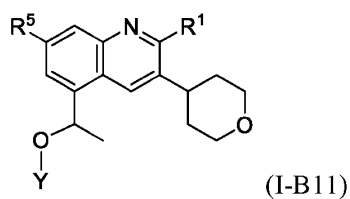
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-B10):



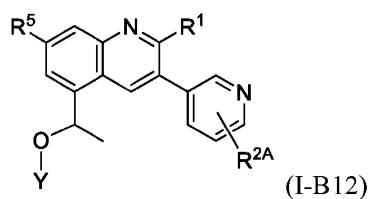
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-B11):



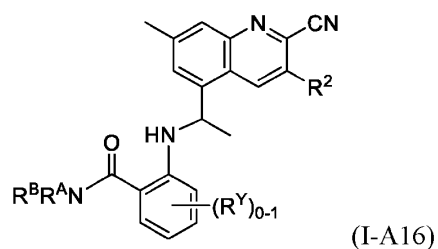
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-B12):



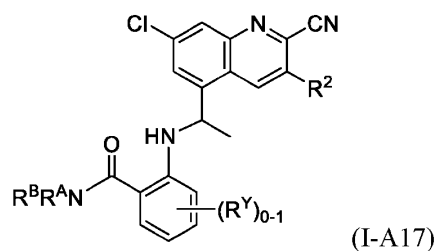
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A16):



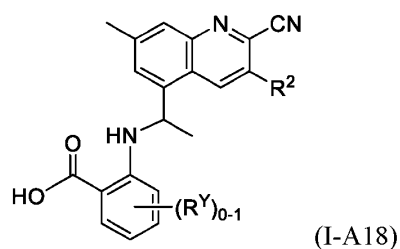
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A17):



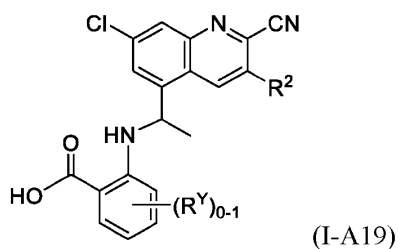
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A18):



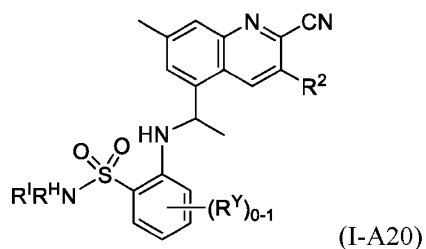
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A19):



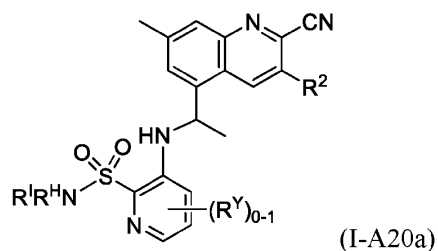
or a pharmaceutically acceptable salt thereof.

5 In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A20):



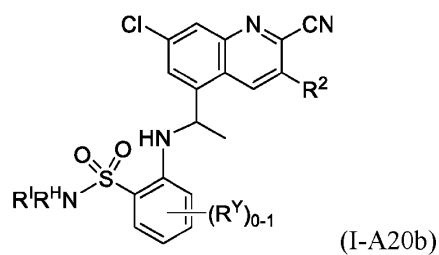
or a pharmaceutically acceptable salt thereof.

10 In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A20a):



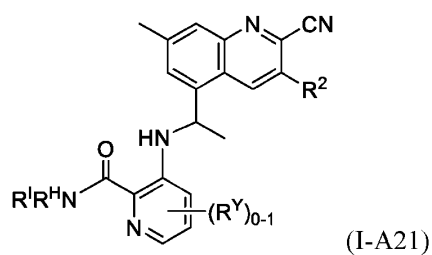
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A20b):



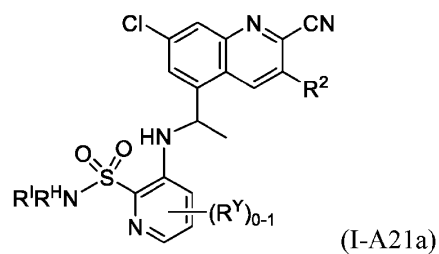
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A21):



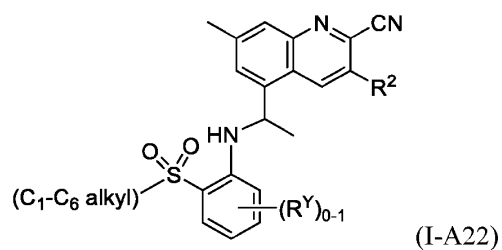
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A21a):



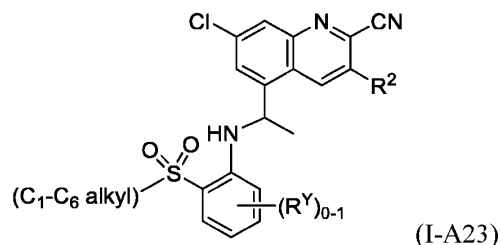
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A22):



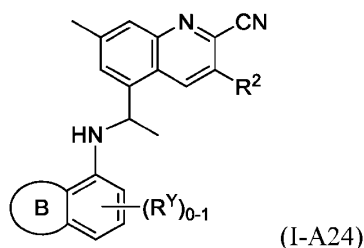
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A23):



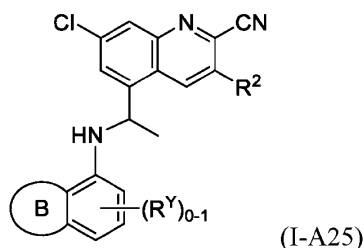
5 or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A24):



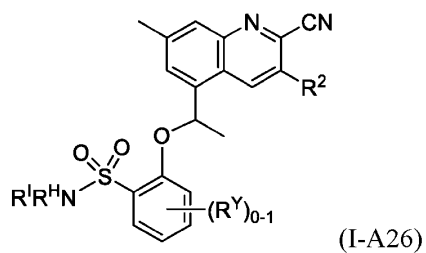
10 or a pharmaceutically acceptable salt thereof, wherein Ring B is C₆ aryl or C₅-C₆ heteroaryl optionally substituted with 1-2 independently selected R^Y.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A25):



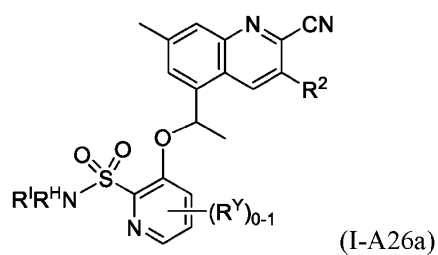
15 or a pharmaceutically acceptable salt thereof, wherein Ring B is C₆ aryl or C₅-C₆ heteroaryl optionally substituted with 1-2 independently selected R^Y.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A26):



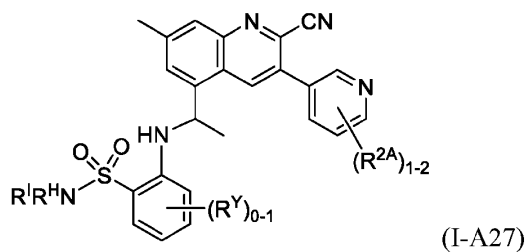
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A26a):



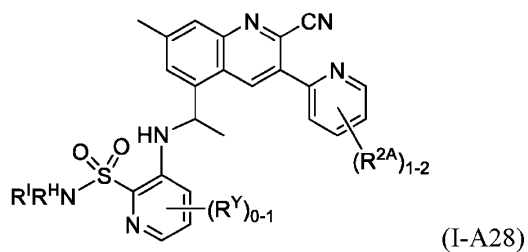
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A27):



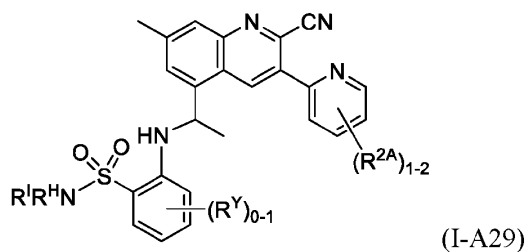
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A28):



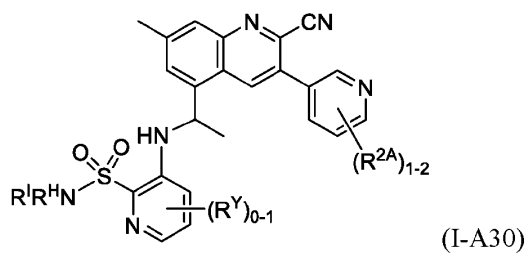
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A29):



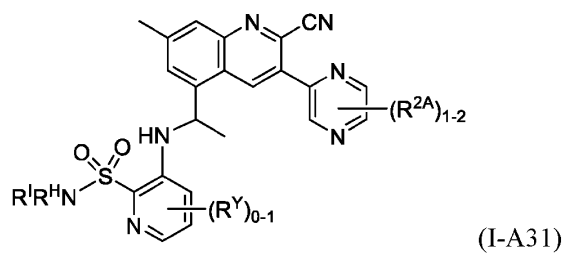
5 or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A30):



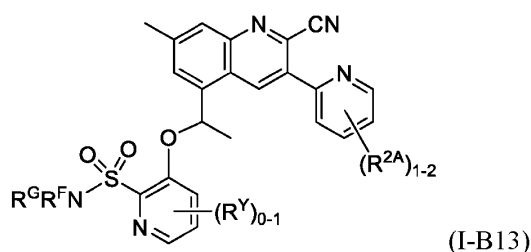
or a pharmaceutically acceptable salt thereof.

10 In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-A31):



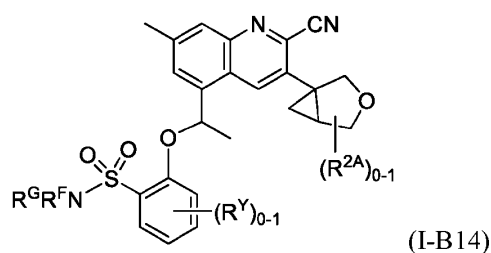
or a pharmaceutically acceptable salt thereof.

15 In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-B13):



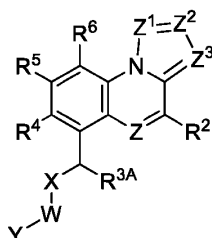
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of Formula (I-B14):



or a pharmaceutically acceptable salt thereof.

Also provided herein are compounds of Formula (II),



or a pharmaceutically acceptable salt thereof, wherein:

Z^1 , Z^2 , and Z^3 are each independently N or CH, wherein one or two of Z^1 , Z^2 , and Z^3 is N;
 Z is N or CH;

R^2 is phenyl optionally substituted with 1-4 independently selected R^{2A} , 5-10 membered heteroaryl optionally substituted with 1-4 independently selected R^{2A} , 4-10 membered heterocyclyl optionally substituted with 1-4 independently selected R^{2A} , C4-C10 cycloalkyl optionally substituted with 1-4 independently selected R^{2A} , 4-10 membered heterocyclyloxy optionally substituted with 1-4 independently selected R^{2A} , 5-10 heteroaryloxy optionally

substituted with 1-4 independently selected R^{2A} , C1-C6 alkoxyalkyl optionally substituted with $-C(=O)NR^A R^C$, or C1-C6 alkoxy optionally substituted with $-C(=O)NR^A R^C$, C4-C10 cycloalkyl, 4-10 membered heterocyclyl, 5-10 membered heteroaryl, or phenyl;

5 each R^{2A} is independently selected from:

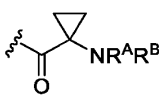
(i) halogen;

(ii) cyano;

(iii) hydroxyl;

(iv) $-NR^A R^B$;

10 (v) $-C(=O)NR^A R^B$;

(vi)  ;

(vii) $-NHC(=O)R^C$;

(viii) $-C(=O)OR^D$;

(ix) $-SO_2R^D$;

15 (x) $-NH SO_2R^D$;

(xi) $-SO_2NR^D R^E$;

(xii) $-NHC(=O)C1-C6$ alkyl optionally substituted with $NR^A R^B$;

(xiii) C1-C6 haloalkyl;

(xiv) C1-C6 hydroxyalkyl;

20 (xv) 5-10 membered heteroaryl optionally substituted with 1-3 substituents independently selected from hydroxyl, cyano, C1-C6 alkyl optionally substituted with hydroxyl, halogen, $-C(=O)NR^A R^B$, $-NR^A R^B$, and 4-10 membered heterocyclyl optionally substituted with hydroxyl or C1-C6 alkyl;

(xvi) 4-10 membered heterocyclyl optionally substituted with 1-3 substituents independently selected from hydroxyl, cyano, halogen, C1-C6 haloalkyl, $-C(=O)C1-C6$ alkyl, $-SO_2(C1-C6$ alkyl), $-SO_2NR^D R^E$, C1-C6 alkoxy, $-C(=O)NR^A R^B$, $-NR^A R^B$, $-NHC(=O)C1-C6$ alkyl optionally substituted with $-NR^A R^B$, and C1-C6 alkyl optionally substituted with C1-C6 alkoxy or hydroxyl;

25 (xvii) C1-C6 alkyl optionally substituted with 1-3 substituents independently selected from hydroxyl, oxo, $-NR^A R^B$, $-C(=O)NR^A R^B$, C1-C6 alkoxy, and 4-10 membered heterocyclyl

optionally substituted with hydroxyl, C1-C6 alkyl, aralkyl, heteroaralkyl, $-C(=O)NR^A R^B$, or $-C(=O)C3-C6$ cycloalkyl;

(xviii) C1-C6 alkoxy optionally substituted with $-NR^A R^B$ or 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl, aralkyl, heteroaralkyl, or $-C(=O)C3-C6$ cycloalkyl; and

5 (xix) C3-C6 cycloalkyl optionally substituted with hydroxyl, $-C(=O)NR^A R^B$, $-C(=N)OR^D$, or 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl;

each R^A and R^B is independently selected from hydrogen, hydroxyl, C1-C6 alkoxy, C3-C6 cycloalkyl, C2-C6 alkenyl, and C1-C6 alkyl optionally substituted with hydroxyl or C1-C6 alkoxy, or R^A and R^B together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclyl optionally substituted with 1-2 substituents independently selected from halogen, C1-C6 alkyl, and $-C(=O)C1-C6$ alkyl;

each R^C is independently selected from C3-C6 cycloalkyl, $-C(=O)NHR^{Y1}$, and a C1-C6 alkyl optionally substituted with $-NR^A R^B$ or with 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl or with C1-C6 hydroxylalkyl;

15 each R^D and R^E is independently selected from hydrogen, hydroxyl, phenyl, C1-C6 alkoxy, and C1-C6 alkyl optionally substituted with oxo or $-NR^A R^B$;

each R^{3A} and R^{3B} is independently selected from hydrogen, C1-C6 alkyl, C1-C6 alkoxy, and C1-C6 haloalkyl;

or R^{3A} and R^{3B} , together with the carbon and nitrogen atoms, respectively, to which they are attached together form a 4-8 membered heterocyclyl group;

R^4 is hydrogen, halogen, C1-C6 alkyl, or acrylamido;

R^5 is hydrogen, halogen, C1-C6 alkyl, cyano, $-NR^{5A}R^{5B}$, $-NR^{5A}C(=O)R^{5B}$, or $-C(=O)NR^{5A}R^{5B}$;

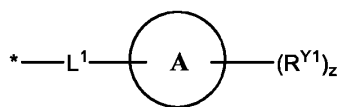
25 R^{5A} and R^{5B} are independently selected from hydrogen, C1-C6 alkyl, C2-C6 alkenyl, and C1-C6 hydroxyalkyl;

R^6 is hydrogen, halogen, or C1-C6 alkyl;

X is a bond, CH_2 , $CH(CH_3)$, $C(CH_3)_2$, or ;

W is NR^{3B} or O;

Y is phenyl, naphthyl, or 5-10 membered heteroaryl, wherein the phenyl, naphthyl, and 5-10 membered heteroaryl are optionally and independently substituted with 1-3 independently



selected R^Y or , wherein * represents the connection of L^1 to the remainder of the compound of Formula (I);

each R^Y is independently selected from: halogen, cyano, hydroxyl, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkoxy, C1-C6 hydroxyalkyl, $-(CH_2)_n-C(=O)R^F$, $-(CH_2)_n-NHC(=O)R^F$, $-(CH_2)_n-NHC(=O)OR^F$, $-CO_2R^G$, $-(CH_2)_n-SO_2NR^HR^I$, $-(CH_2)_n-NHSO_2R^J$, $-(CH_2)_n-S(=O)(=NR^H)R^J$, $-(CH_2)_n-SO_2R^J$, $-(CH_2)_n-C(=O)NR^HR^I$, $-(CH_2)_n-C(=O)NR^HOR^I$, and C1-C6 haloalkyl optionally substituted with hydroxyl;

each R^F is independently selected from: C3-C6 cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocyclyl, and C1-C6 alkyl optionally substituted with hydroxyl or $-SO_2$ (C1-C6 alkyl);

each R^G is independently selected from: hydrogen, C3-C6 cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocyclyl, and C1-C6 alkyl optionally substituted with hydroxyl or $-SO_2$ (C1-C6 alkyl);

each R^H and R^I is independently selected from: hydrogen, C1-C6 alkoxy, C3-C6 cycloalkyl, C2-C6 alkenyl, C1-C6 alkyl optionally substituted with hydroxyl, $-SO_2$ (C1-C6 alkyl), or C1-C6 alkoxy, $-(CH_2)_n-C(=O)NH_2$, $-(CH_2)_n-SO_2NH_2$, and $-(CH_2)_n-SO_2$ (C1-C6 alkyl), or R^H and R^I together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclyl optionally substituted with 1-2 substituents independently selected from halogen, C1-C6 alkyl, and $-C(=O)$ C1-C6 alkyl;

R^J is C1-C6 alkyl, C3-C6 cycloalkyl, or C1-C6 alkoxy;

Ring A is phenyl, 4-10 membered heteroaryl, 4-10 membered heterocyclyl, or C4-C10 cycloalkyl;

L^1 is a bond, C1-C6 alkoxy, $-(CH_2)_n-NHC(=O)-$, $-C(=O)NH-(CH_2)_n-$, $-CO_2-$, $-SO_2-$, $-NHSO_2-$, $-SO_2NH-$, $-S(=O)(=NR^G)-$, $-SO_2$ (C1-C6 alkylene)-, $-C(=O)C(=O)NH-$, or C1-C6 alkylene optionally substituted with oxo;

each R^{Y1} is independently selected from: cyano, hydroxyl, halogen, $-C(=O)R^F$, $-NHC(=O)R^F$, $-CO_2R^G$, $-SO_2NR^HR^I$, $-NHSO_2R^J$, $-S(=O)(=NR^H)R^J$, $-SO_2$ (C1-C6 alkyl), $-C(=O)NR^HR^I$, 4-6 membered heteroaryl, C1-C6 alkoxy optionally substituted with R^{Y2} , C1-C6

haloalkyl, C1-C6 alkyl optionally substituted with R^{Y2} , and 4-6 membered heterocyclyl optionally substituted with hydroxyl or C1-C6 alkyl;

R^{Y2} is hydroxyl, $-NR^H R^I$, $-C(=O)NR^H R^I$, or $-SO_2NR^H R^I$;

n is 0, 1, or 2; and

5 z is 0, 1, 2, or 3.

Z , R^2 , R^{2A} , R^{3A} , R^{3B} , R^4 , R^5 , R^{5A} , R^{5B} , R^6 , R^A , R^B , R^C , R^D , R^E , R^F , R^G , R^H , R^I , R^J , X, W, Y, R^Y , R^{Y1} , R^{Y2} , Ring A, L^1 , n, and z are further defined as disclosed above in Formula (I).

In some embodiments, Z^1 is N.

In some embodiments, Z^1 is CH.

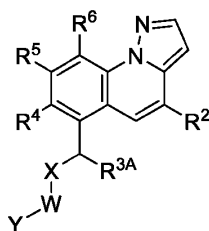
10 In some embodiments, Z^2 is N.

In some embodiments, Z^2 is CH.

In some embodiments, Z^3 is N.

In some embodiments, Z^3 is CH

15 Provided herein are compounds of Formula (II-A), or a pharmaceutically acceptable salt thereof:

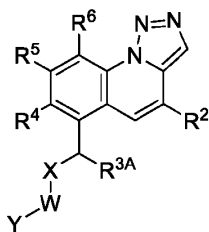


Formula (II-A)

wherein:

R^2 , R^{3A} , R^4 , R^5 , R^6 , X, W, Y, are defined as disclosed above in Formula (I).

20 Provided herein are compounds of Formula (II-B), or a pharmaceutically acceptable salt thereof:

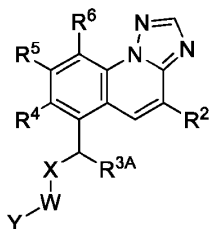


Formula (II-B)

wherein:

R^2 , R^{3A} , R^4 , R^5 , R^6 , X, W, Y, are defined as disclosed above in Formula (I).

Provided herein are compounds of Formula (II-C), or a pharmaceutically acceptable salt thereof:

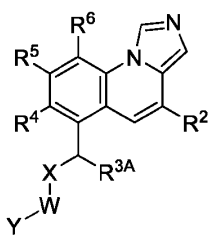


Formula (II-C)

5 wherein:

R^2 , R^{3A} , R^4 , R^5 , R^6 , X, W, Y, are defined as disclosed above in Formula (I).

Provided herein are compounds of Formula (II-D), or a pharmaceutically acceptable salt thereof:

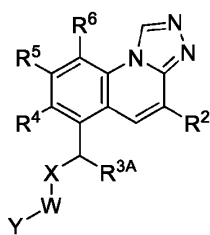


Formula (II-D)

10 wherein:

R^2 , R^{3A} , R^4 , R^5 , R^6 , X, W, Y, are defined as disclosed above in Formula (I).

Provided herein are compounds of Formula (II-E), or a pharmaceutically acceptable salt thereof:

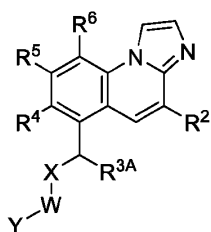


Formula (II-E)

15 wherein:

R^2 , R^{3A} , R^4 , R^5 , R^6 , X, W, Y, are defined as disclosed above in Formula (I).

Provided herein are compounds of Formula (II-F), or a pharmaceutically acceptable salt thereof:



Formula (II-F)

wherein:

5 R^2 , R^{3A} , R^4 , R^5 , R^6 , X, W, Y, are defined as disclosed above in Formula (I).

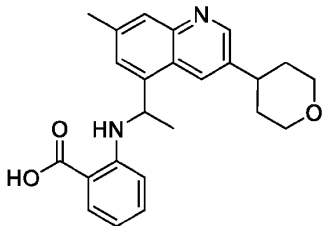
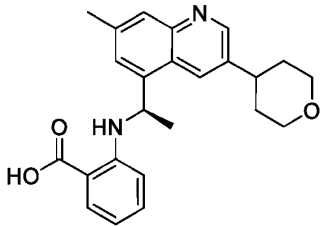
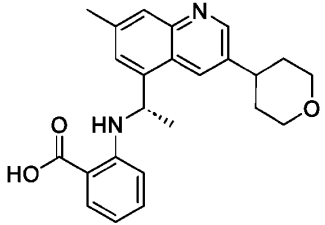
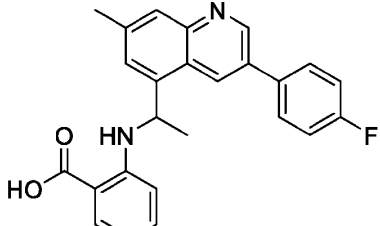
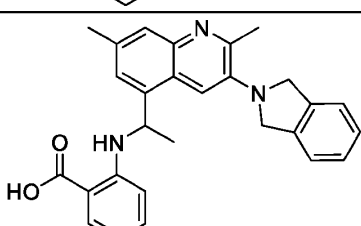
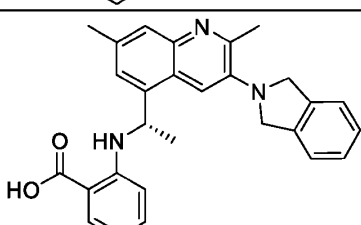
Non-Limiting Exemplary Compounds

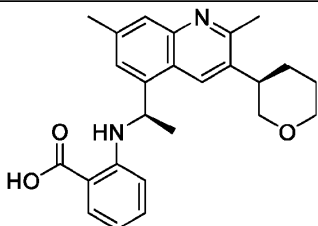
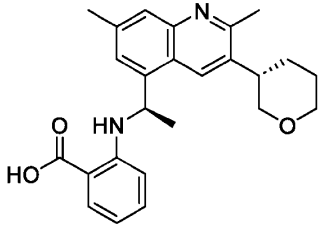
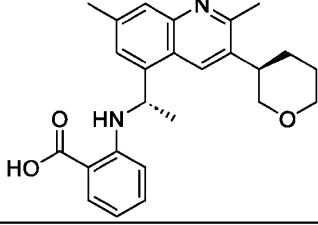
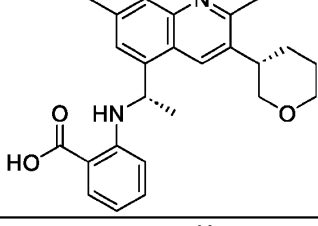
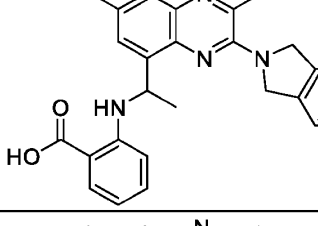
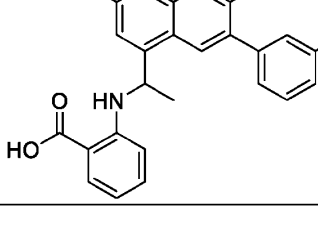
In some embodiments, the compound is selected from the group consisting of the compounds in Examples 1-668 (e.g., Compound 1, Compound 2, or Compound 620), or a pharmaceutically acceptable salt thereof.

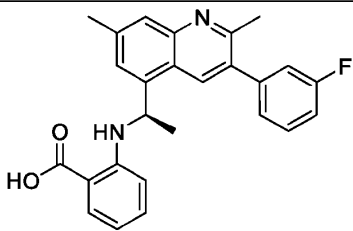
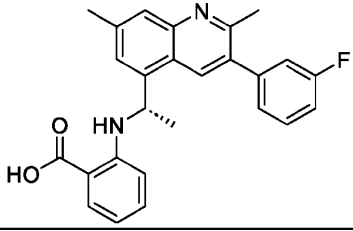
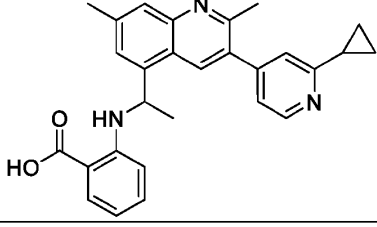
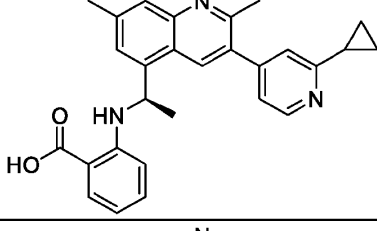
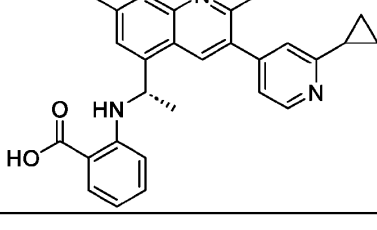
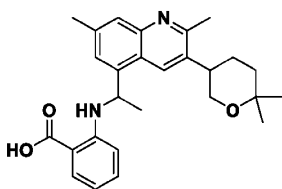
In some embodiments, the compound is selected from the group consisting of the compounds in Table A, or a pharmaceutically acceptable salt thereof. Stereochemistry shown for the compounds in Table A has been arbitrarily assigned.

15 **Table A**

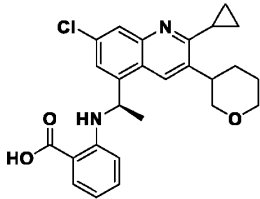
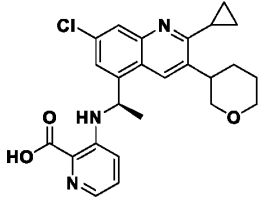
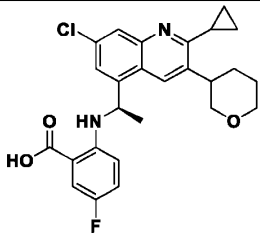
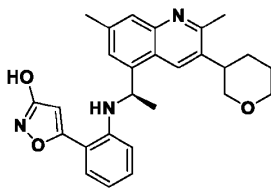
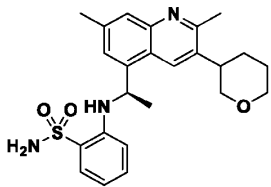
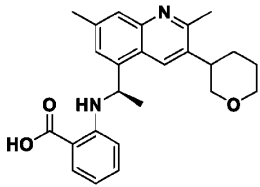
Compound Number.	Structure
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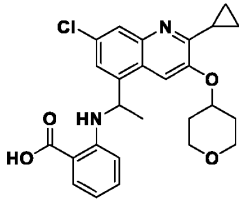
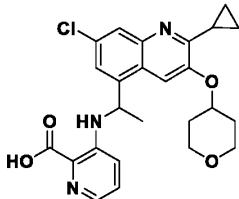
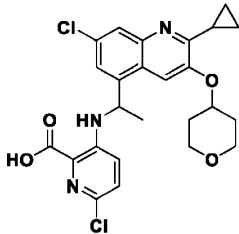
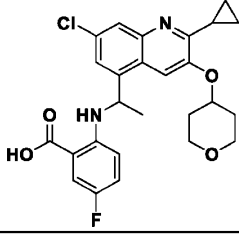
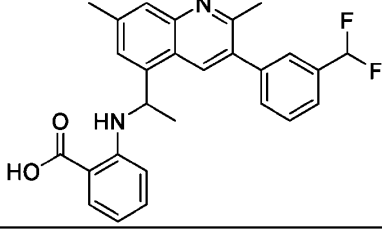
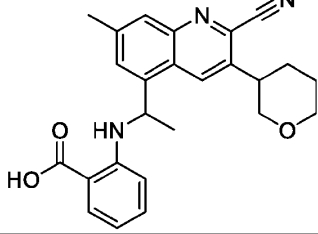
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8A	
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8D	
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10A	
10B	
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11A	
11B	
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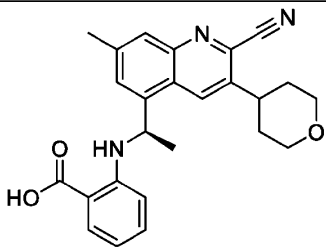
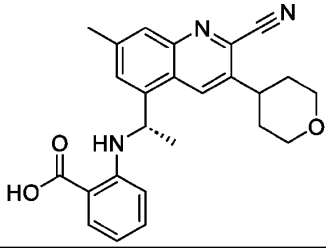
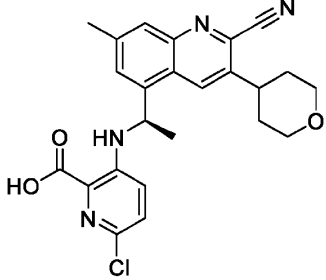
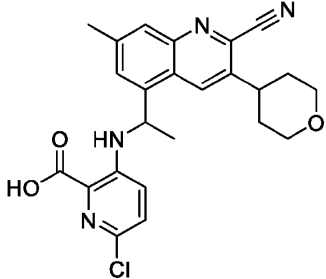
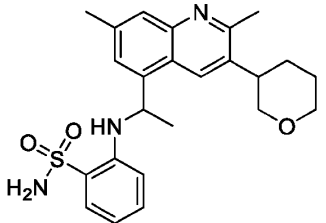
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14	 <chem>CC1=CC=C(C=C1N2C=CC(=C(C=C2)C3=CC(=CC=C3)C(=O)N[C@@H](C)C4=CC=CC=C4C5=CC=C(C=C5)OC6=CC=CC=C6C)C7=CC=CC=C7C8=CC=C(C=C8)OC9=CC=CC=C9C</chem>
15	 <chem>CC1=CC=C(C=C1N2C=CC(=C(C=C2)C3=CC(=CC=C3)C(=O)N[C@@H](C)C4=CC=CC=C4C5=CC=C(C=C5)OC6=CC=CC=C6C)C7=CC=CC=C7C8=CC=C(C=C8)OC9=CC=CC=C9C</chem>
16	 <chem>CC1=CC=C(C=C1N2C=CC(=C(C=C2)C3=CC(=CC=C3)C(=O)N[C@@H](C)C4=CC=CC=C4C5=CC=C(C=C5)OC6=CC=CC=C6C)C7=CC=CC=C7C8=CC=C(C=C8)OC9=CC=CC=C9C</chem>
17	 <chem>CC1=CC=C(C=C1N2C=CC(=C(C=C2)C3=CC(=CC=C3)C(=O)N[C@@H](C)C4=CC=CC=C4C5=CC=C(C=C5)OC6=CC=CC=C6C)C7=CC=CC=C7C8=CC=C(C=C8)OC9=CC=CC=C9C</chem>
18	 <chem>CC1=CC=C(C=C1N2C=CC(=C(C=C2)C3=CC(=CC=C3)C(=O)N[C@@H](C)C4=CC=CC=C4C5=CC=C(C=C5)OC6=CC=CC=C6C)C7=CC=CC=C7C8=CC=C(C=C8)OC9=CC=CC=C9C</chem>

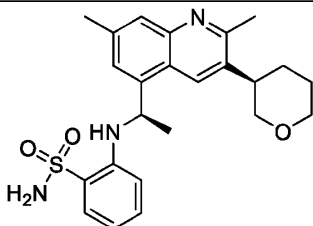
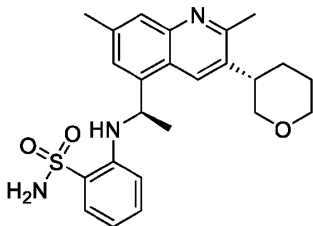
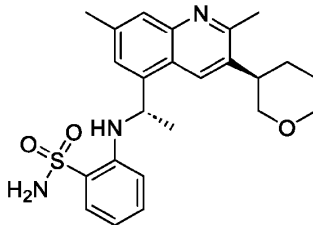
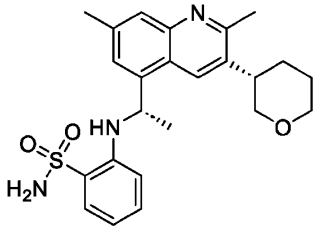
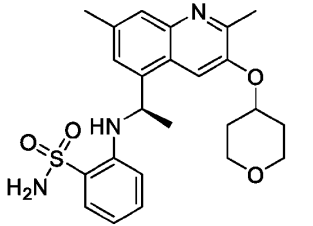
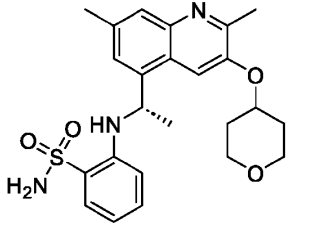
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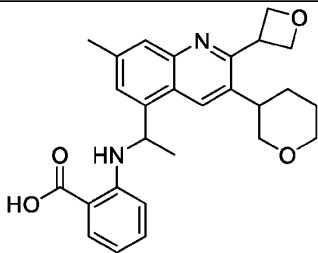
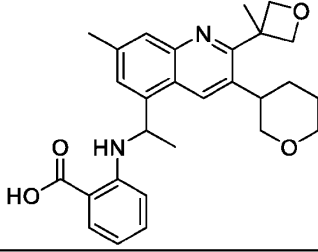
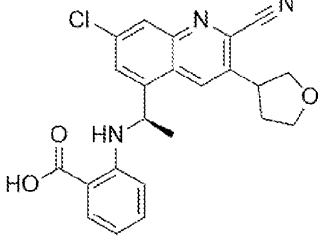
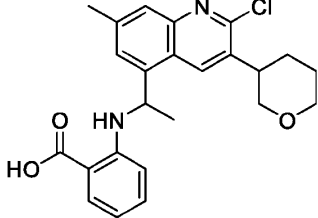
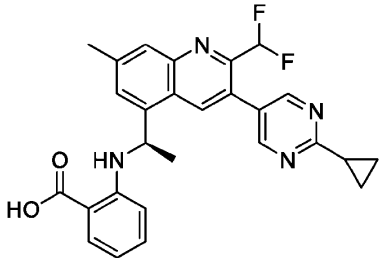
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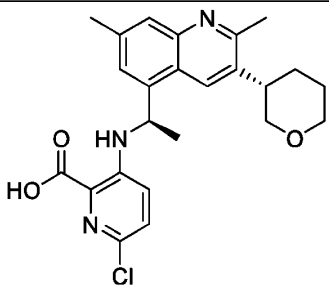
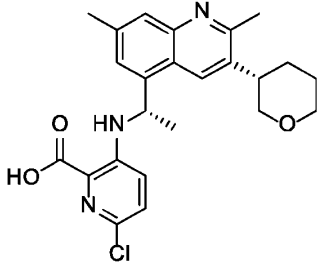
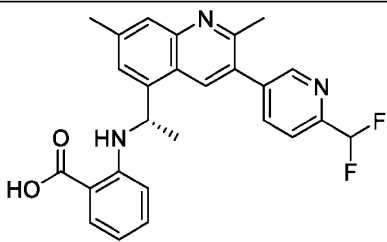
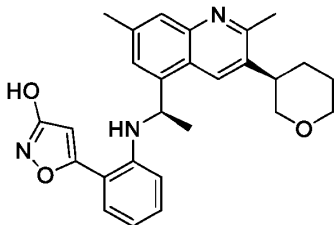
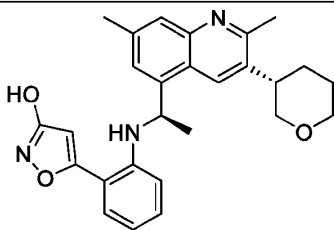
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32	 <chem>CC1=CC=C(C=C1)NC(=O)O</chem> <chem>CC(C)Nc1ccc(cc1)C2=CC=C(C=C2)C3=CC=C(C=C3)N4C(=O)NCCO4</chem>
33	 <chem>CC1=CC=C(C=C1)NC(=O)O</chem> <chem>CC(C)Nc1ccc(cc1)C2=CC=C(C=C2)C3=CC=C(C=C3)N4C(=O)NCCO4</chem>
34	 <chem>CC1=CC=C(C=C1)NC(=O)O</chem> <chem>CC(C)Nc1ccc(cc1)C2=CC=C(C=C2)C3=CC=C(C=C3)N4C(=O)NCCO4</chem>
35	 <chem>CC1=CC=C(C=C1)NC(=O)O</chem> <chem>CC(C)Nc1ccc(cc1)C2=CC=C(C=C2)C3=CC=C(C=C3)N4C(=O)NCCO4</chem>

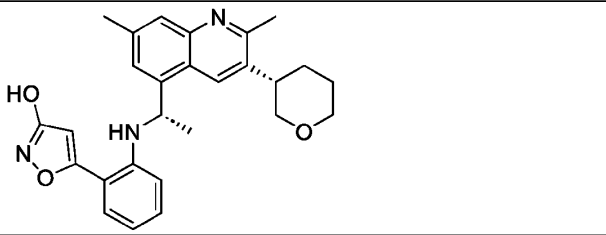
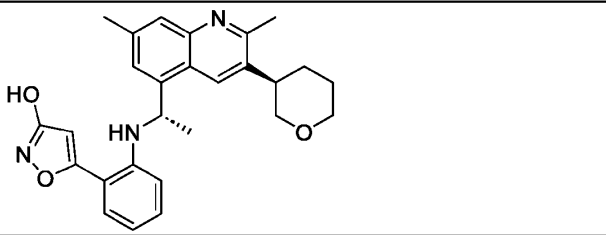
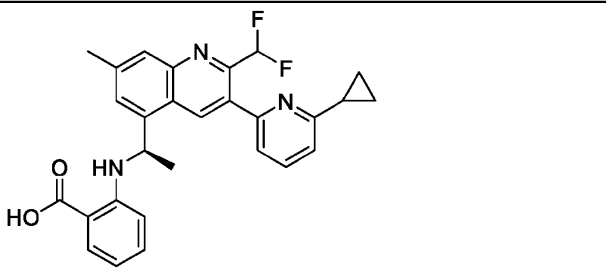
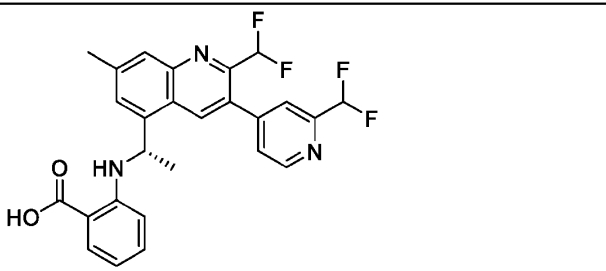
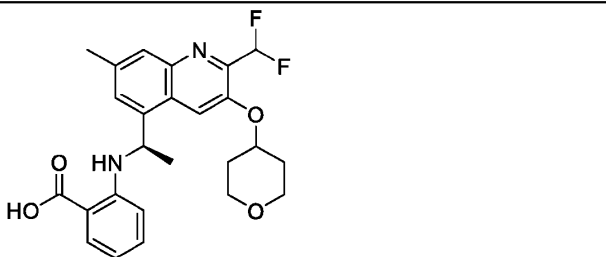
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37	 <chem>CC(C)N(c1ccccc1)c2c(C)c3cc(C)nc(C)c3cc2c4ccc(OCCOCCO4)c5ccccc5</chem>
38	 <chem>CC(C)N(c1ccc(cc1)C(=O)O)c2c(C)c3cc(C)nc(C)c3cc2c4ccc(CF(F)F)cc4O</chem>
39	 <chem>CC(C)N(c1ccc(cc1)C(=O)O)c2c(C)c3cc(C)nc(C)c3cc2c4ccc(CF(F)F)cc4O</chem>
40	 <chem>CC(C)N(c1ccc(cc1)C(=O)O)c2c(C)c3cc(C)nc(C)c3cc2c4ccc(CF(F)F)cc4O</chem>

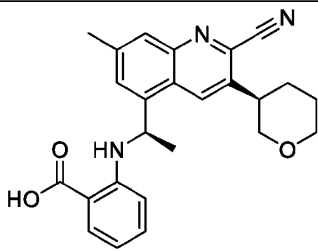
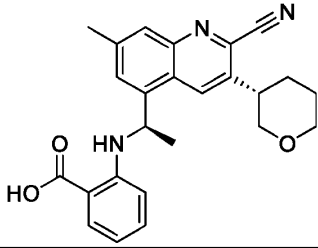
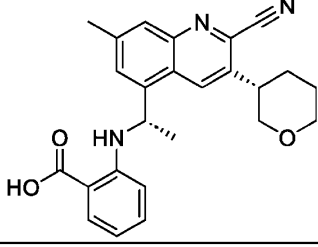
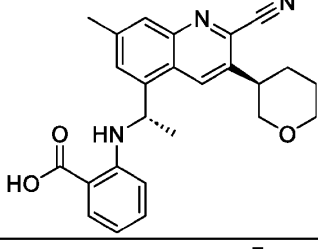
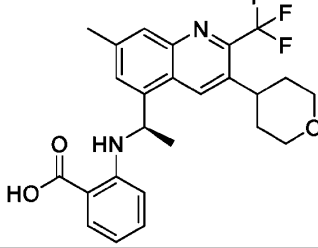
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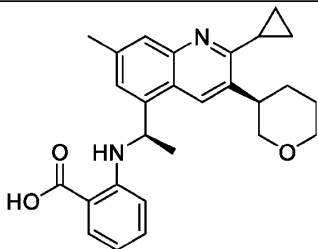
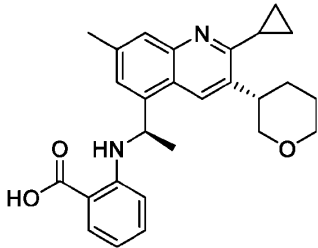
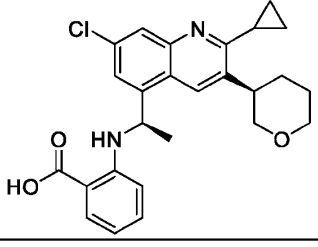
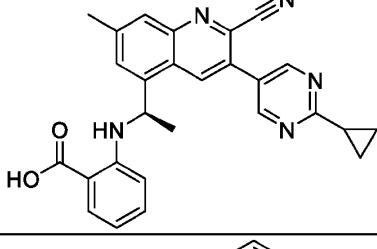
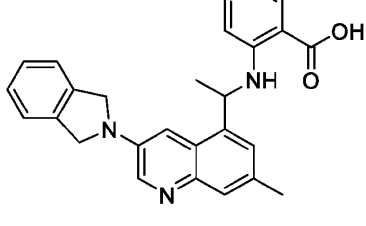
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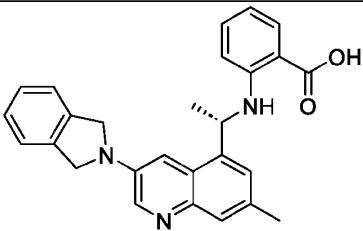
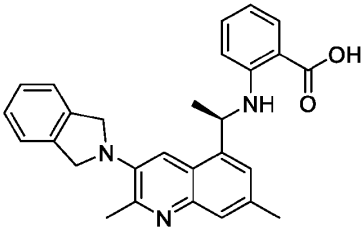
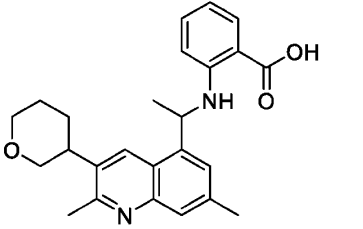
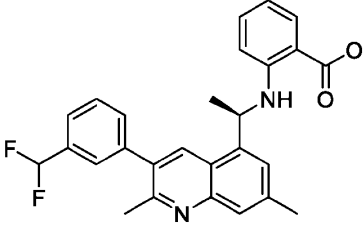
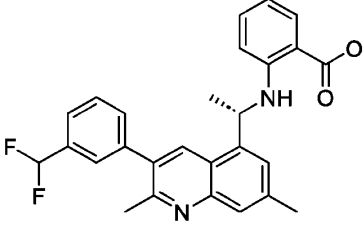
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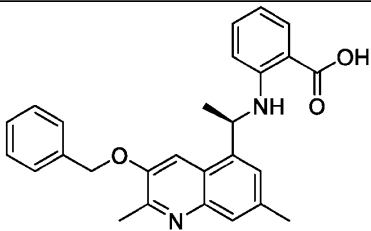
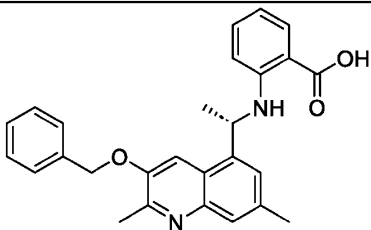
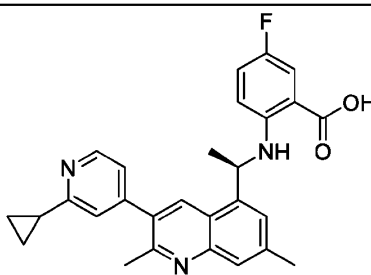
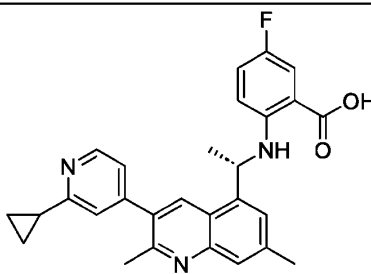
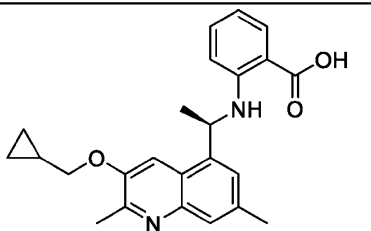
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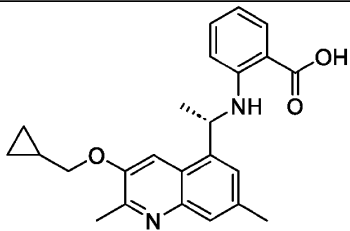
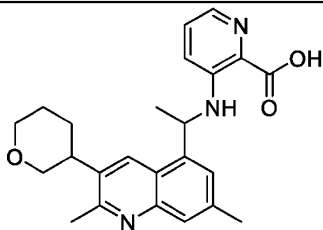
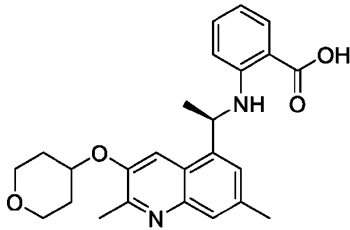
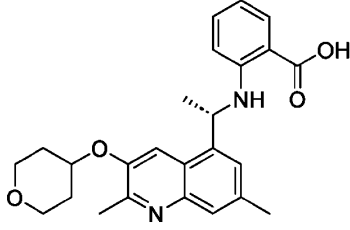
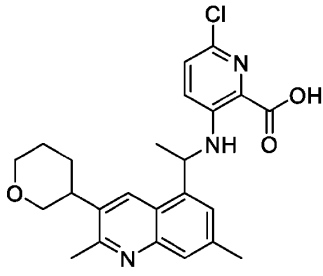
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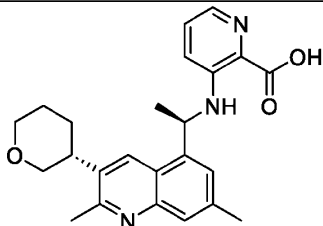
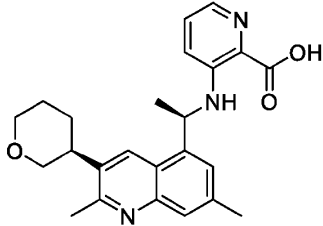
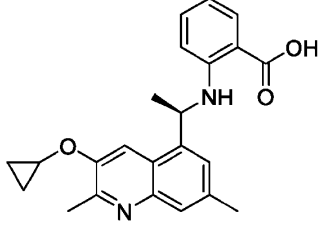
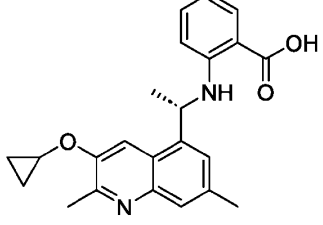
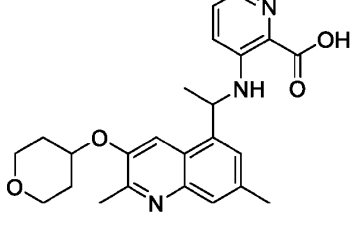
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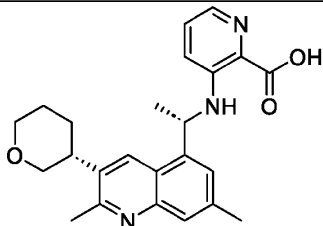
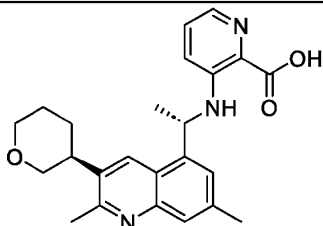
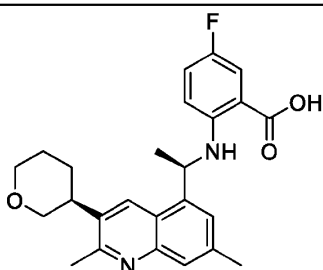
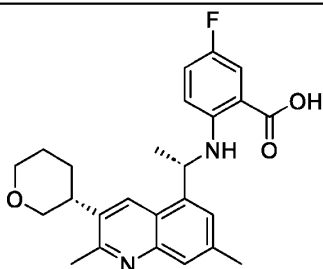
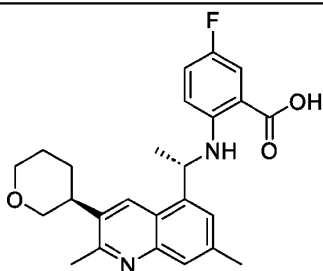
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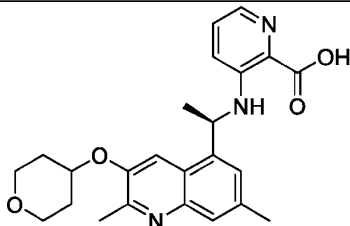
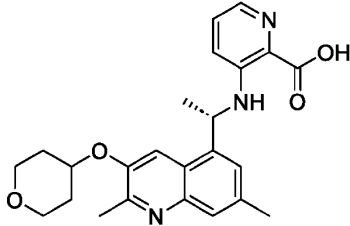
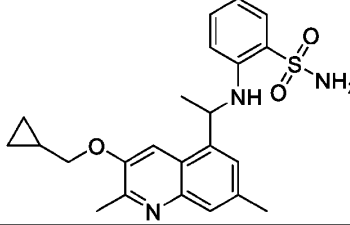
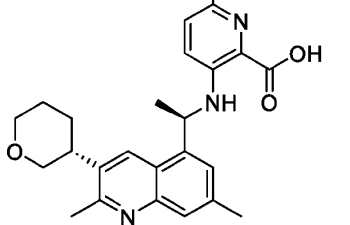
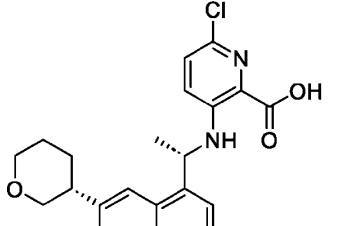
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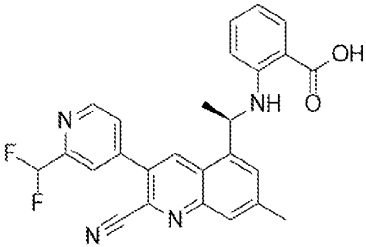
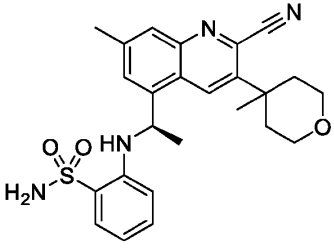
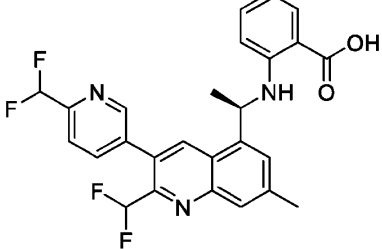
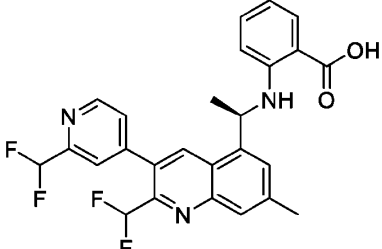
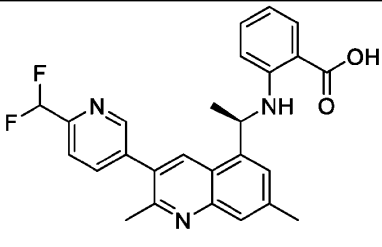
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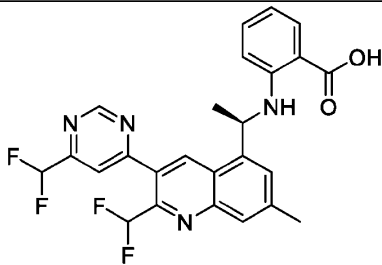
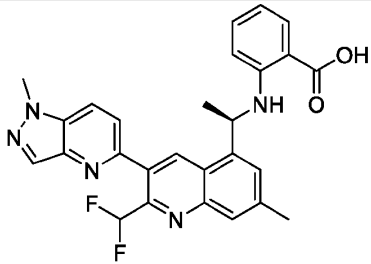
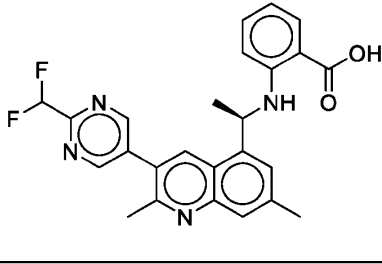
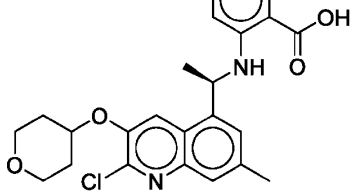
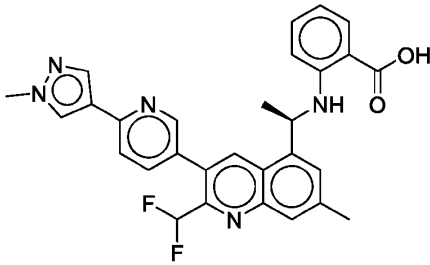
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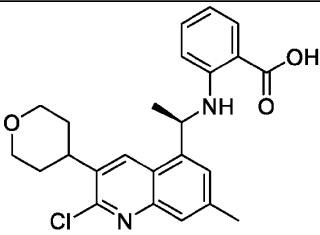
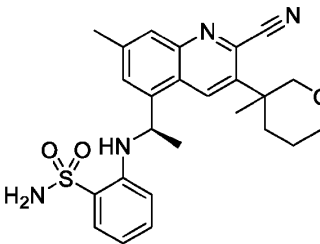
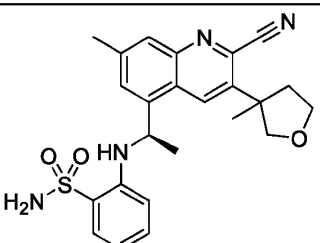
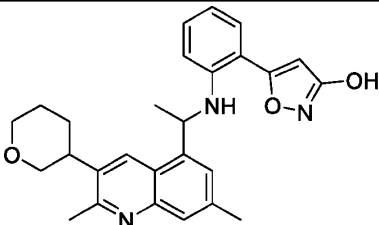
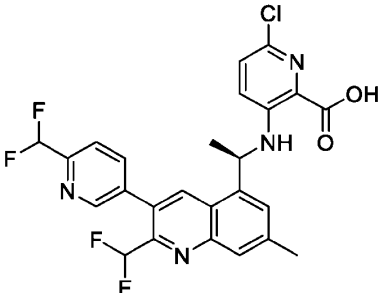
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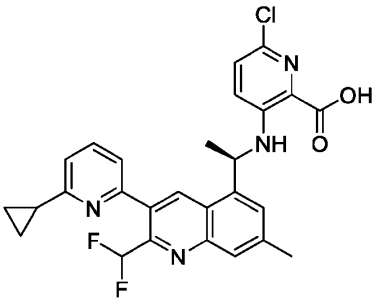
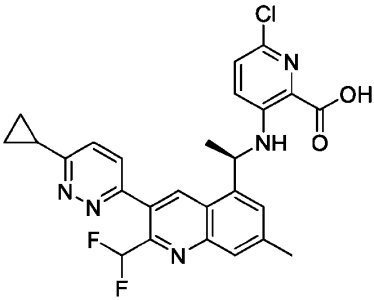
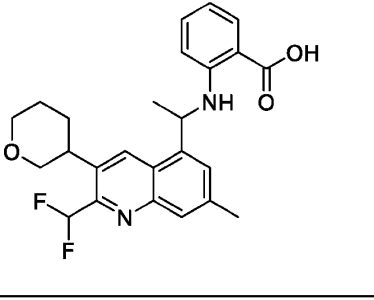
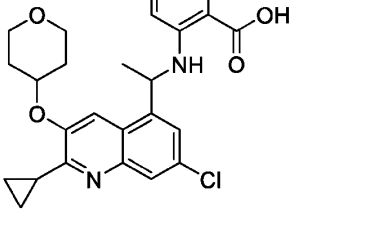
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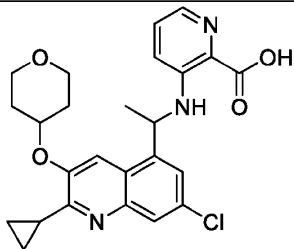
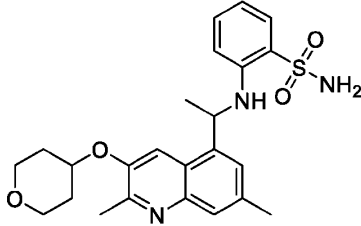
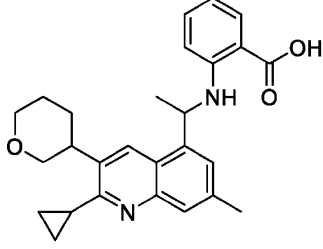
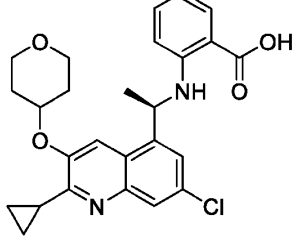
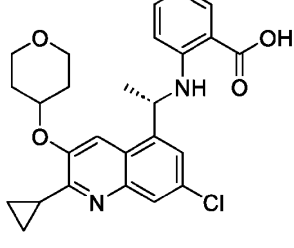
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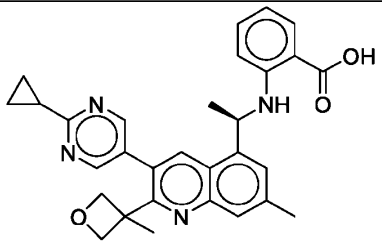
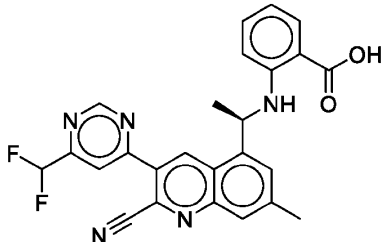
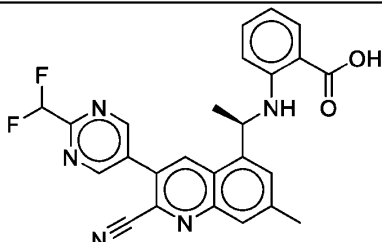
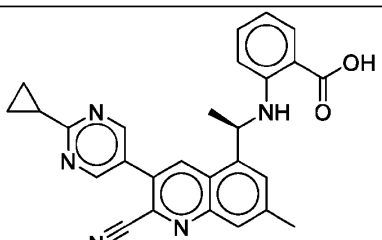
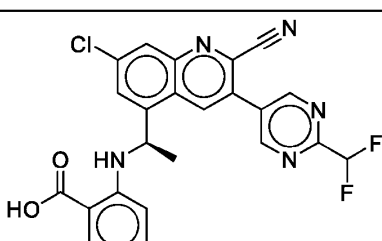
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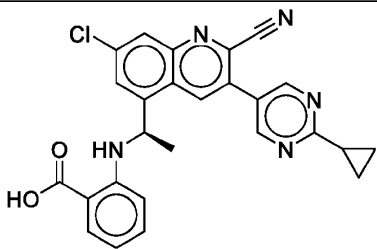
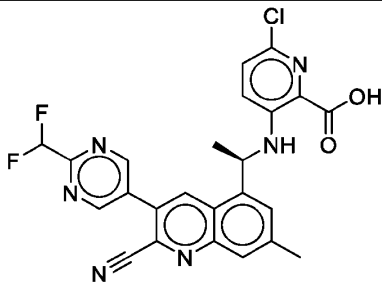
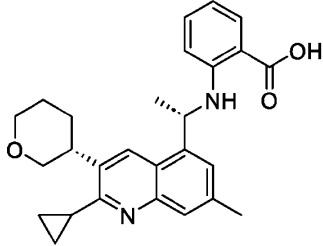
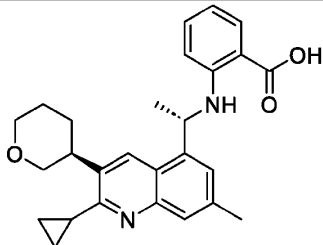
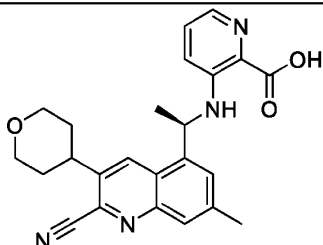
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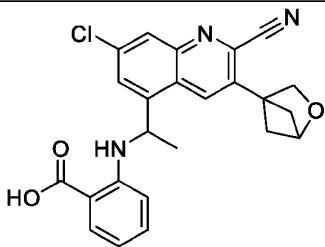
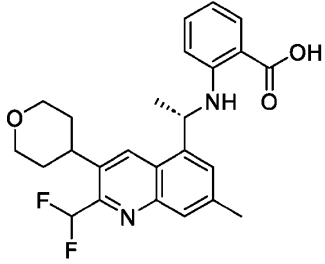
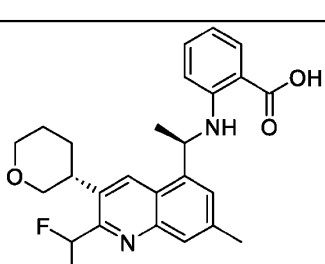
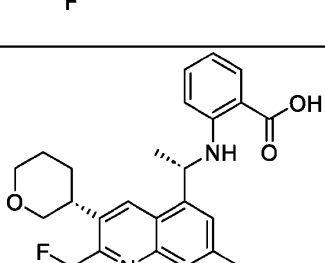
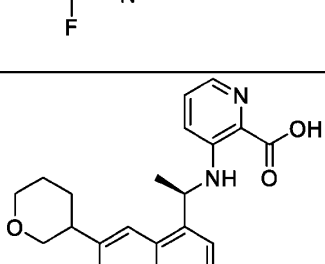
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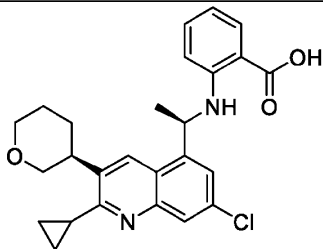
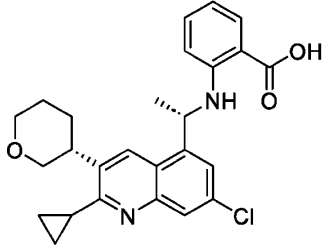
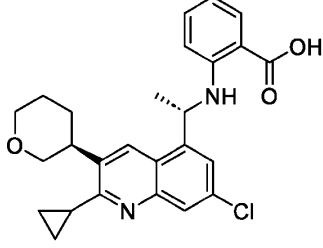
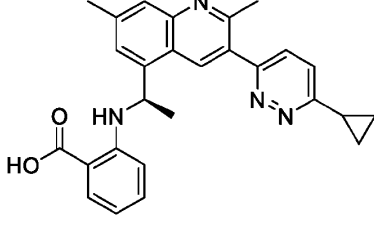
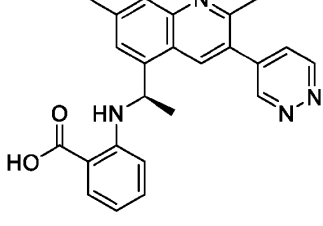
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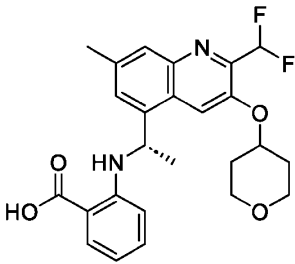
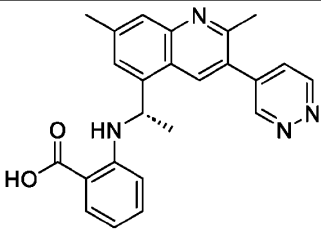
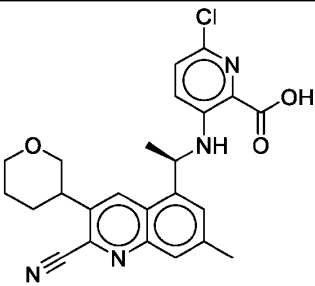
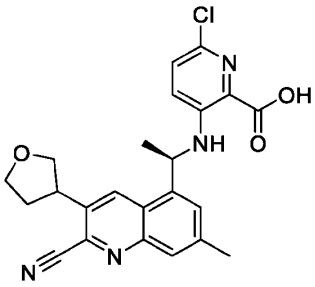
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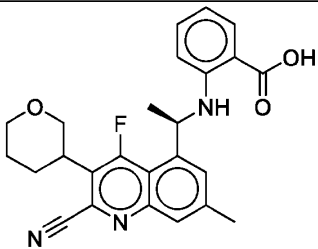
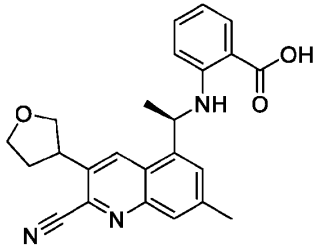
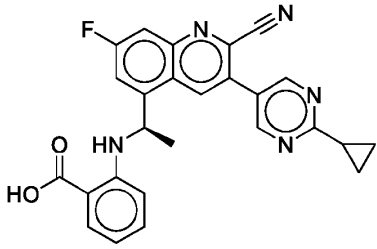
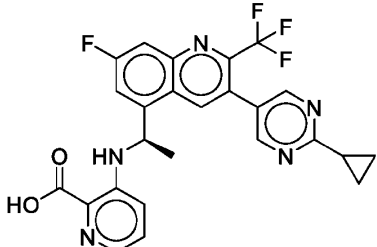
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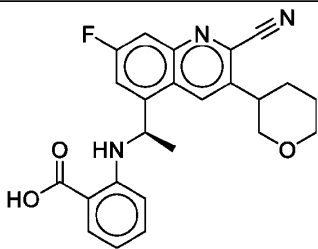
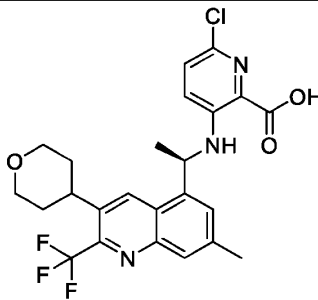
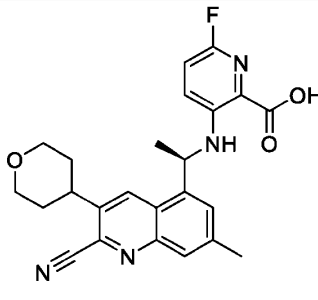
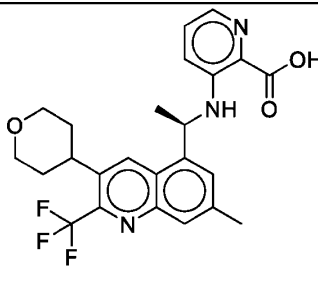
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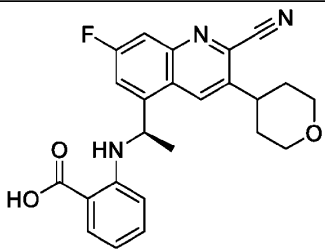
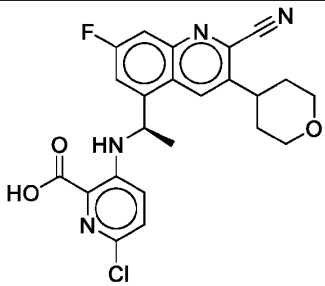
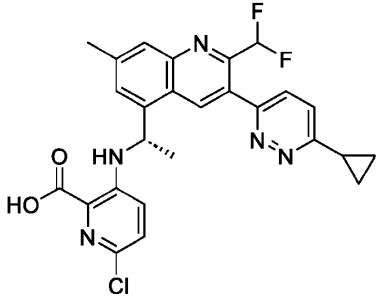
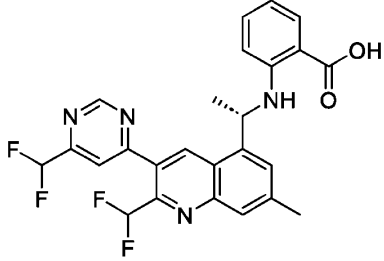
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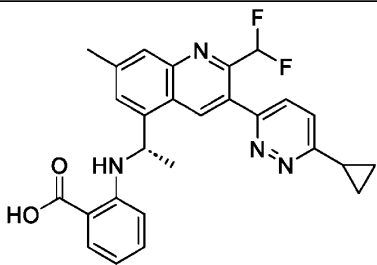
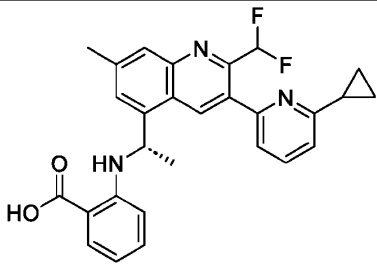
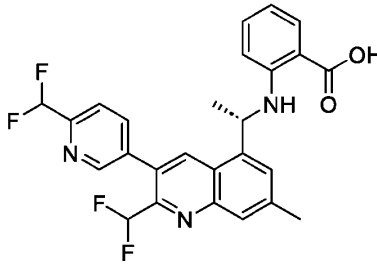
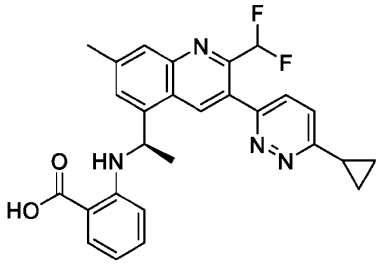
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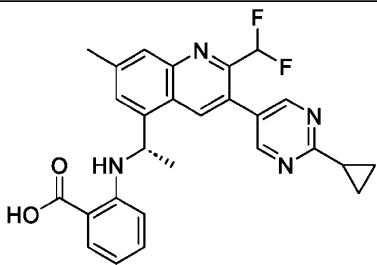
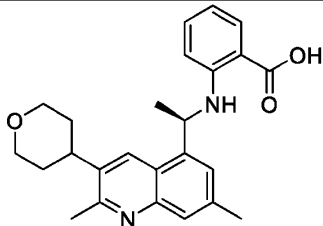
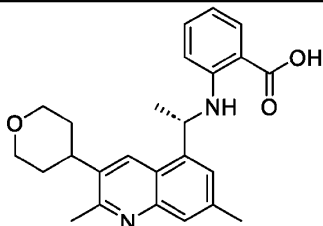
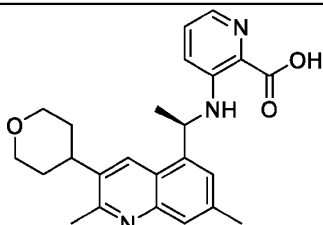
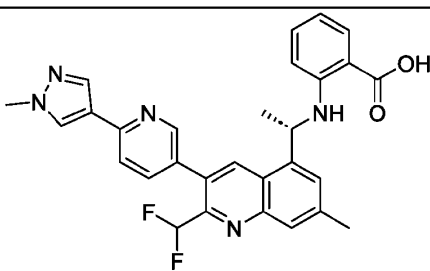
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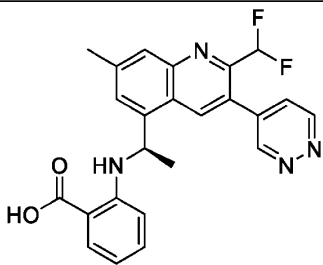
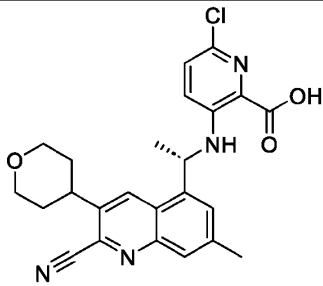
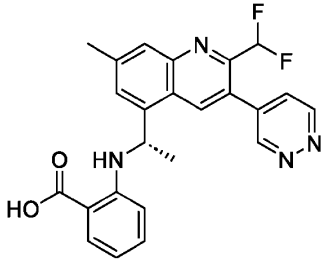
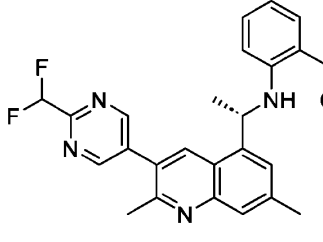
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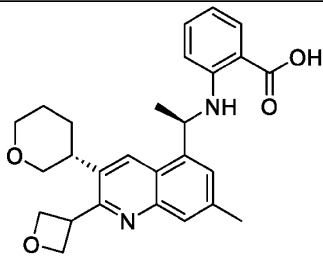
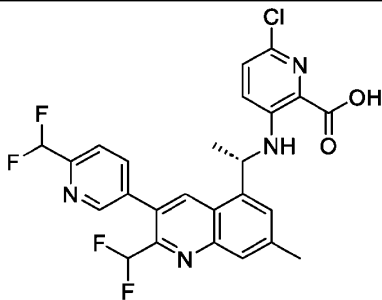
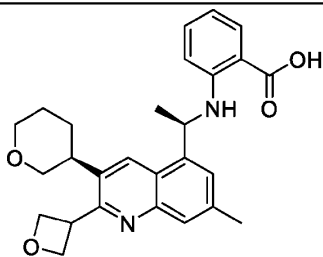
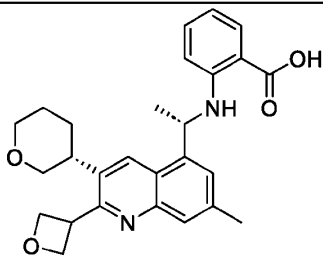
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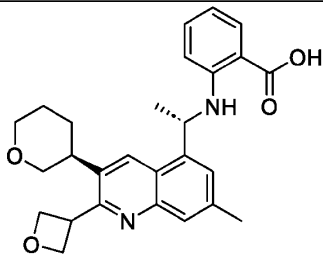
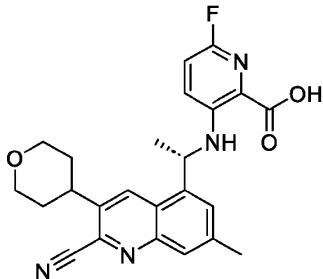
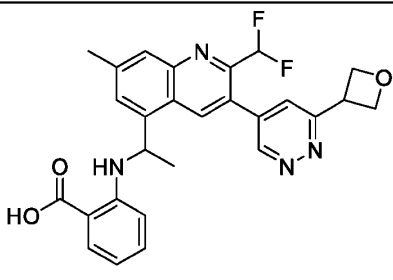
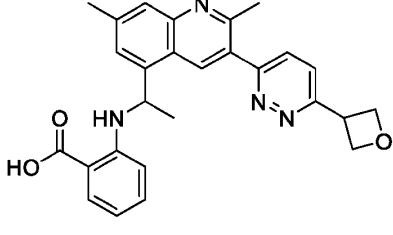
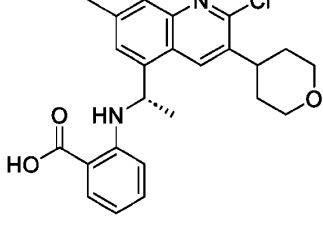
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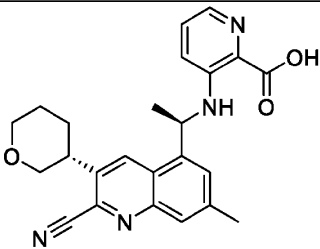
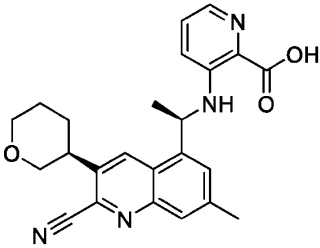
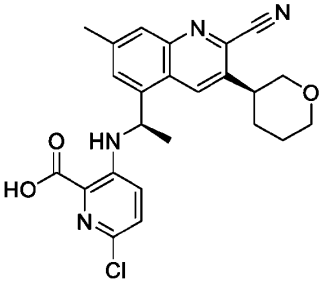
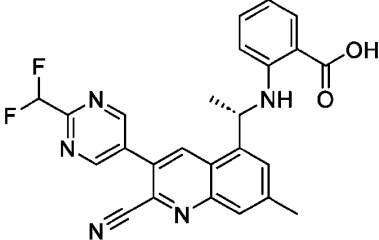
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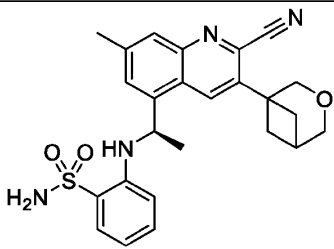
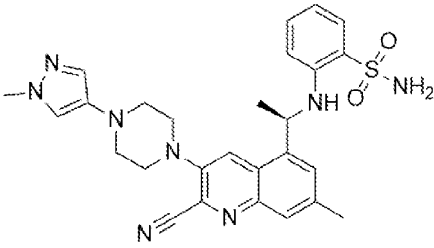
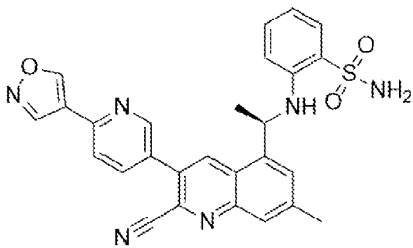
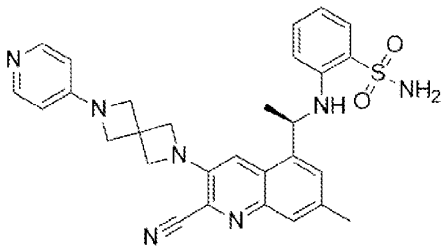
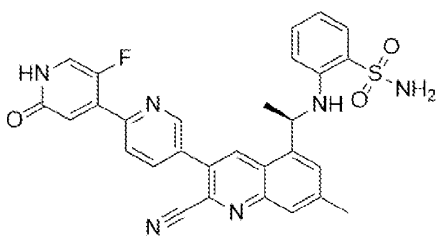
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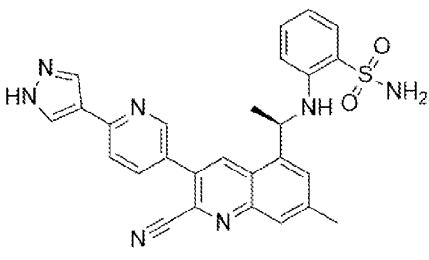
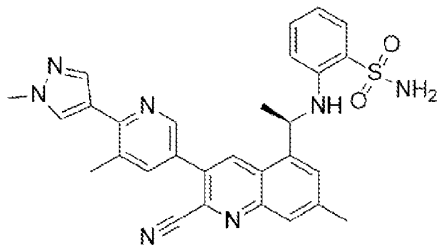
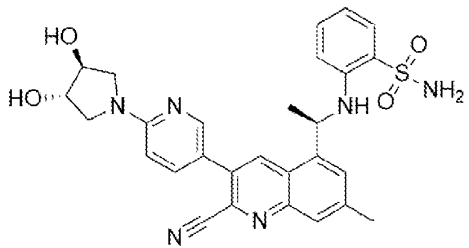
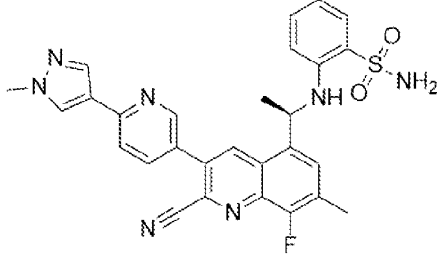
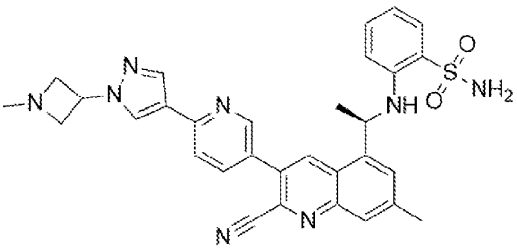
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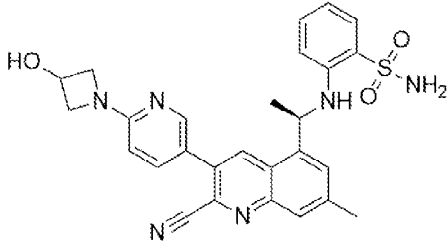
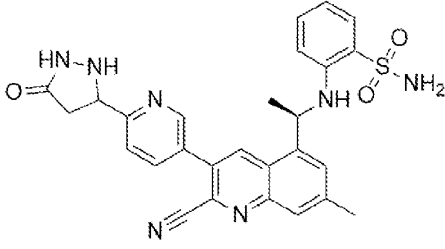
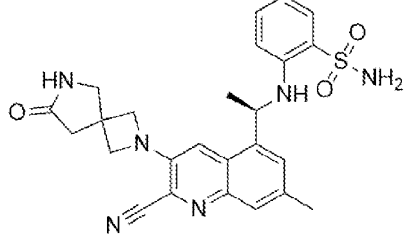
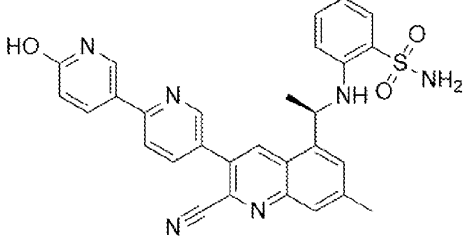
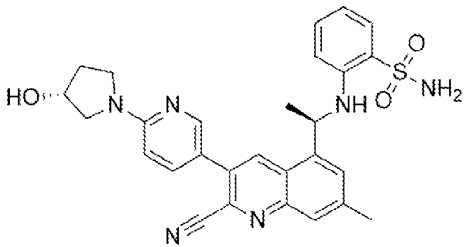
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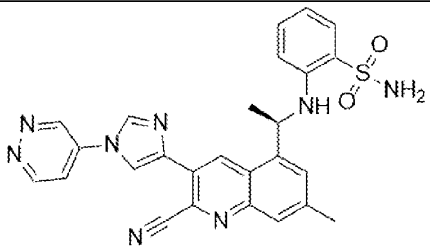
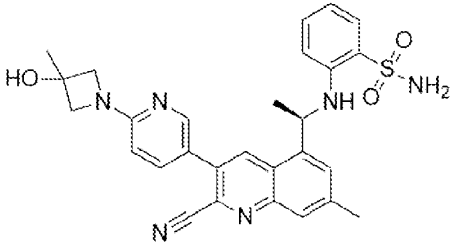
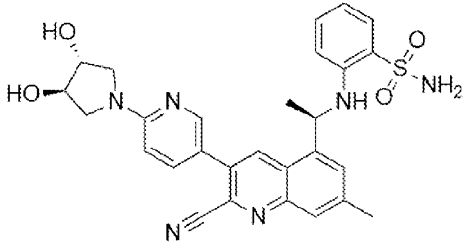
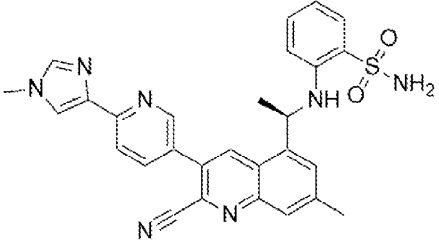
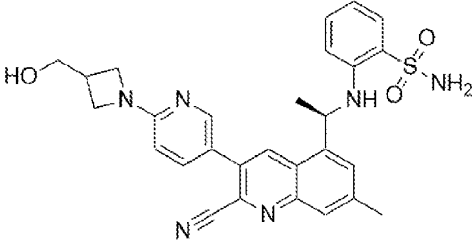
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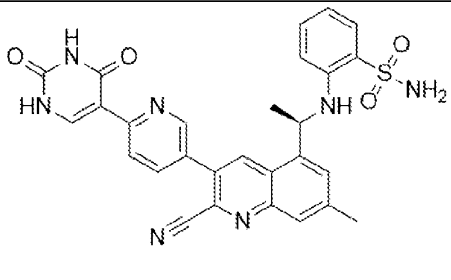
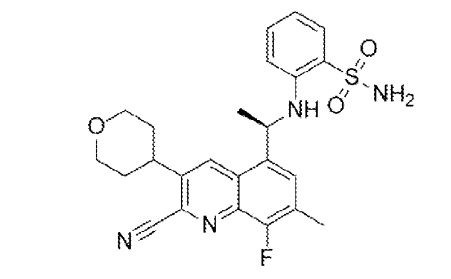
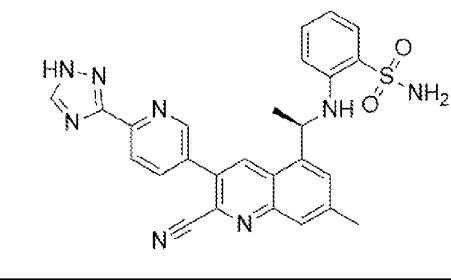
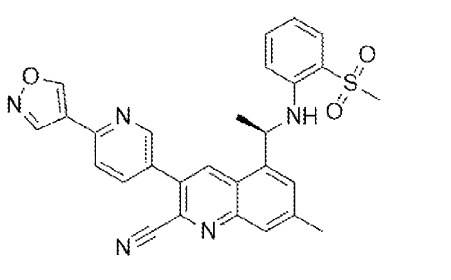
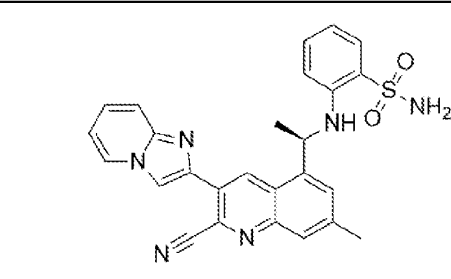
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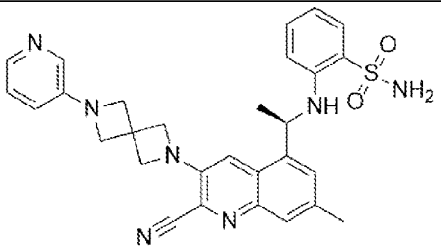
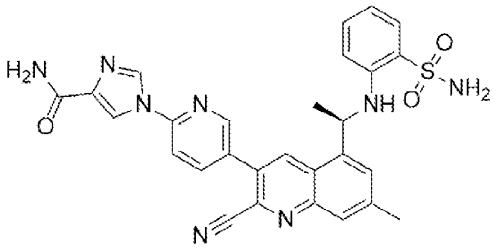
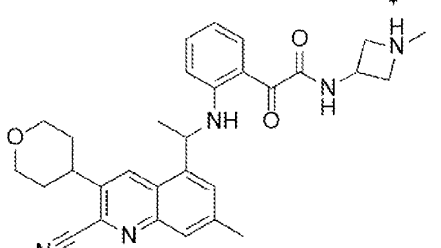
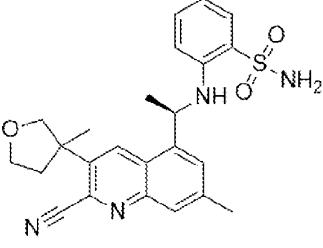
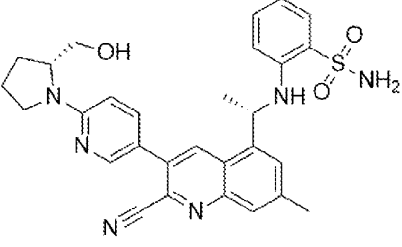
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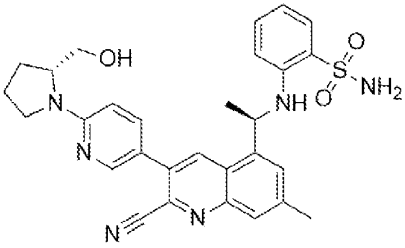
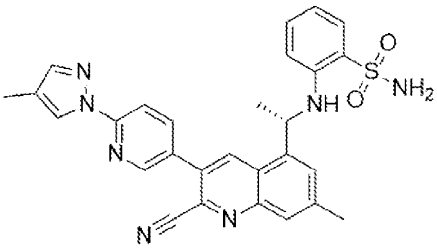
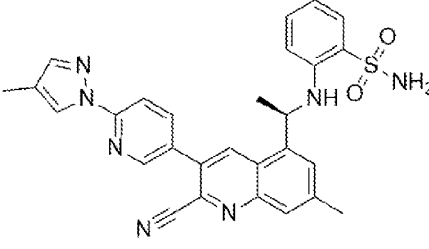
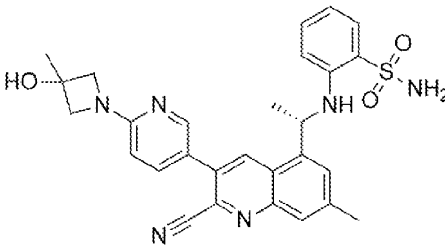
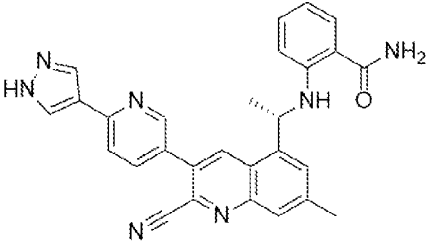
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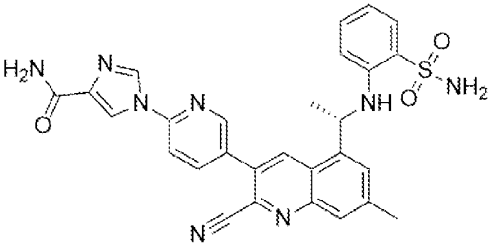
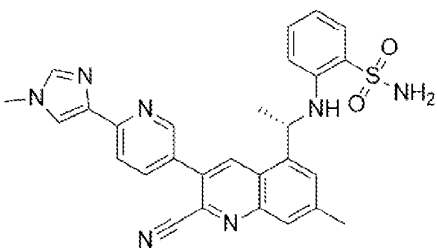
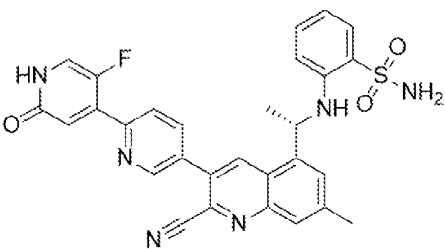
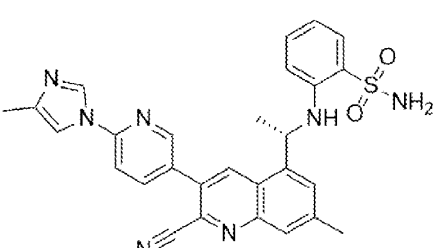
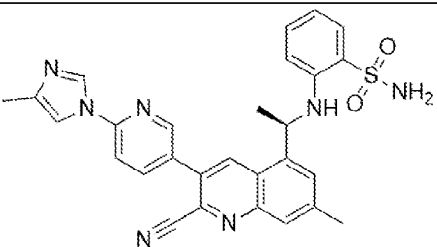
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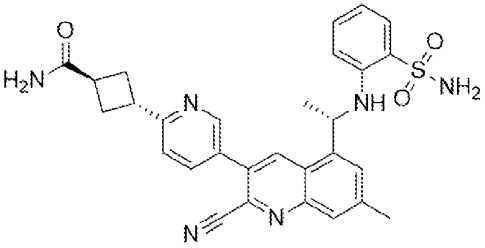
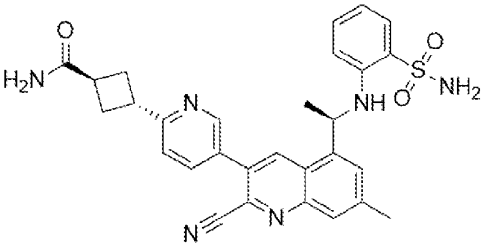
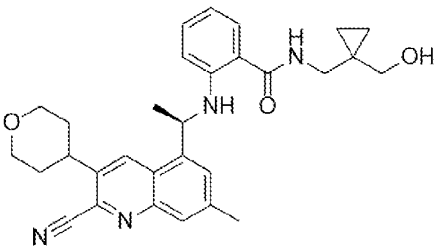
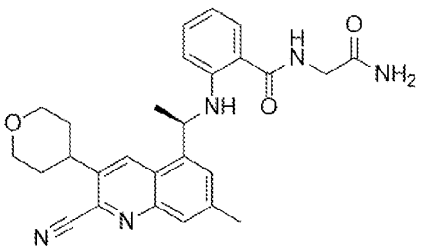
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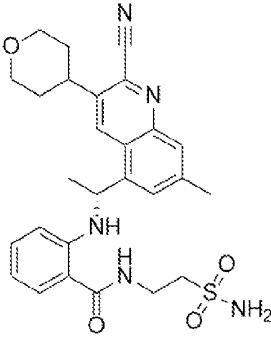
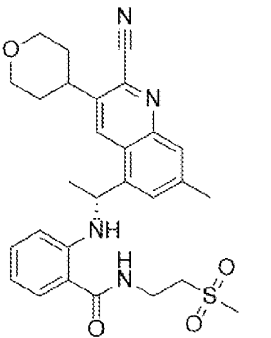
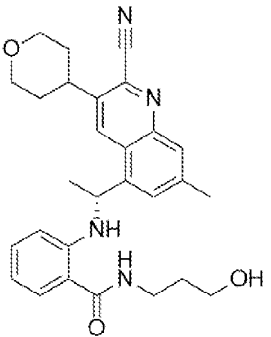
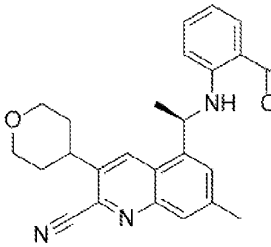
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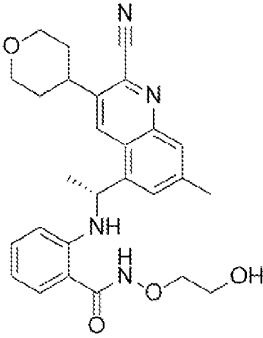
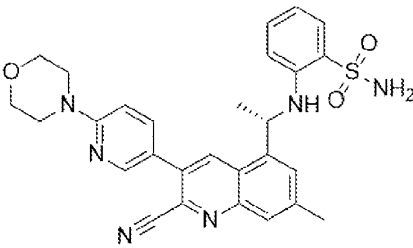
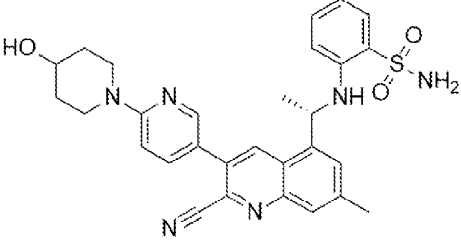
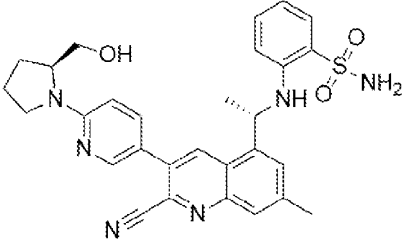
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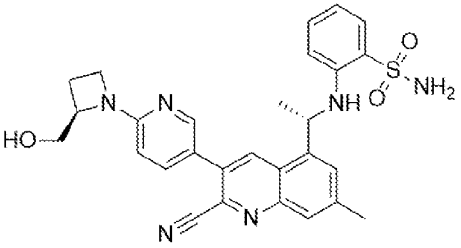
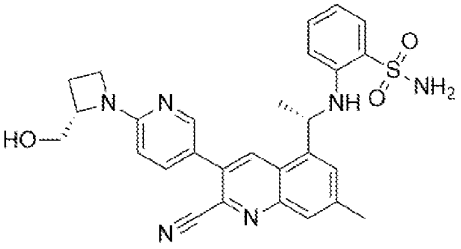
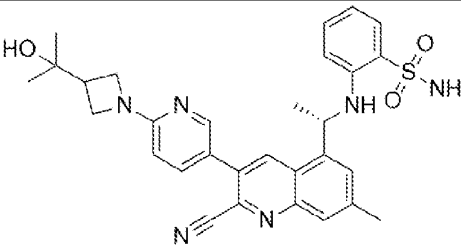
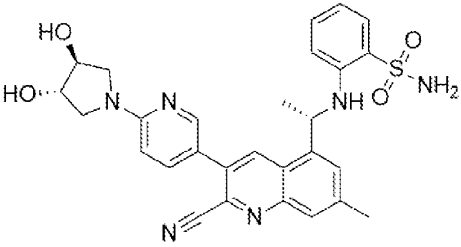
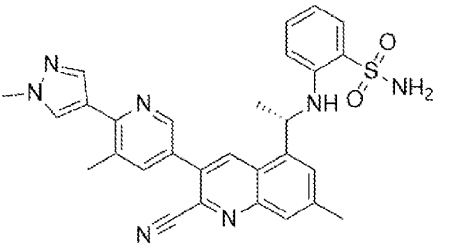
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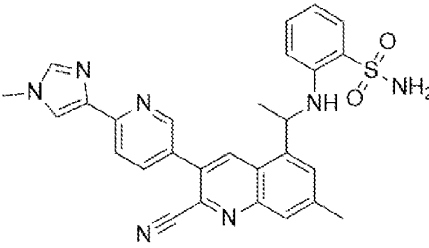
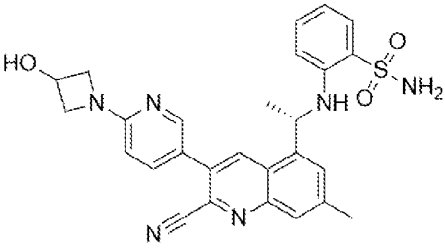
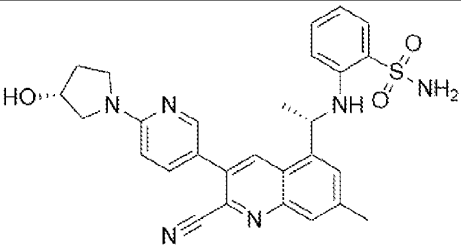
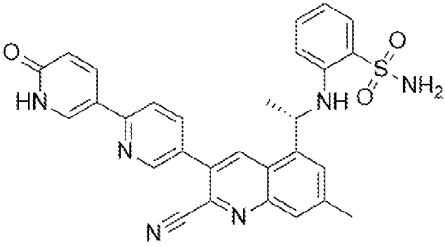
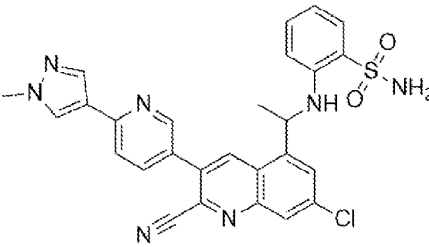
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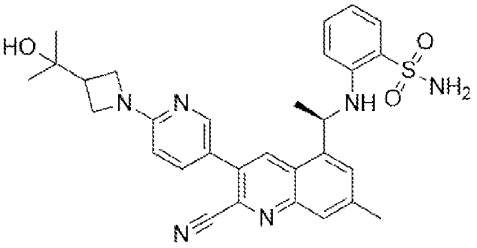
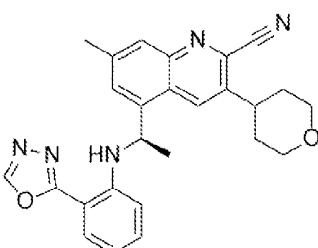
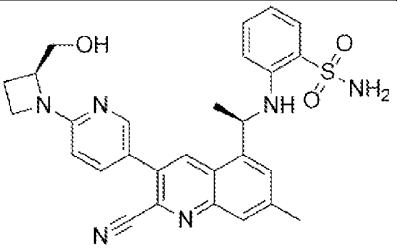
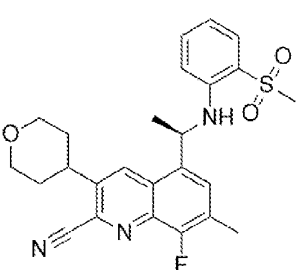
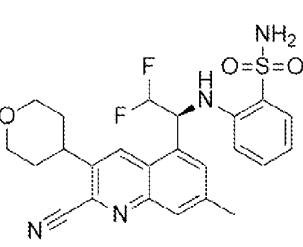
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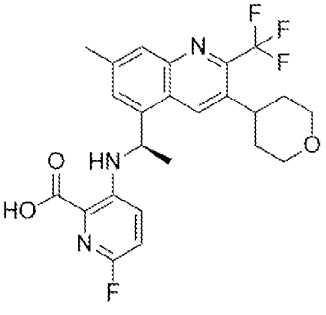
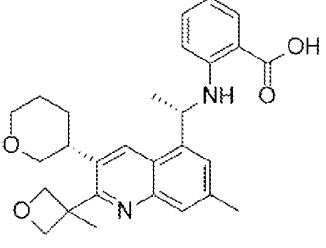
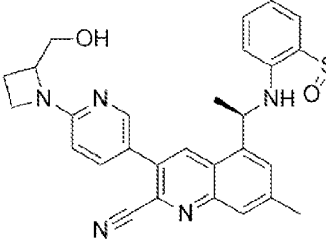
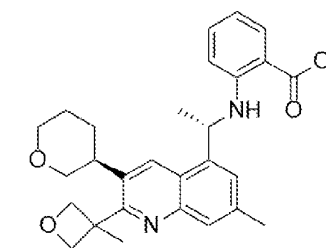
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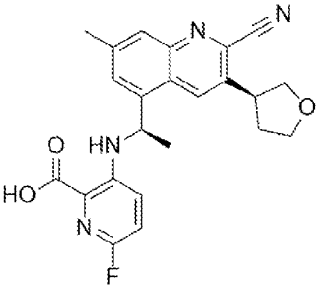
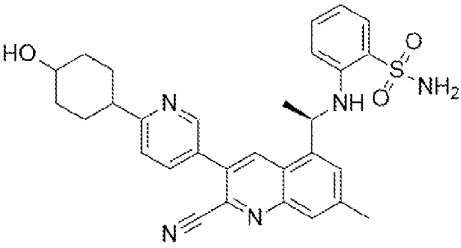
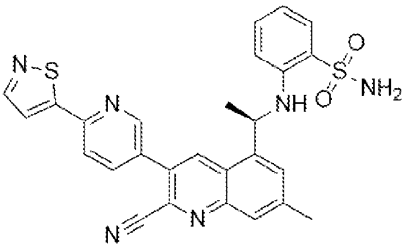
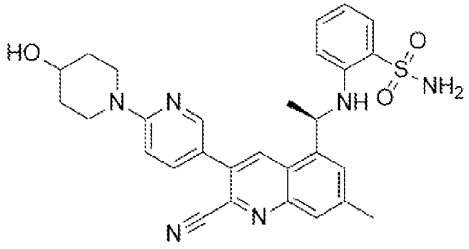
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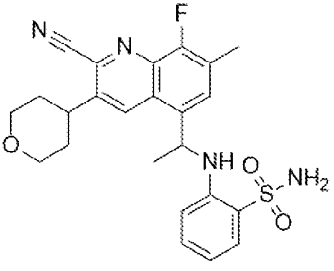
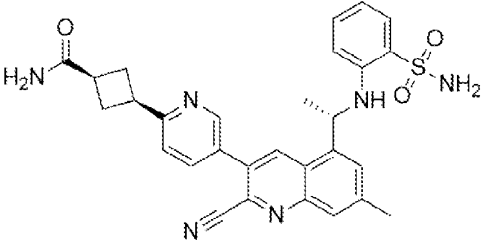
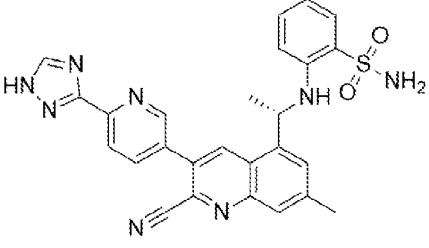
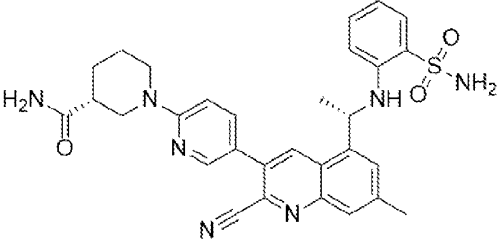
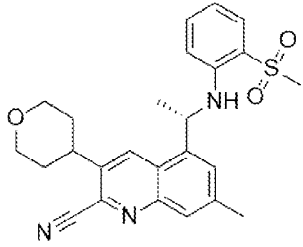
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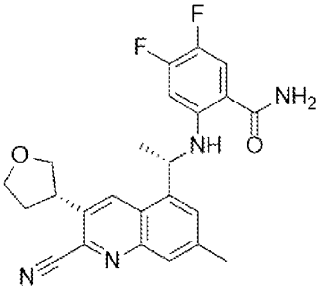
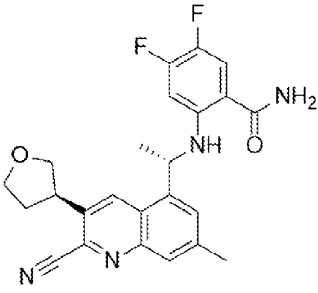
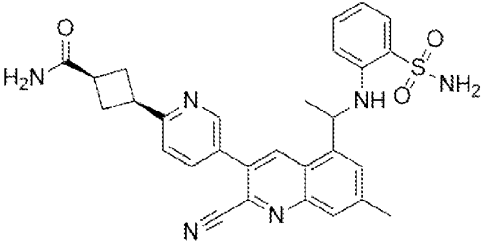
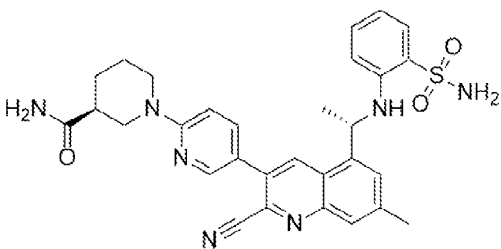
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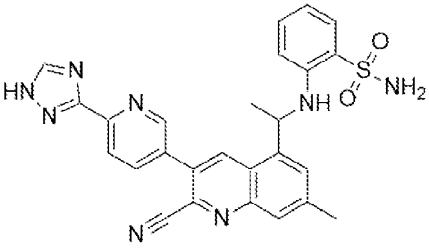
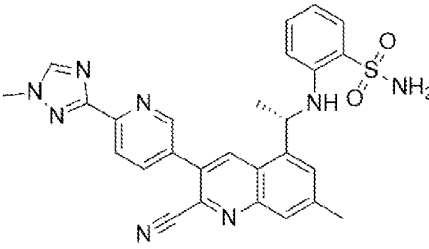
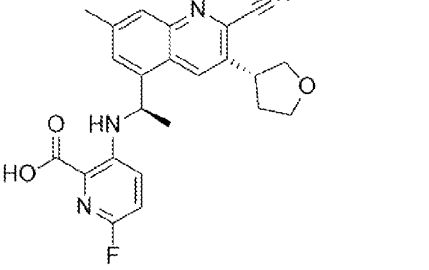
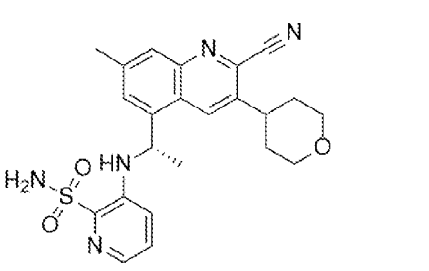
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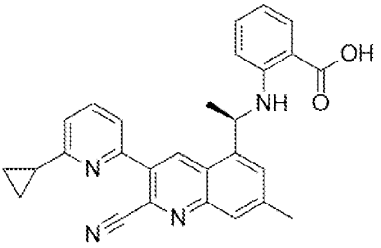
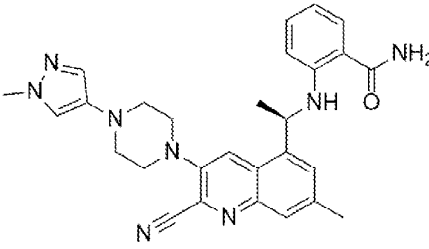
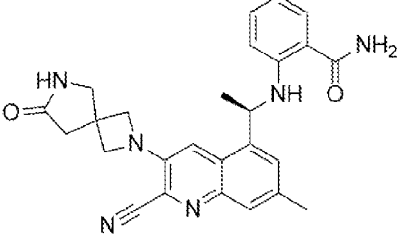
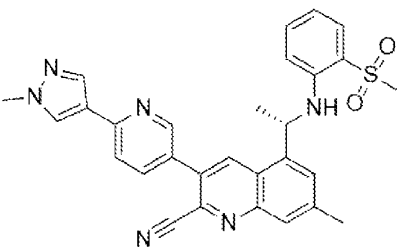
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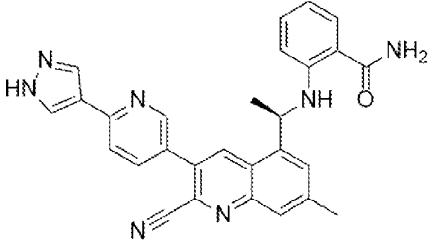
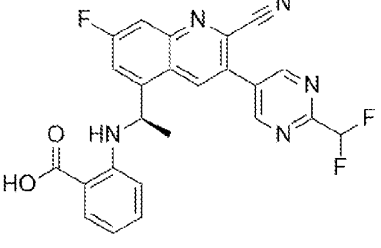
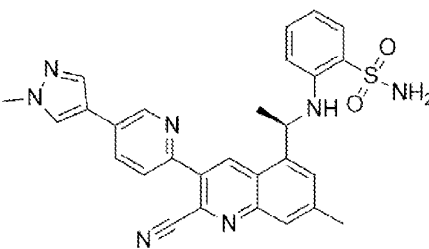
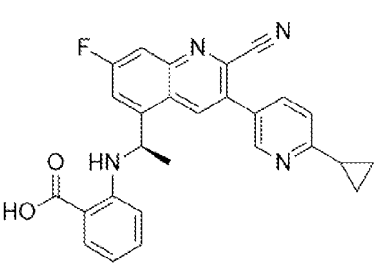
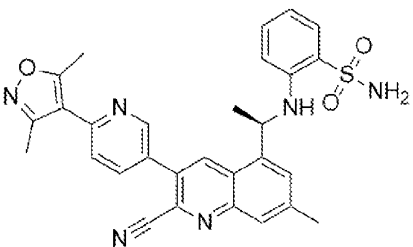
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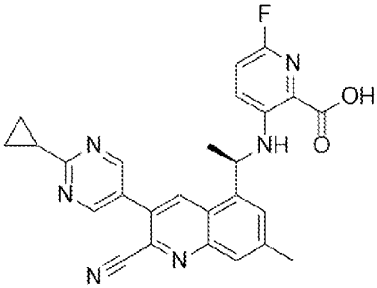
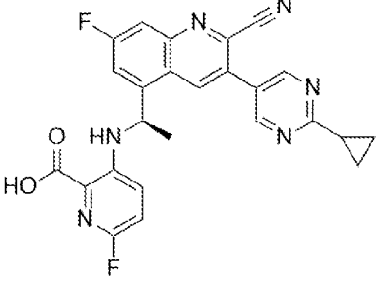
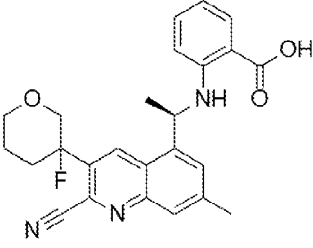
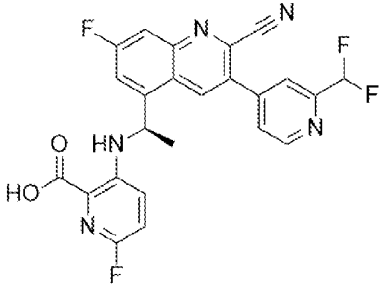
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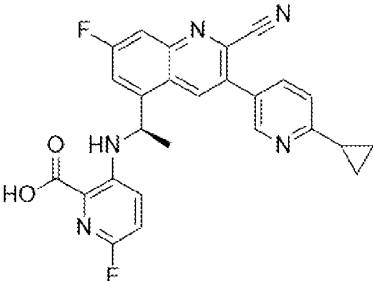
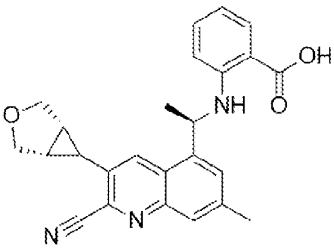
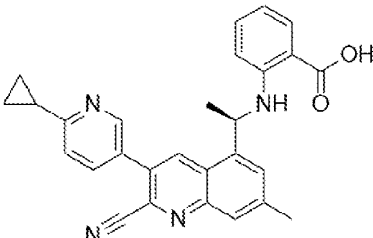
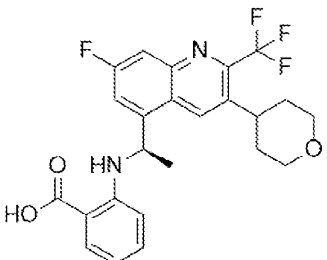
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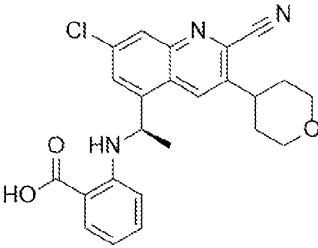
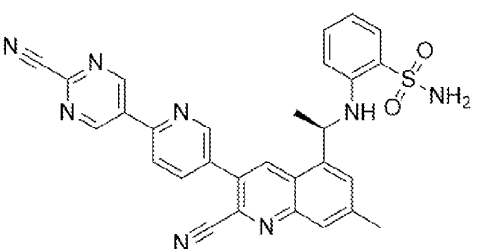
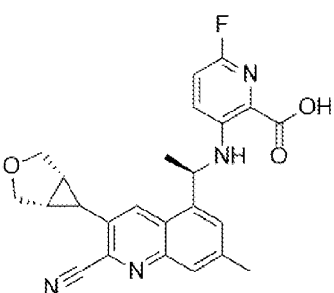
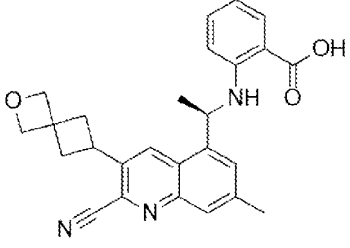
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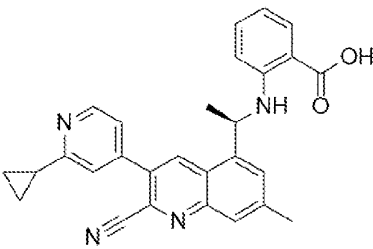
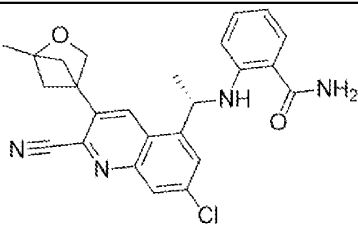
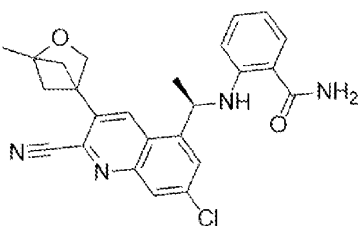
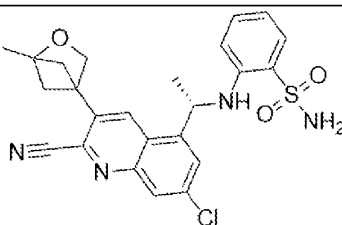
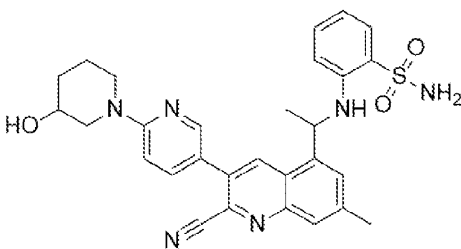
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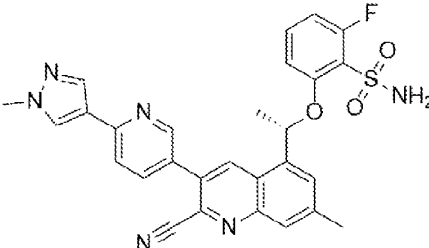
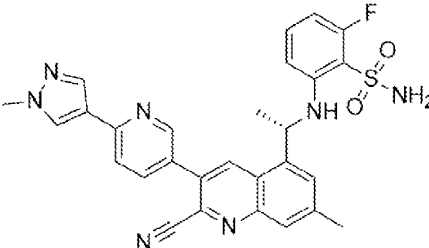
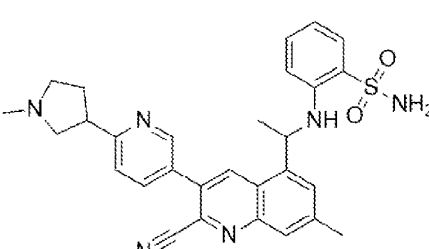
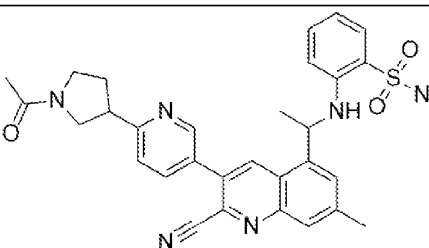
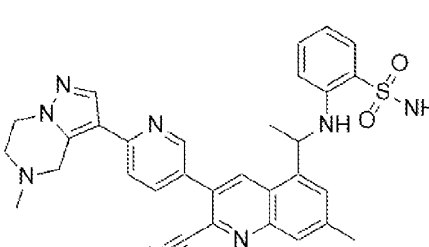
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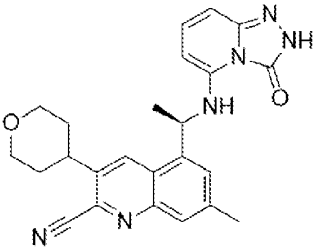
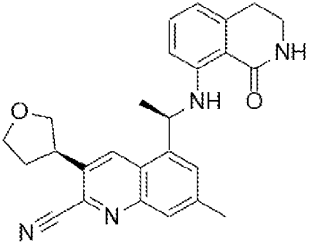
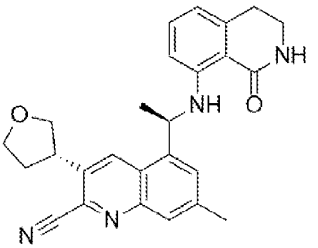
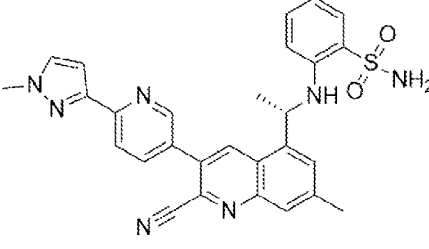
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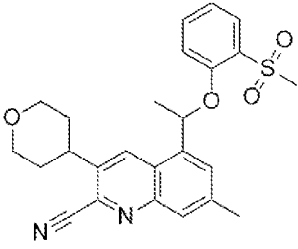
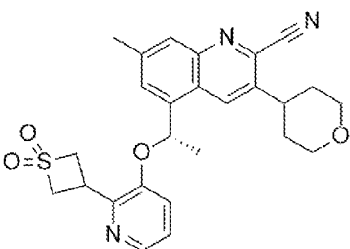
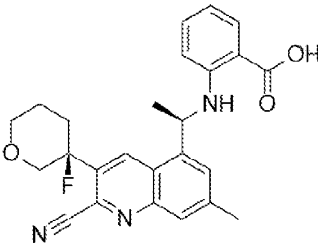
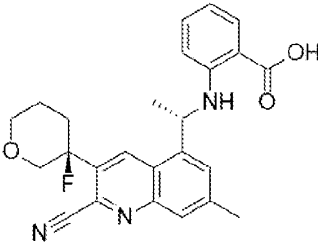
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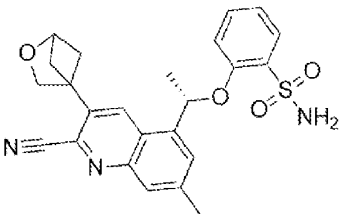
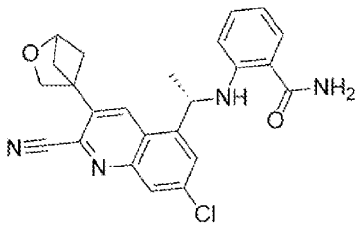
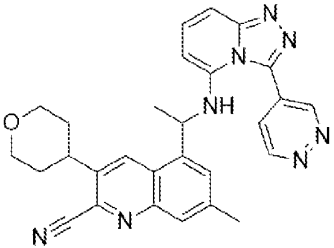
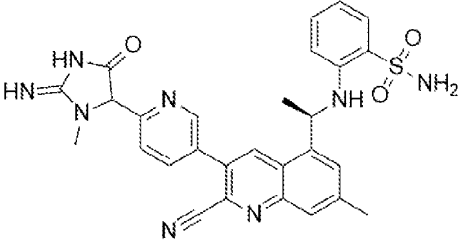
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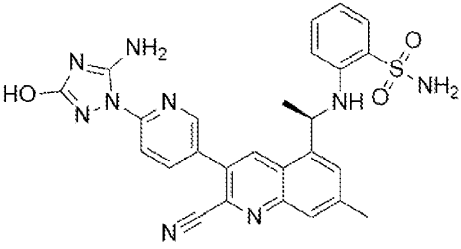
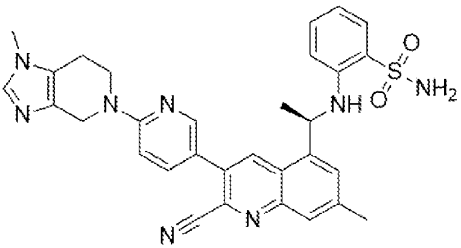
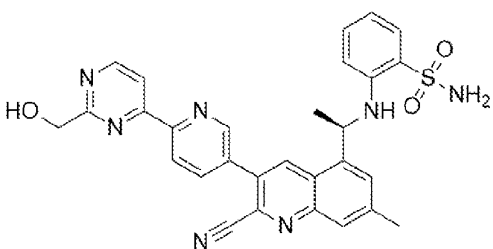
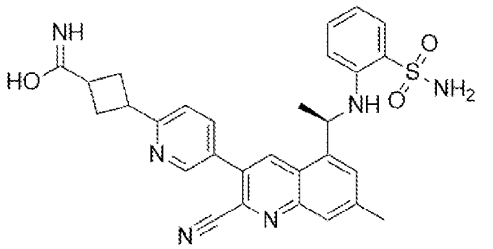
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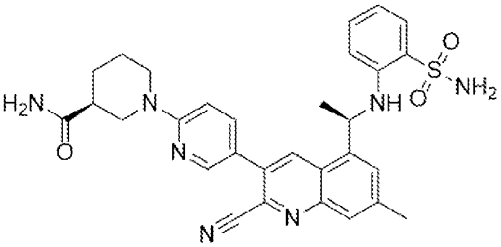
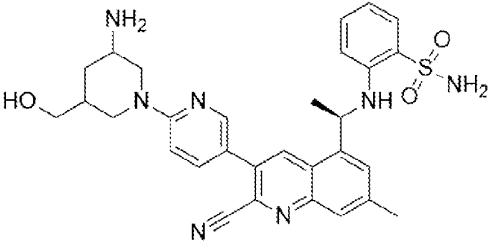
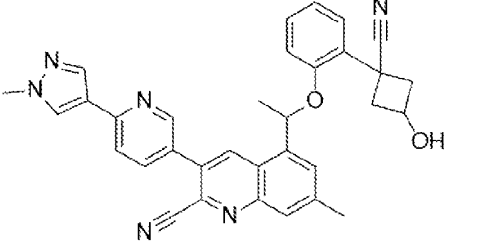
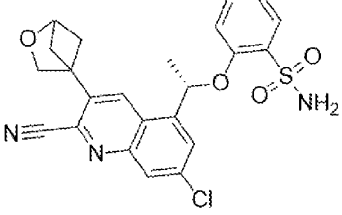
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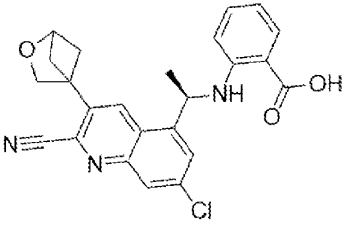
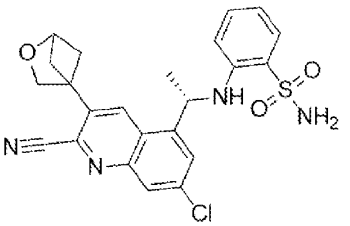
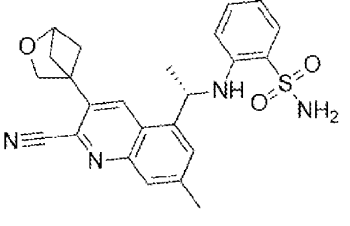
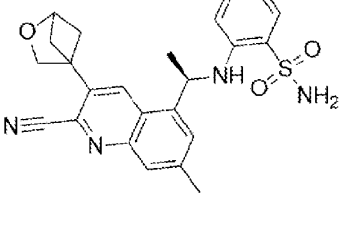
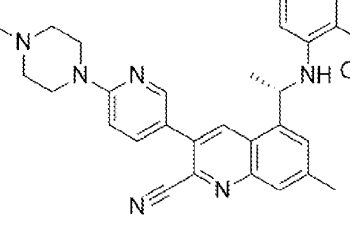
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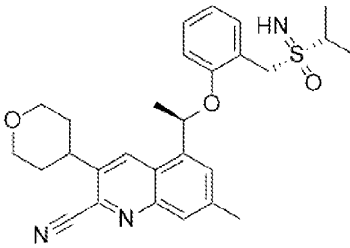
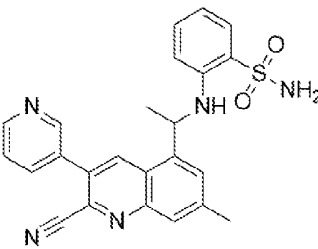
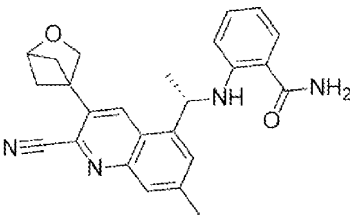
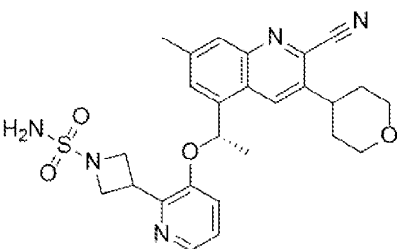
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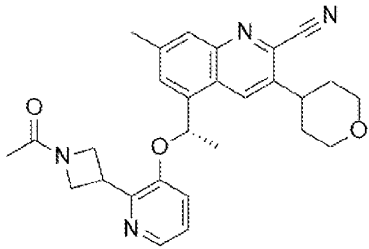
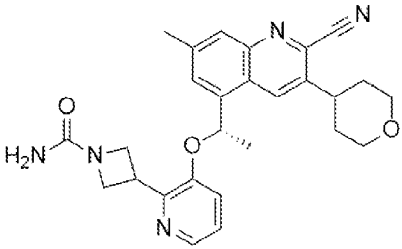
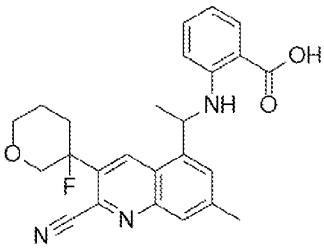
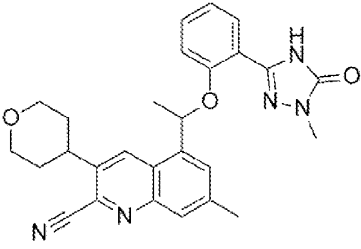
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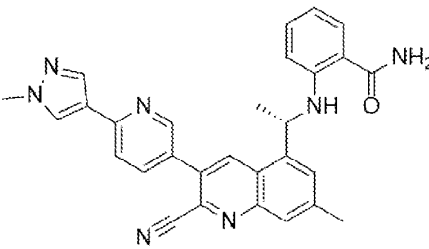
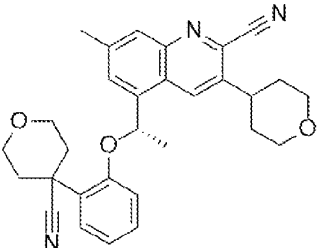
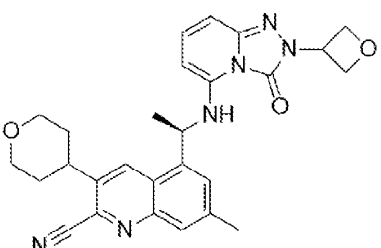
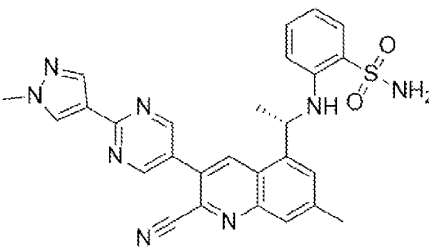
334	 <chem>Nc1nc(O)n(n1)-c2ccc(cc2-c3nc4cc(C)cc(C4)nc3C#N)C5=CC=CC=C5S(=O)(=O)N</chem>
335	 <chem>Nc1cc2cc(C)cc(C2)nc1C#N-c3ccc(cc3N4CCNCC4)C5=CC=CC=C5S(=O)(=O)N</chem>
336	 <chem>OCc1nc2cc(C)cc(C2)nc1C#N-c3ccc(cc3N4=CC=CC=C4S(=O)(=O)N)C5=CC=CC=C5S(=O)(=O)N</chem>
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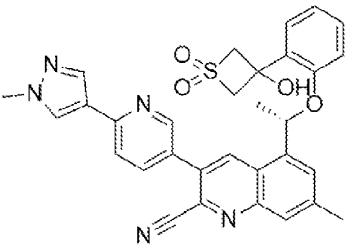
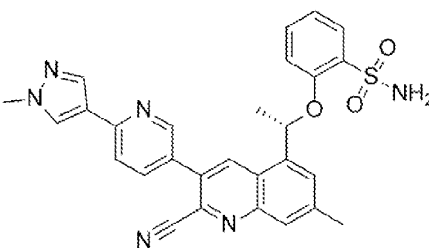
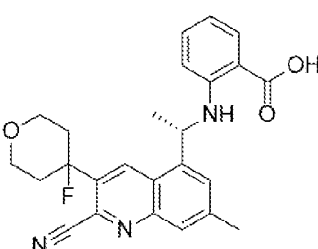
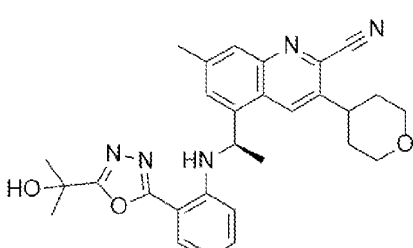
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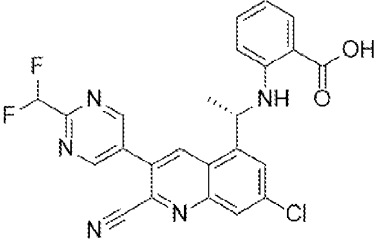
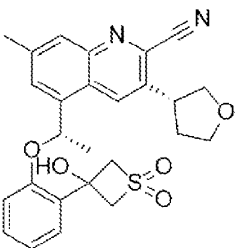
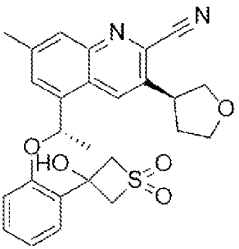
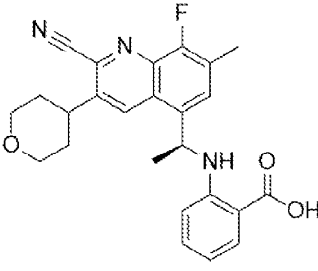
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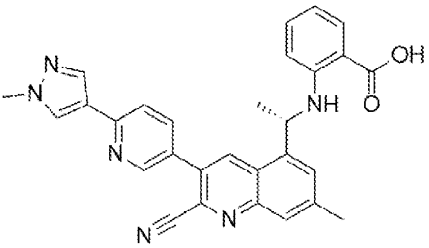
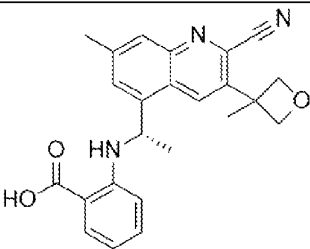
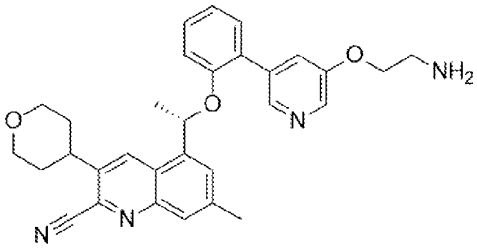
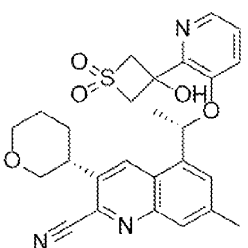
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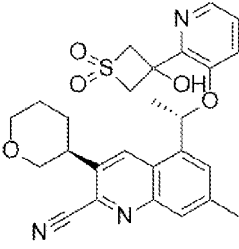
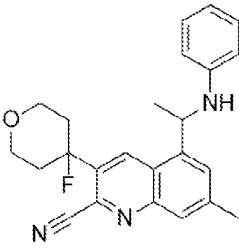
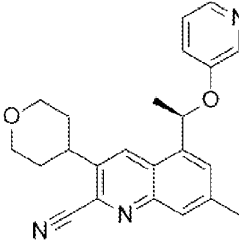
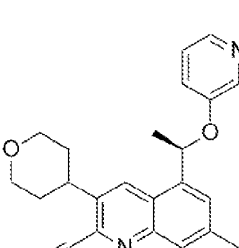
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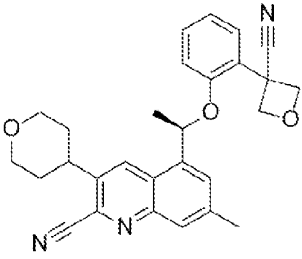
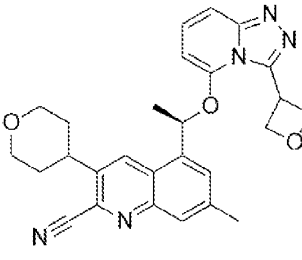
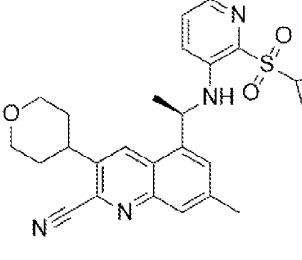
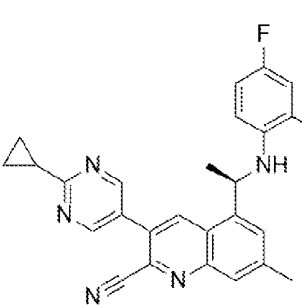
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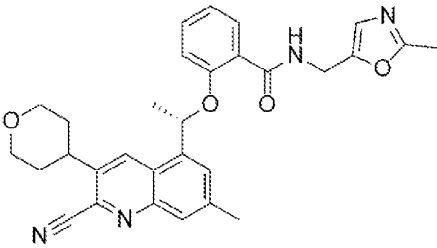
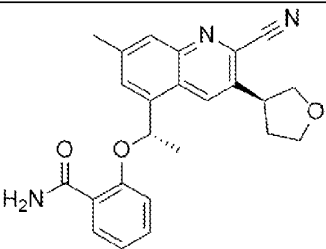
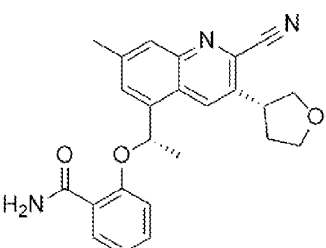
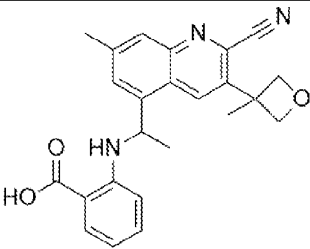
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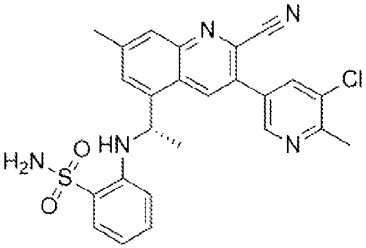
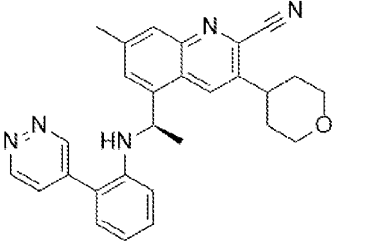
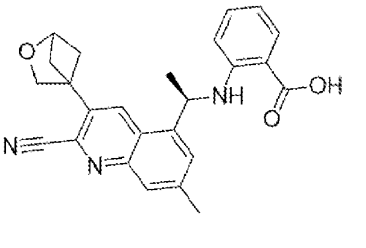
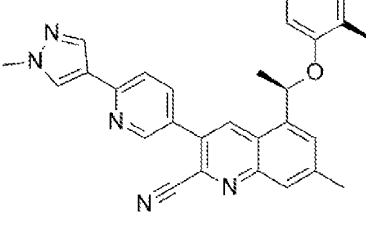
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365	 <chem>CC1=CC=C2C(=C1)N(C#N)C(C2)C3CCOC3C(=O)N(C4C(=O)O[C@H](C4)C5=CC=CC=C5)S(=O)(=O)C6=CC=CC=C6</chem>
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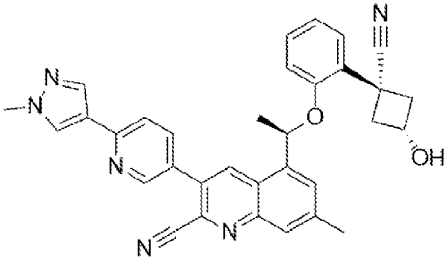
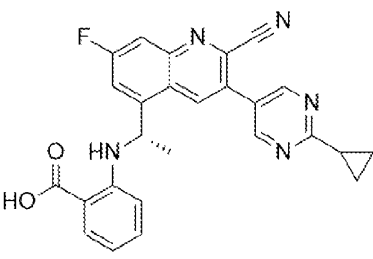
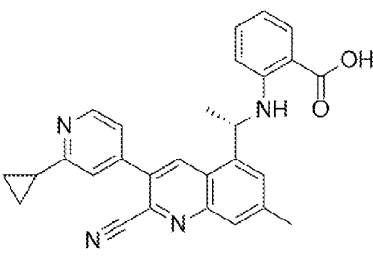
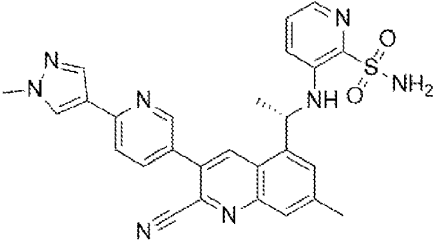
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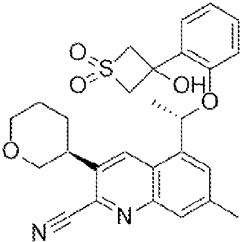
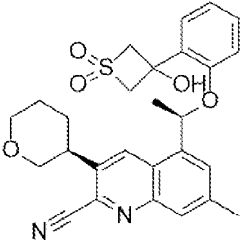
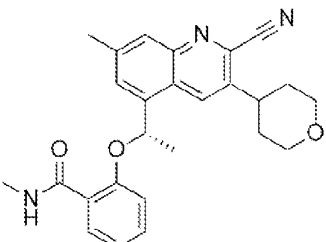
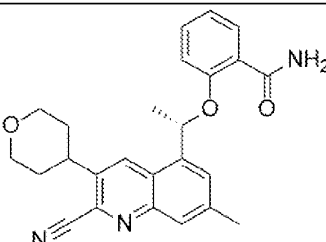
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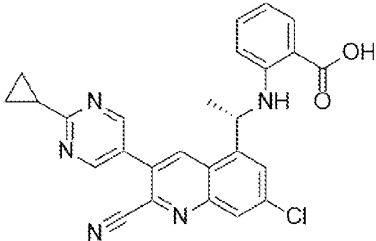
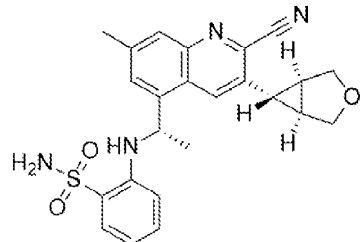
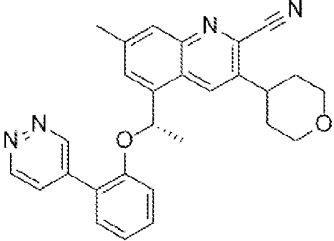
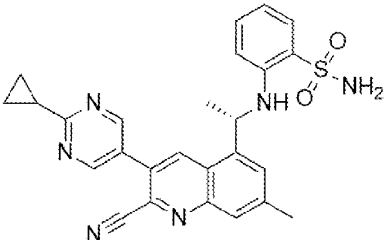
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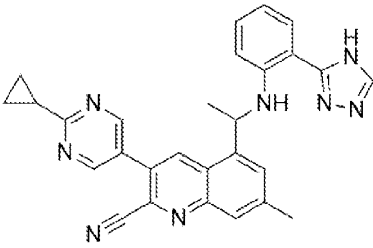
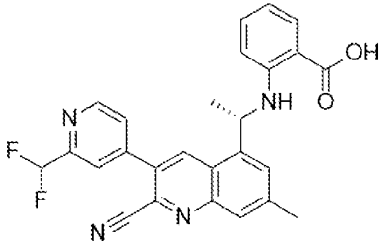
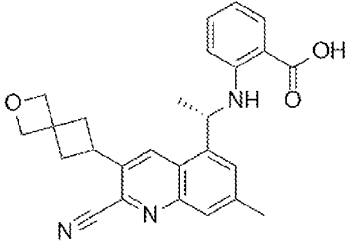
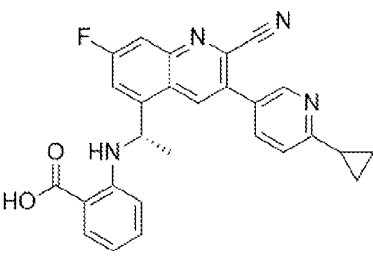
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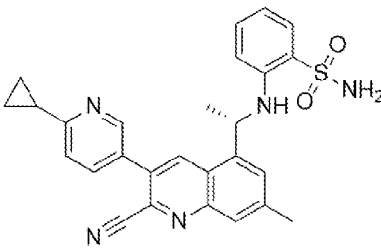
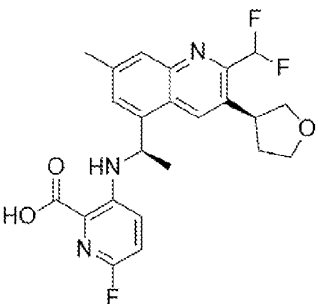
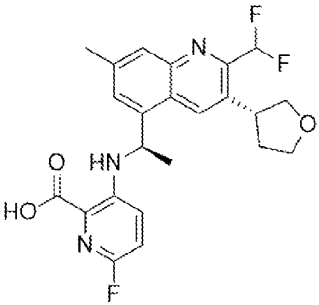
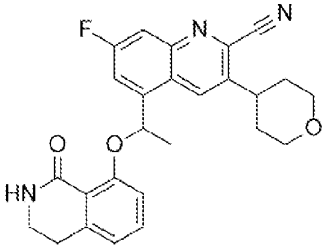
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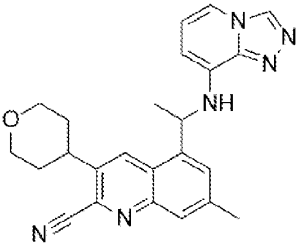
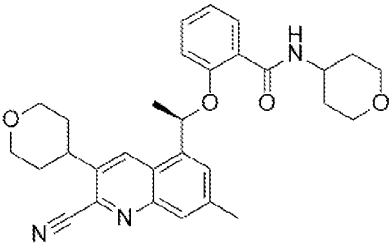
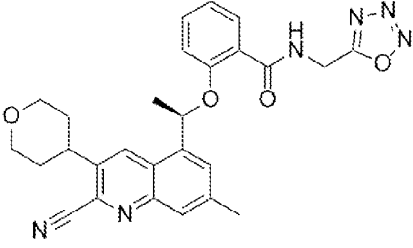
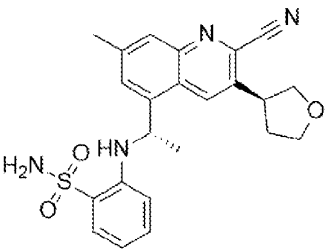
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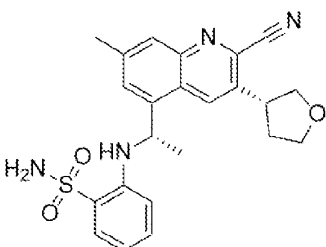
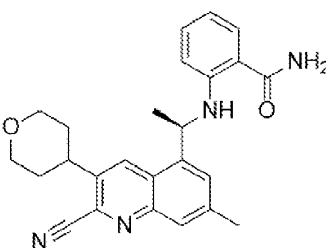
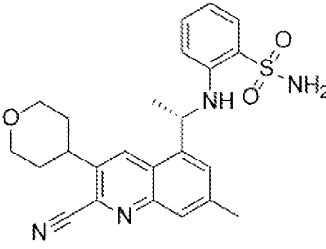
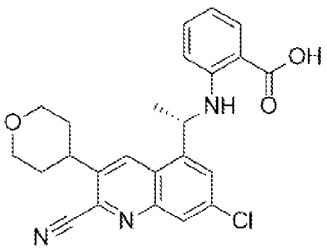
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397	 <chem>Cc1ccc2c(c1)c(cnc2C(COCC3OCCO3)Nc4ccccc4c5nncc5)C#N</chem>
398	 <chem>Cc1ccc2c(c1)c(cnc2C(c3ccccc3S(=O)(=O)N)Nc4ccccc4C(=O)O)C#N</chem>

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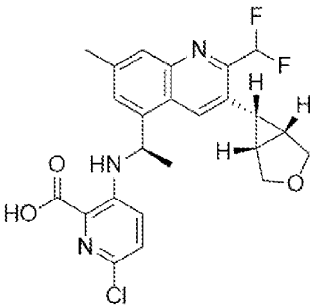
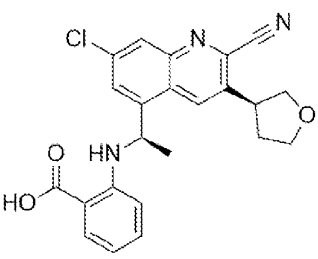
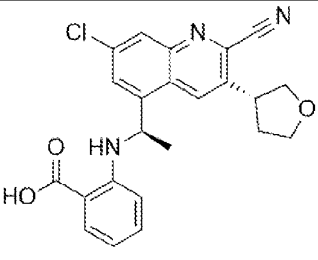
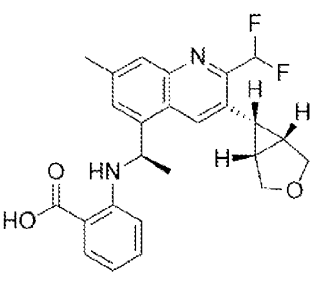
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404	 <chem>Cc1ccc2nc(C#N)c(c3ccccc23)C[C@@H](COc4ccccc4S(=O)(=O)N)n1</chem>
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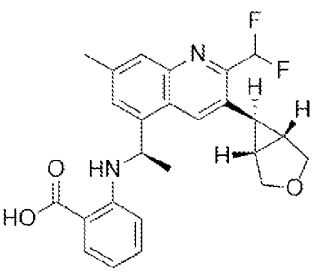
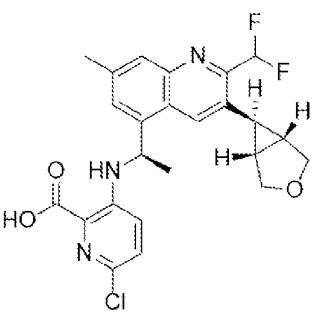
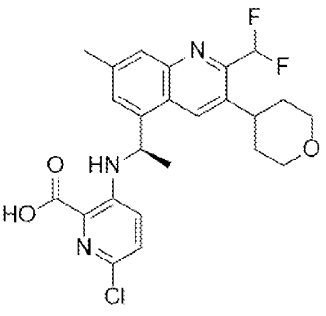
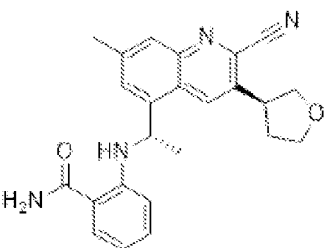
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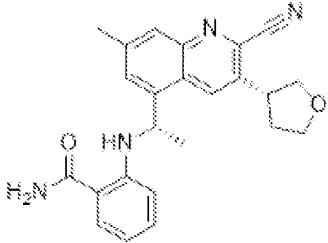
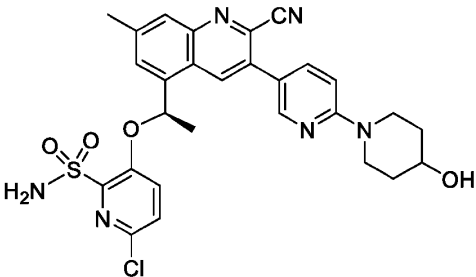
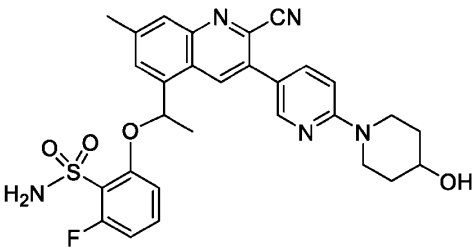
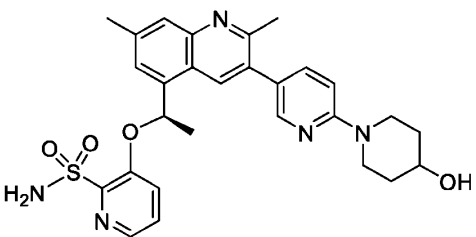
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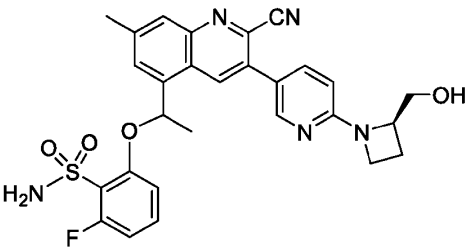
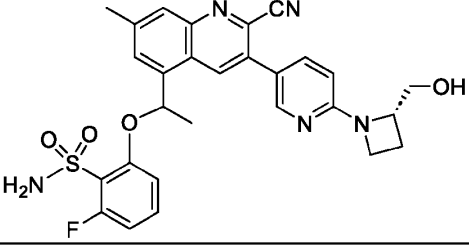
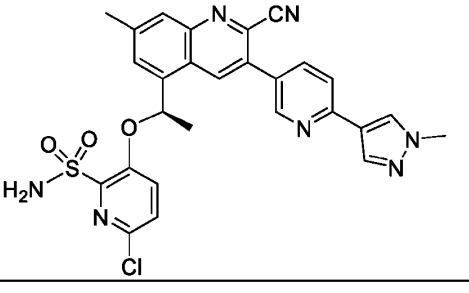
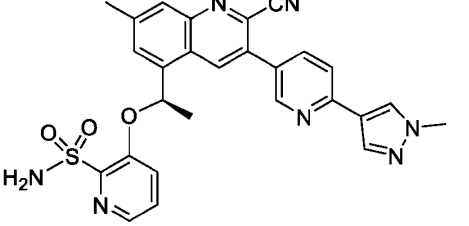
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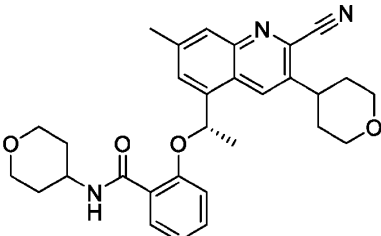
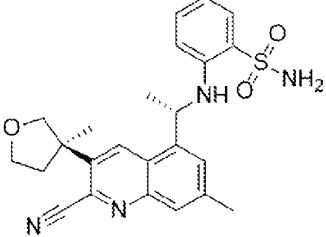
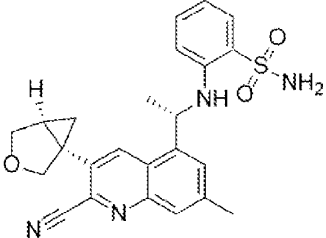
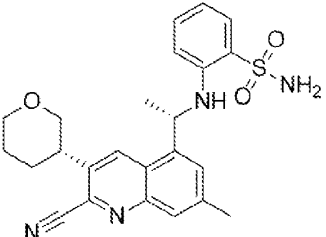
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420	 <chem>CC1=CC=C2C(=C1)N(C=C2)C(C#N)C(C(=O)O)NC3=CC=CC=C3C4=CC=CC=C4O4</chem>
421	 <chem>CC1=CC=C2C(=C1)N(C=C2)C(C#N)C(C(=O)O)NC3=CC=CC=C3C4=CC=CC=C4O4</chem>
422	 <chem>CC1=CC=C2C(=C1)N(C=C2)C(C#N)C(C(=O)O)NC3=CC=CC=C3C4=CC=CC=C4O4</chem>

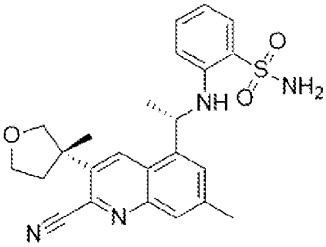
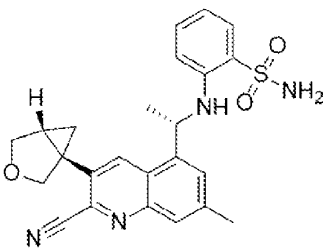
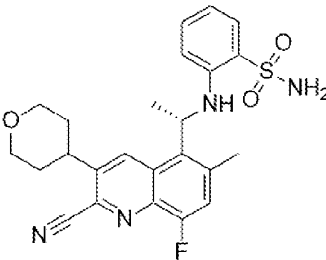
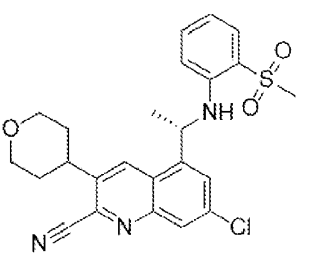
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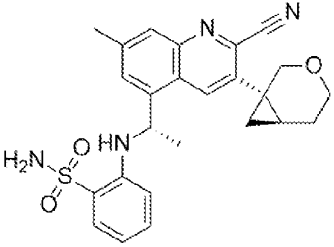
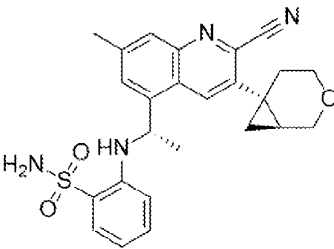
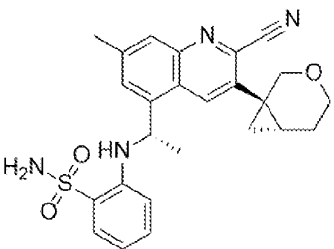
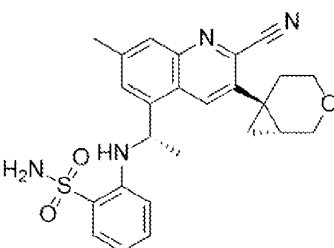
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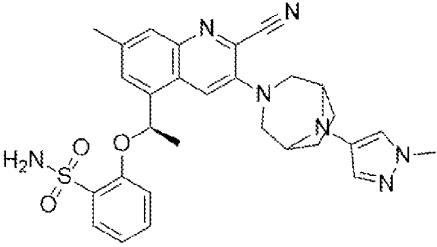
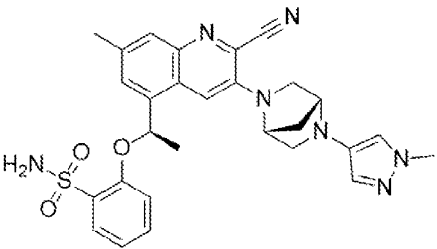
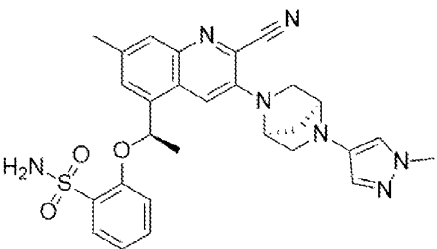
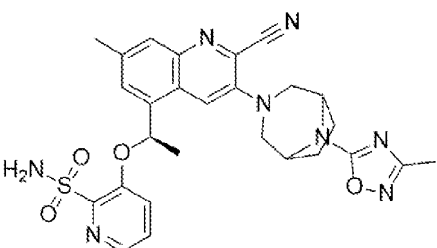
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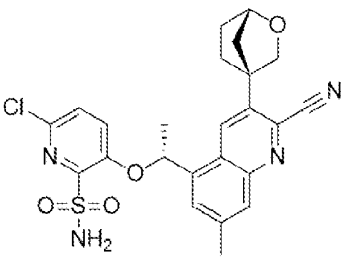
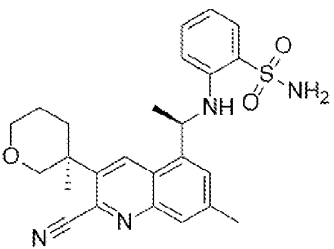
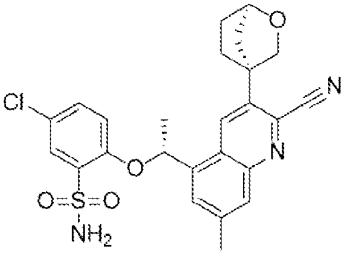
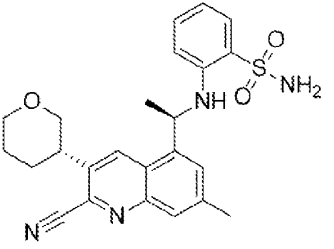
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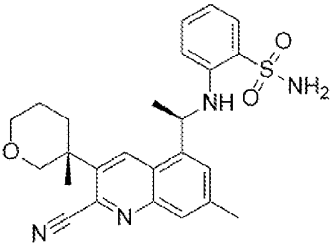
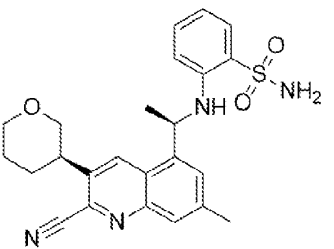
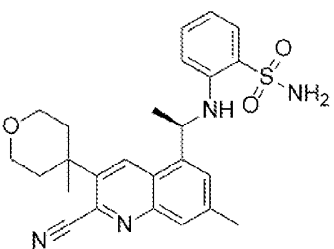
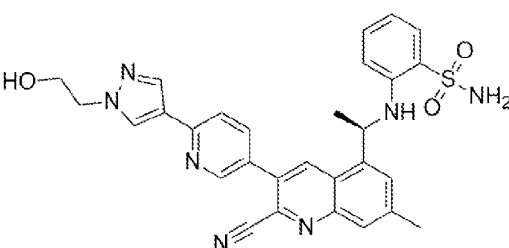
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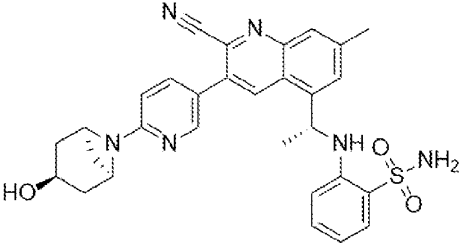
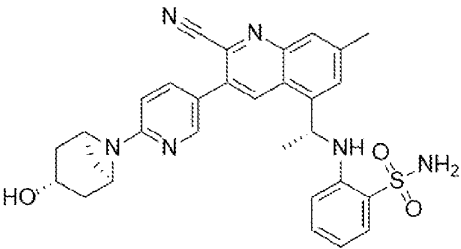
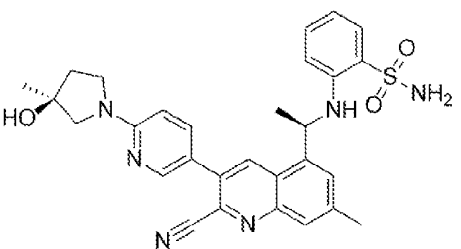
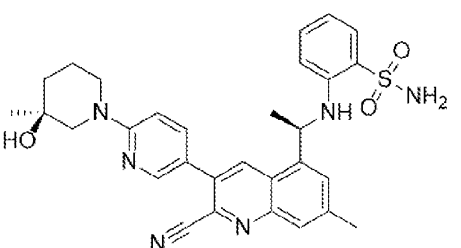
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448	 <chem>Cc1cc(cc2nc(C#N)c(C3CCOCC3)C2c1)C[C@@H](N3CCOC3)C(=O)NS(=O)(=O)c4ccccc4F</chem>
449	 <chem>Cc1cc(cc2nc(C#N)c(C3CCOCC3)C2c1)C[C@@H](N3CCOC3)C(=O)NS(=O)(=O)c4ccccc4Cl</chem>

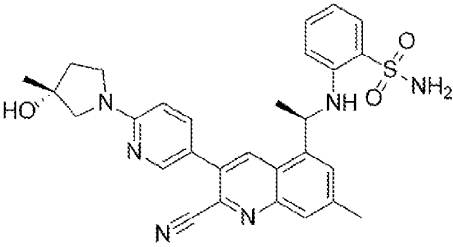
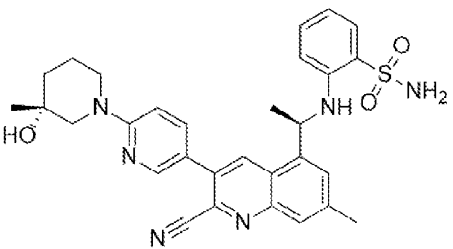
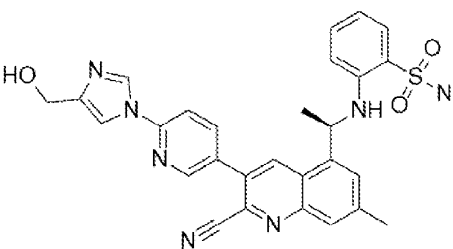
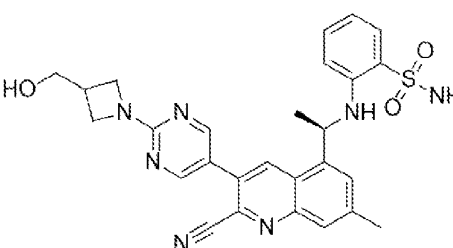
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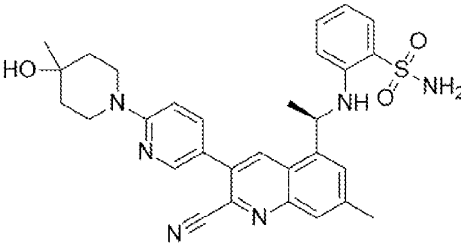
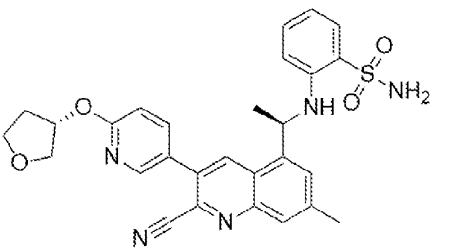
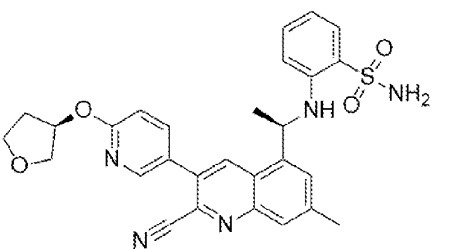
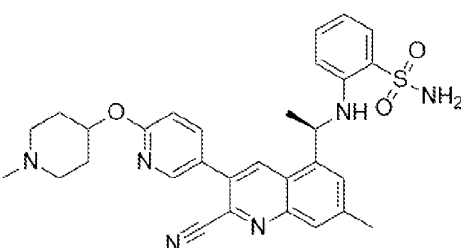
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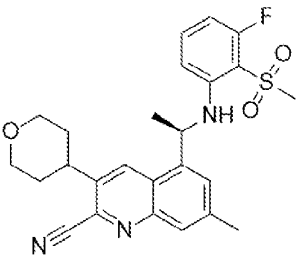
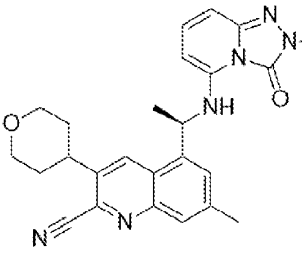
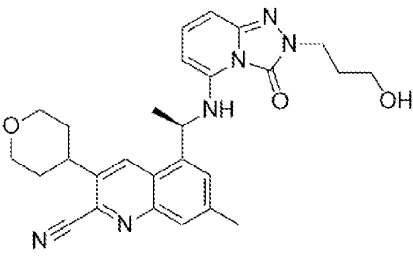
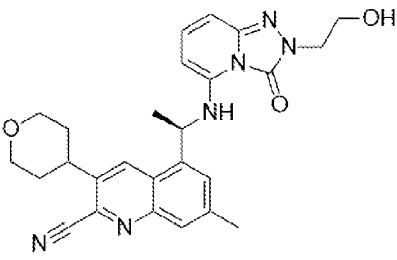
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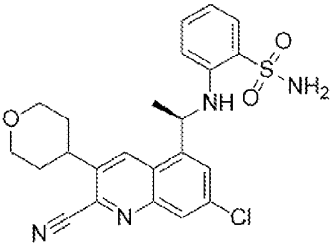
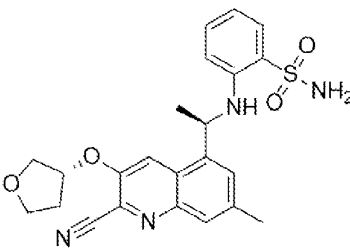
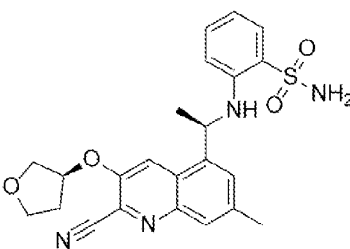
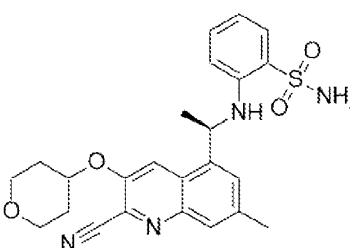
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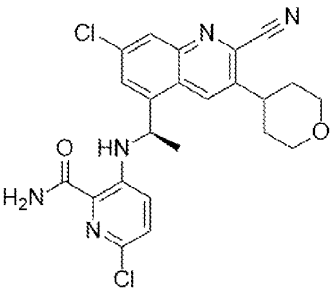
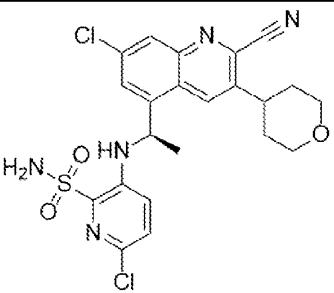
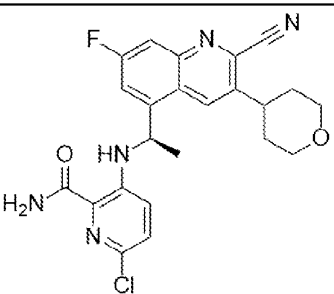
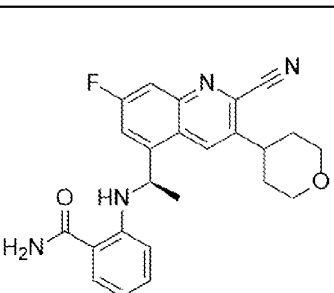
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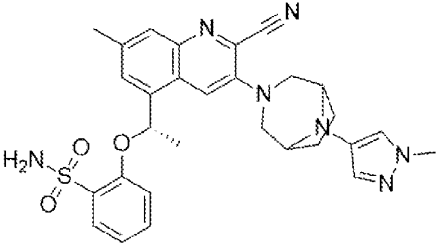
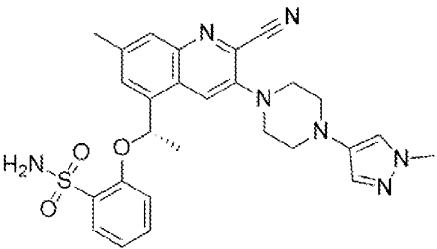
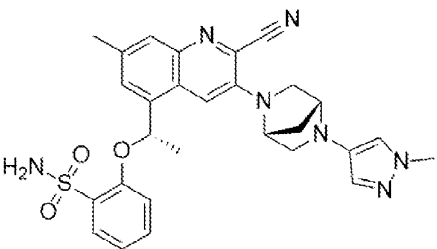
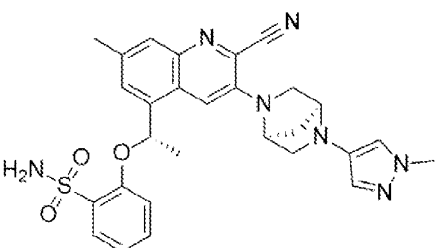
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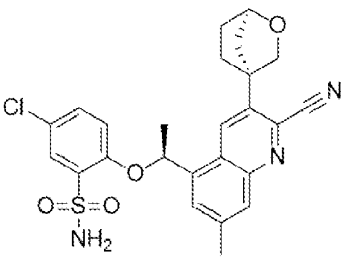
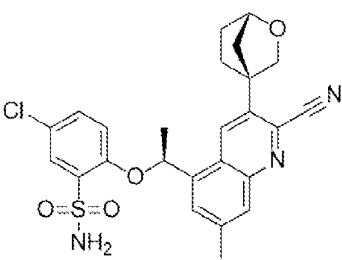
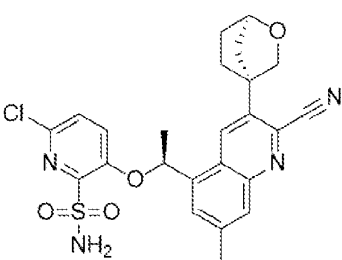
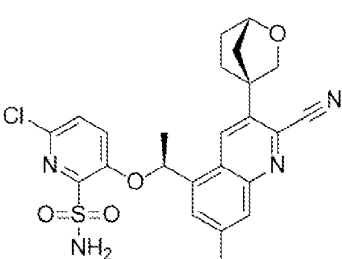
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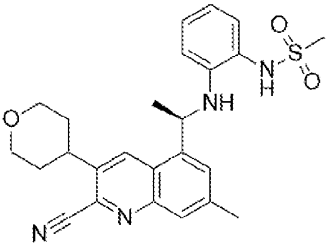
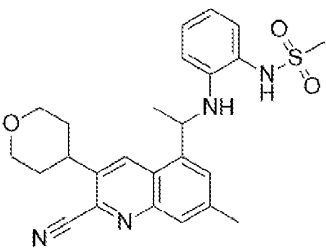
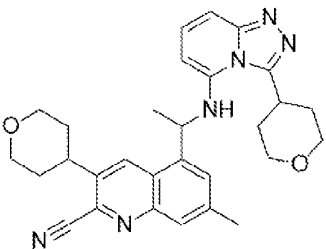
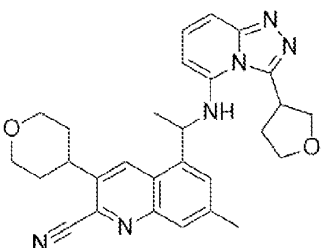
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482	 <chem>CC(NC(=O)S(=O)(=O)c1ccccc1)[C@@H]1C=CC2=C(C=C1)N=C(C=C2)C3=CC=C(C=C3)C4=CCOCC4Cl</chem>
483	 <chem>CC1=CC=C2C(=C1)N=C(C=C2)C3=CC=C(C=C3)C4=CCOCC4C5=CC=CC=C5N(S(=O)(=O)N)C</chem>
484	 <chem>CC1=CC=C2C(=C1)N=C(C=C2)C3=CC=C(C=C3)C4=CCOCC4C5=CC=CC=C5N(S(=O)(=O)N)C</chem>
485	 <chem>CC1=CC=C2C(=C1)N=C(C=C2)C3=CC=C(C=C3)C4=CCOCC4C5=CC=CC=C5N(S(=O)(=O)N)C</chem>

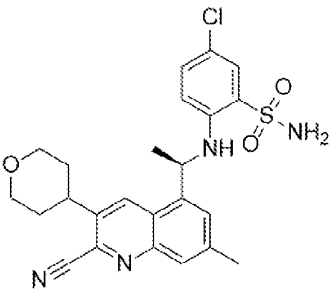
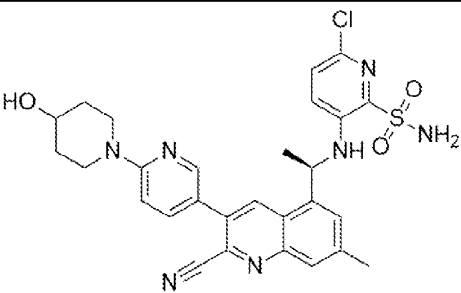
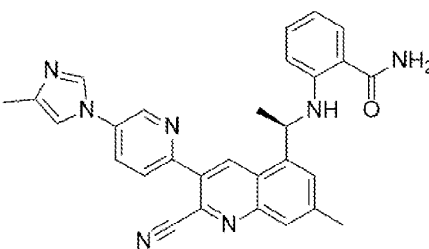
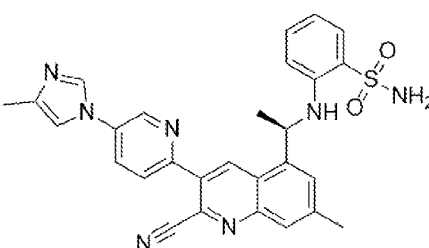
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487	 <chem>N#CC1=CC=C2C(=C1)C(=CC=C2N)C(C3CCOCC3)C(C)NS(=O)(=O)c4cc(Cl)nc(CN)c4</chem>
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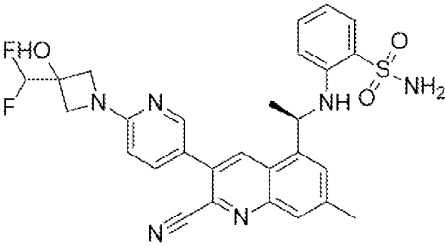
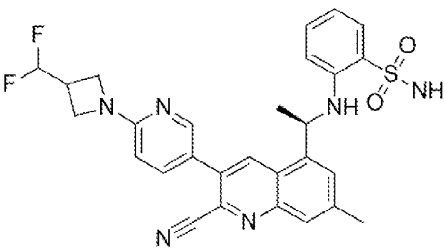
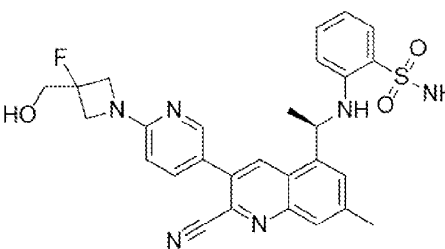
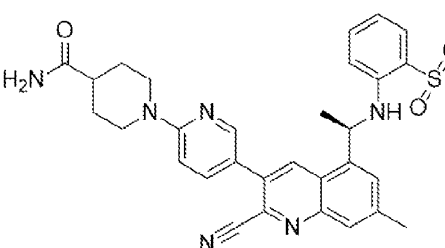
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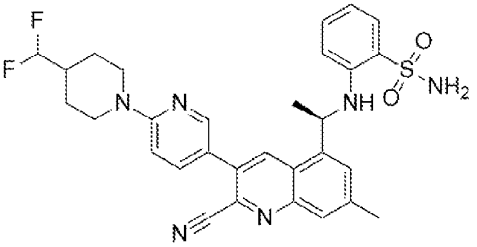
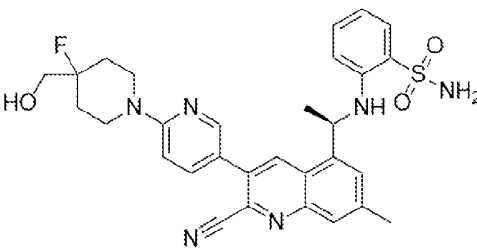
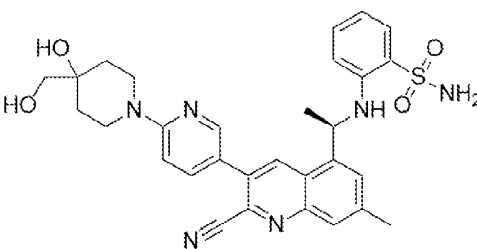
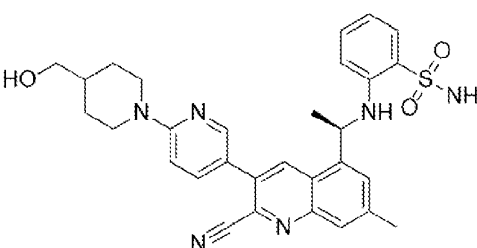
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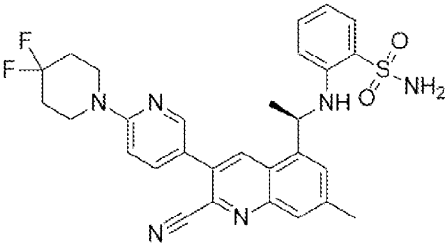
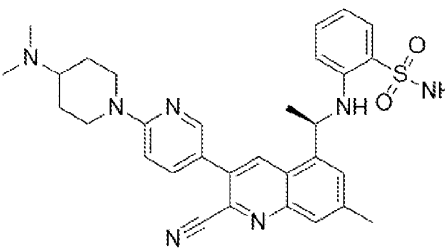
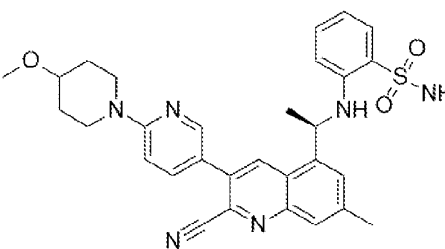
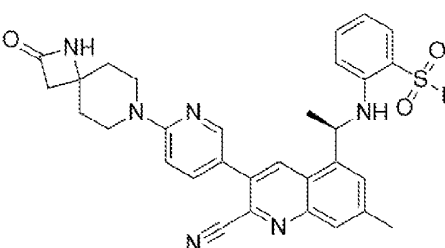
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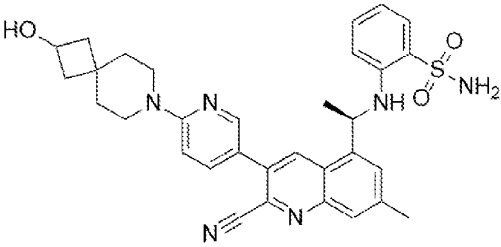
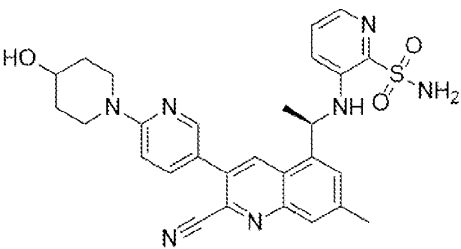
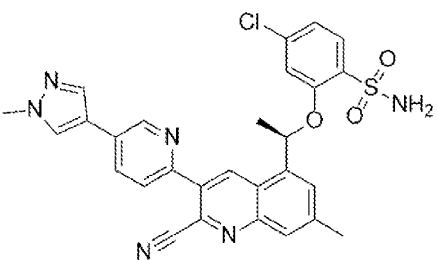
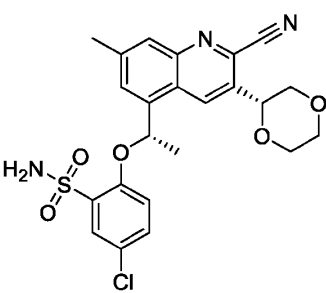
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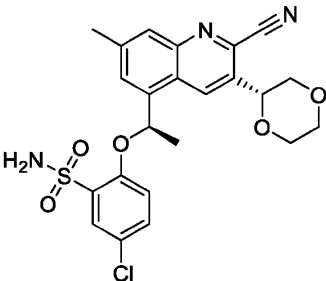
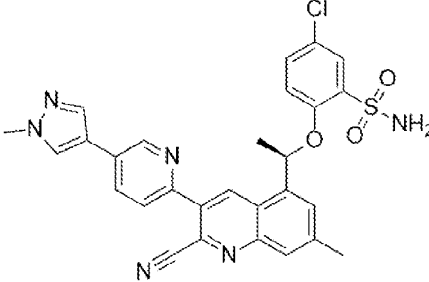
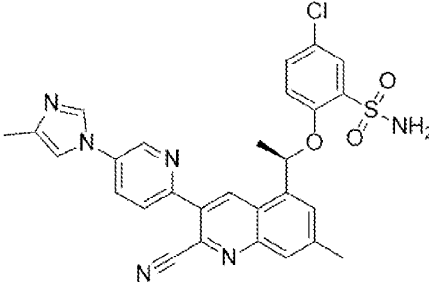
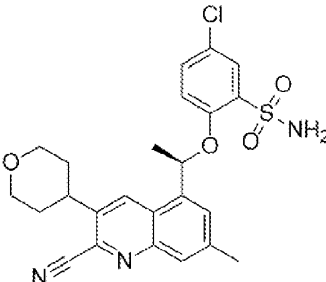
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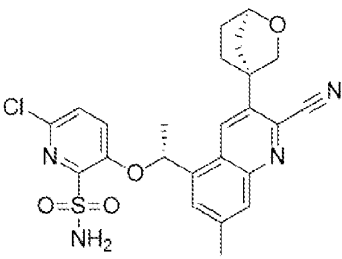
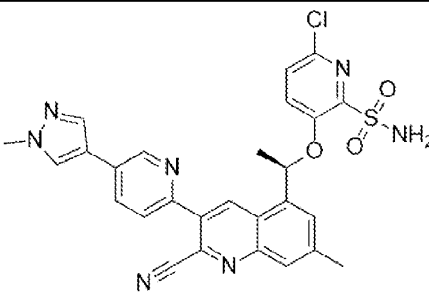
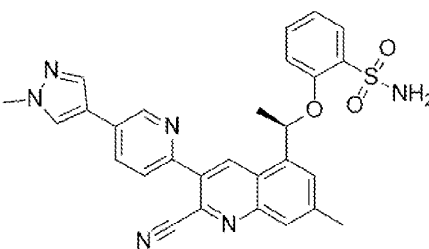
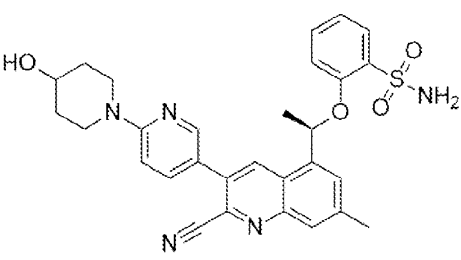
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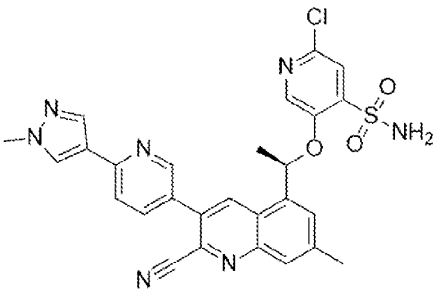
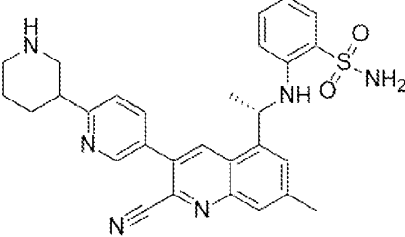
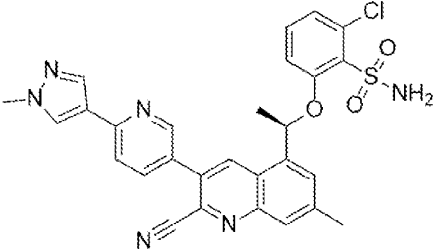
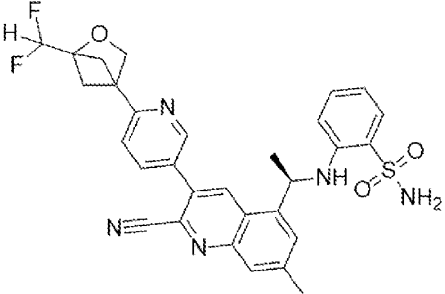
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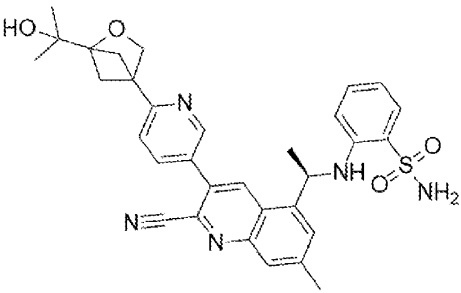
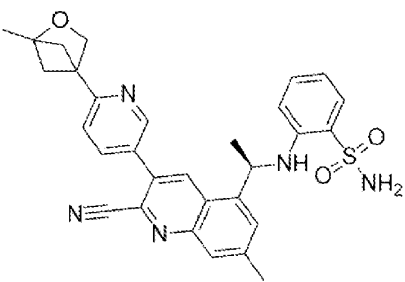
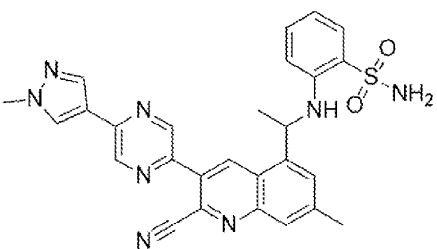
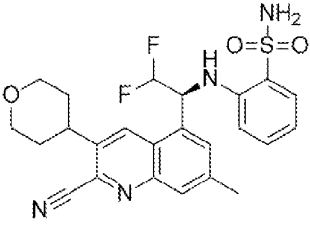
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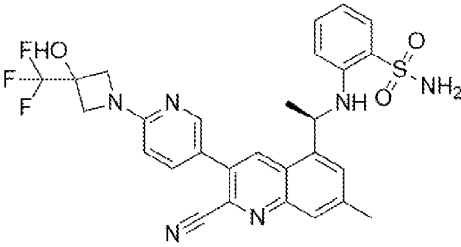
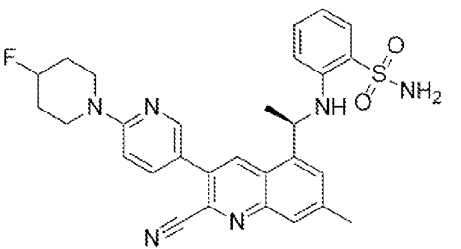
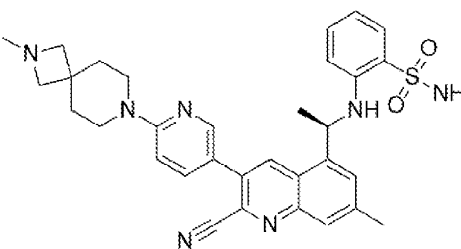
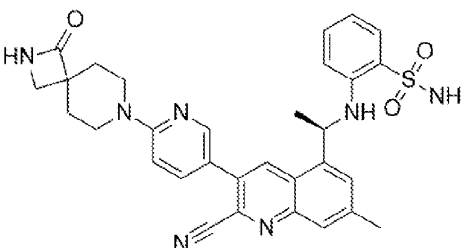
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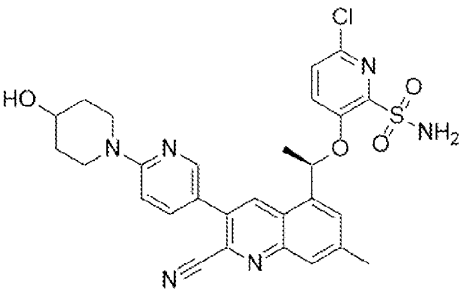
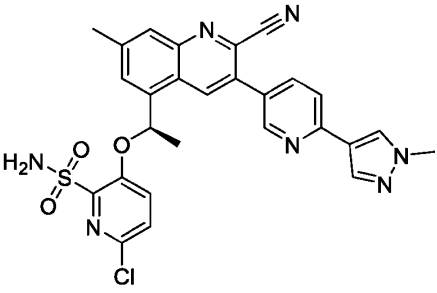
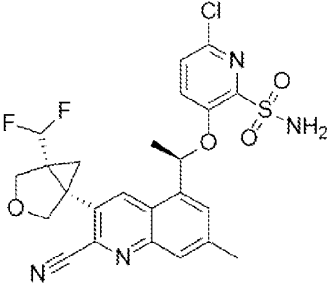
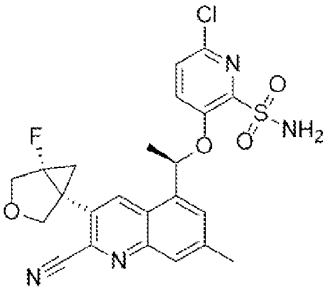
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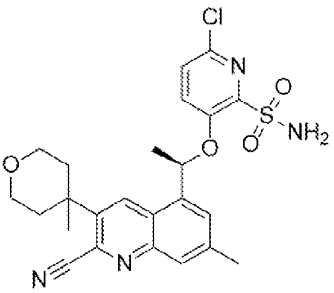
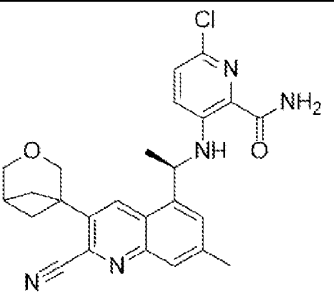
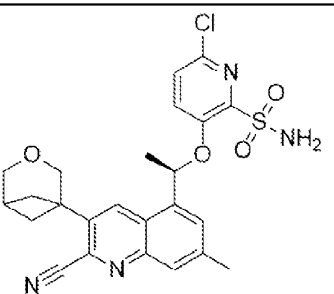
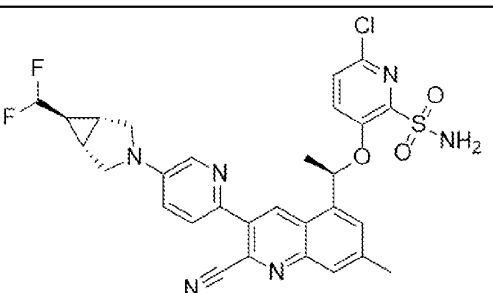
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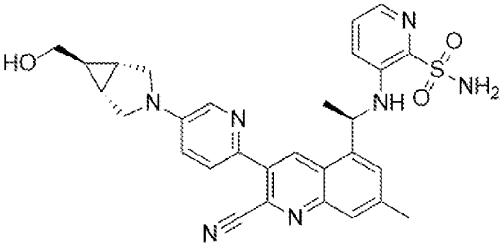
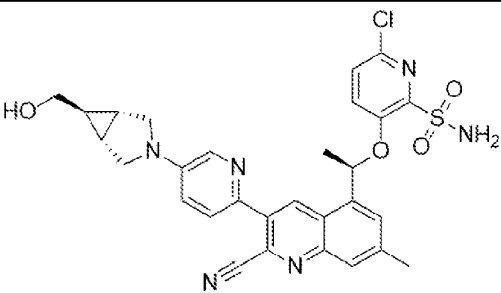
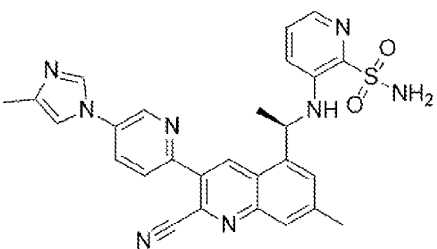
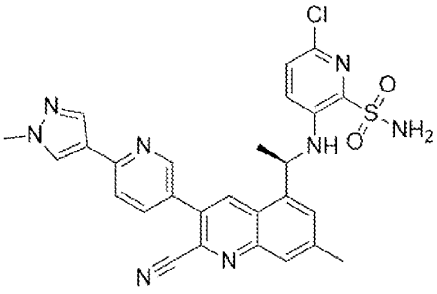
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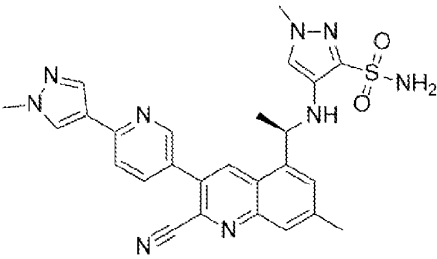
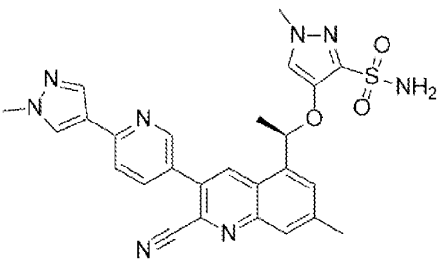
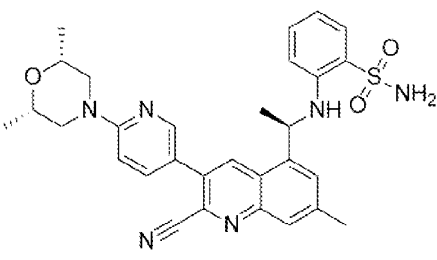
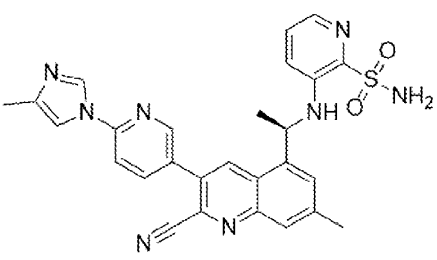
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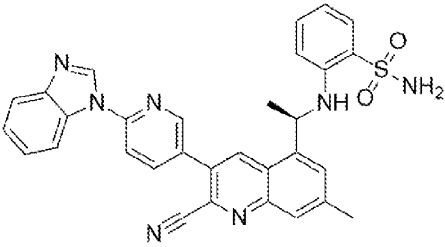
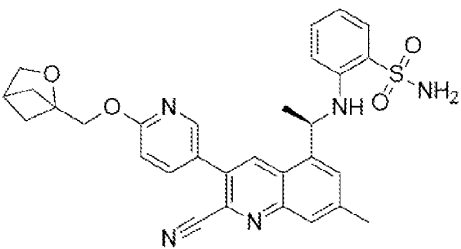
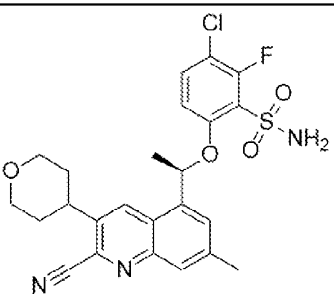
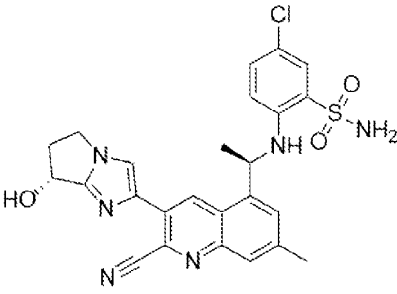
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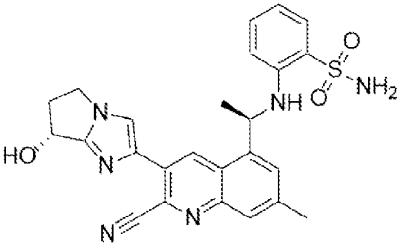
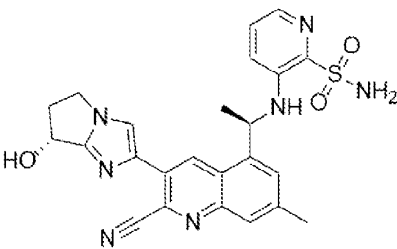
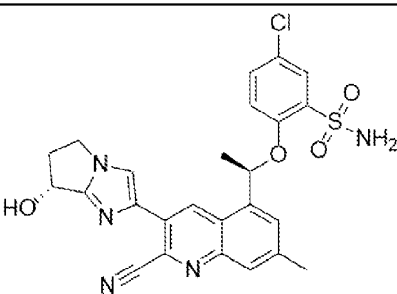
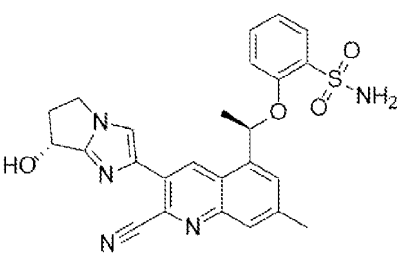
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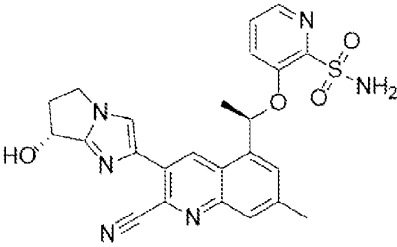
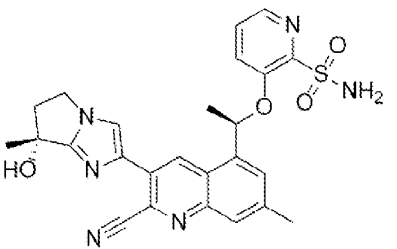
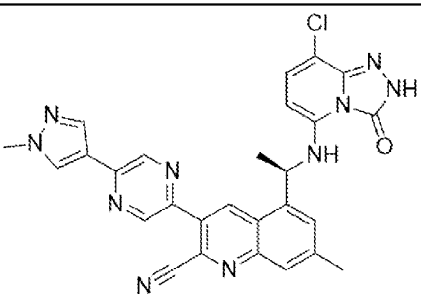
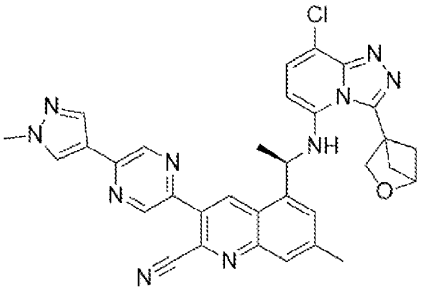
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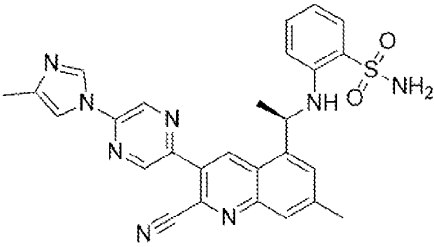
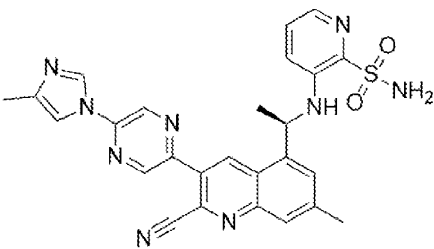
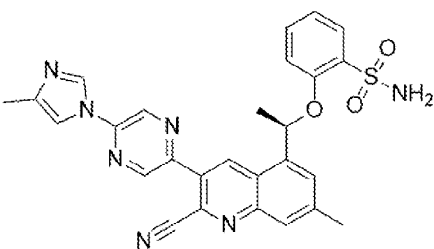
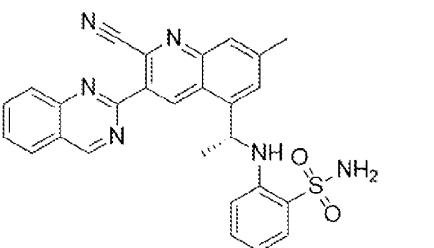
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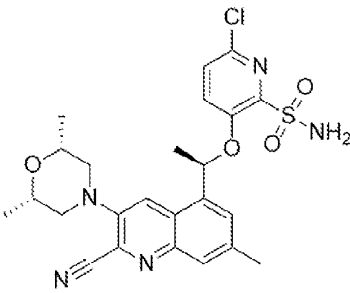
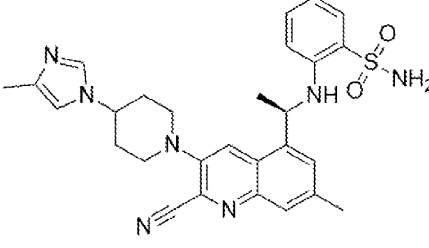
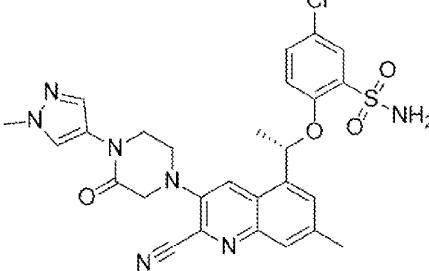
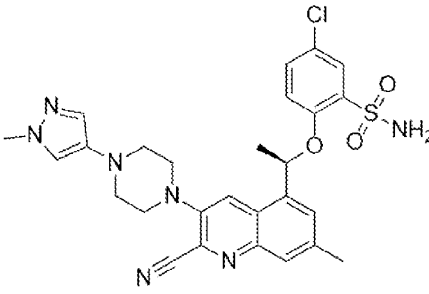
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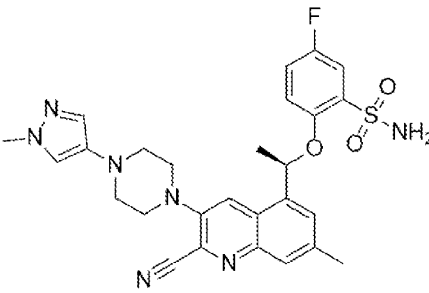
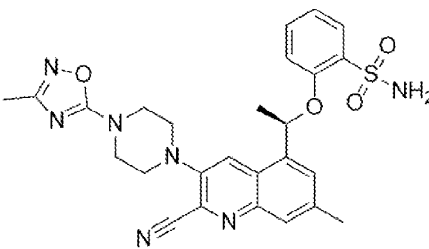
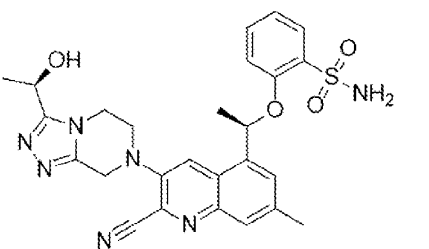
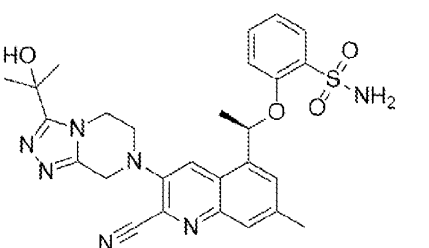
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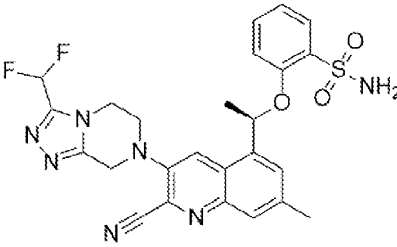
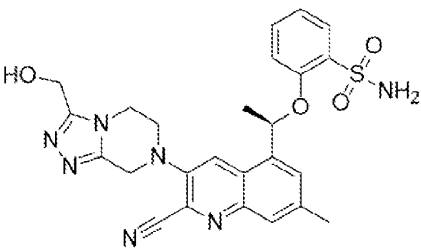
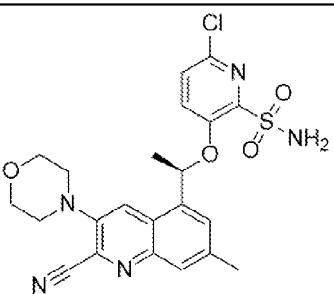
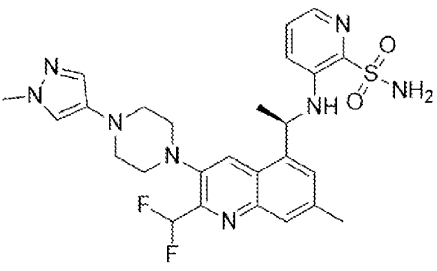
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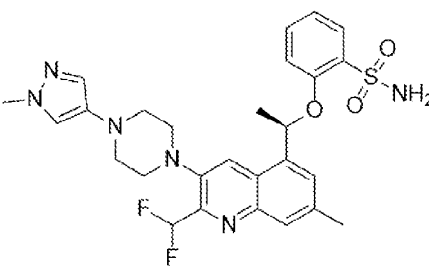
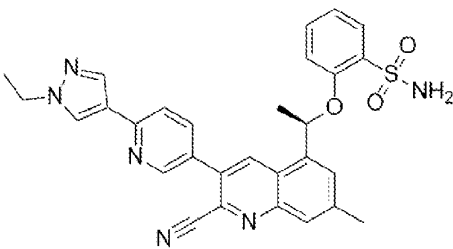
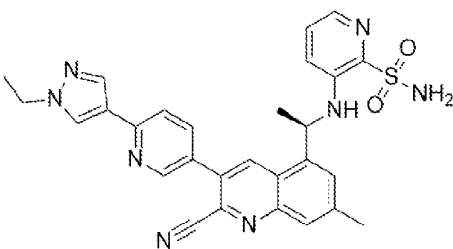
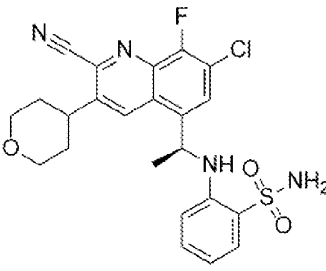
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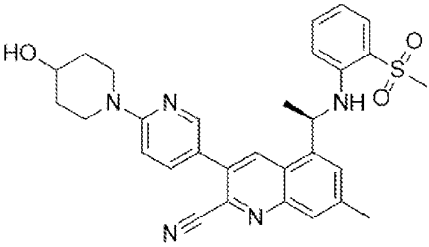
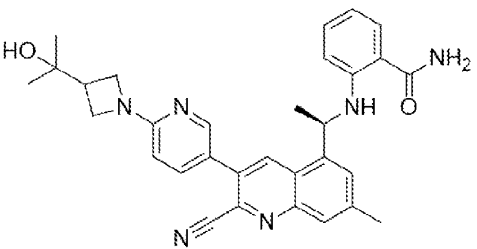
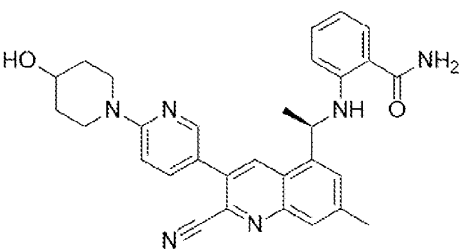
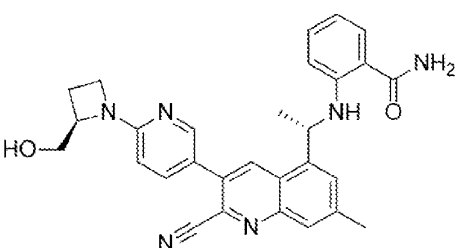
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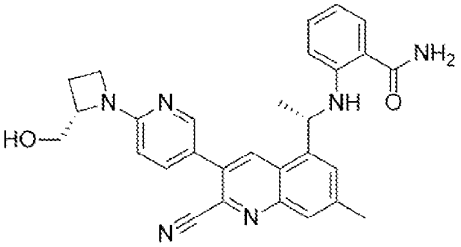
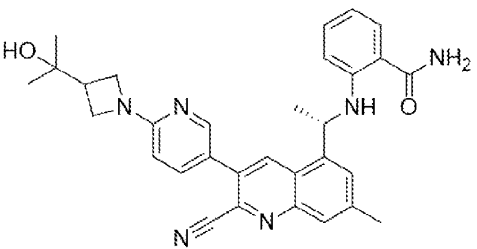
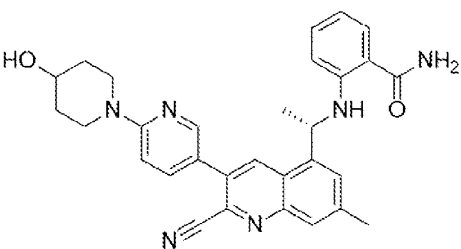
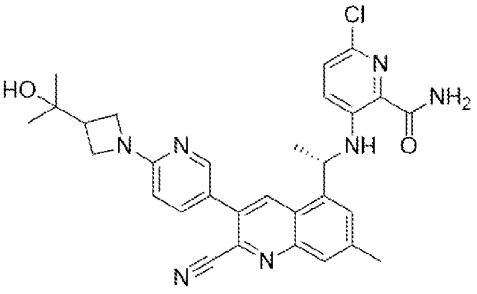
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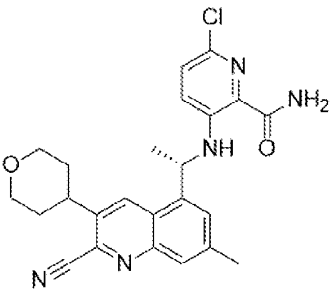
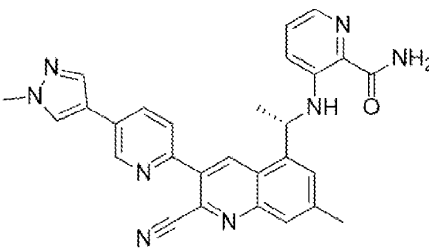
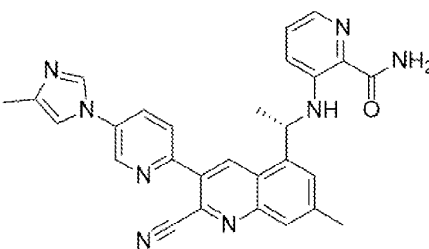
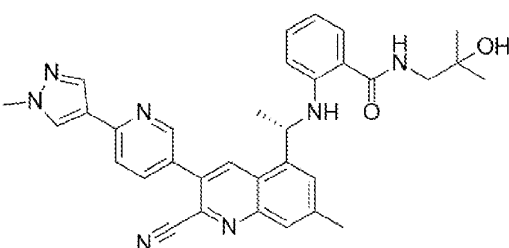
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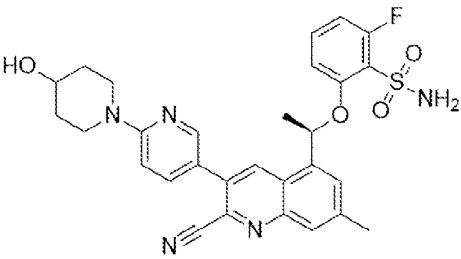
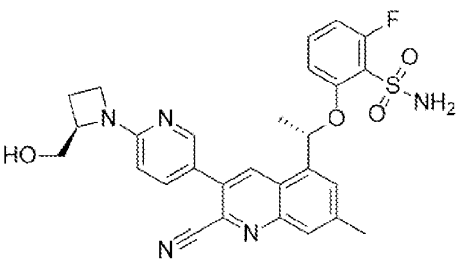
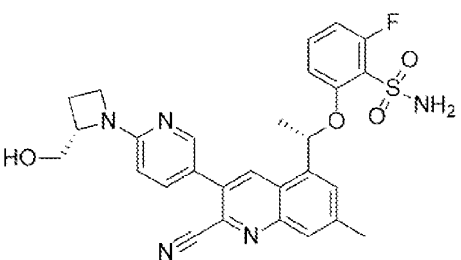
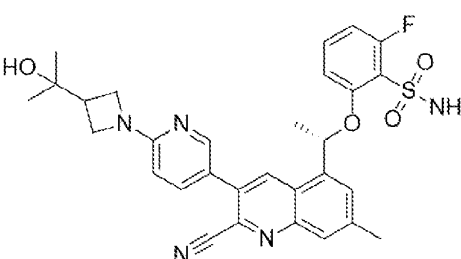
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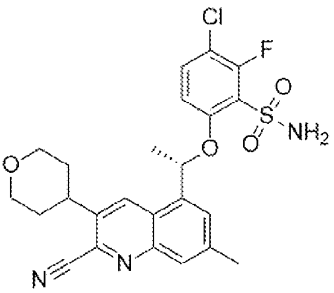
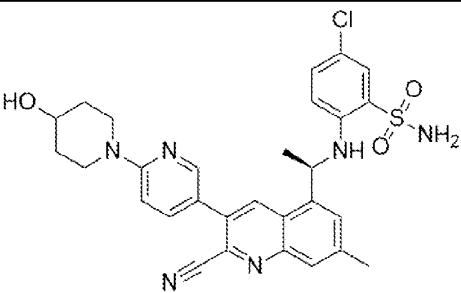
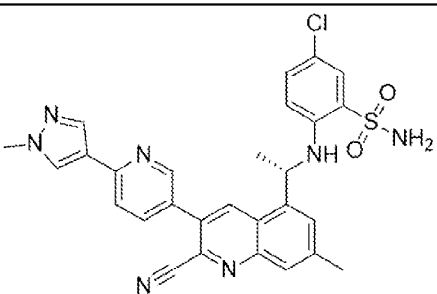
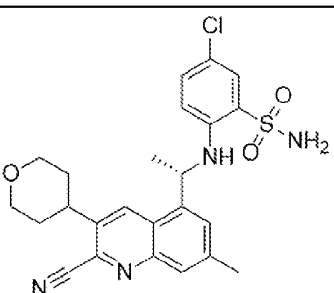
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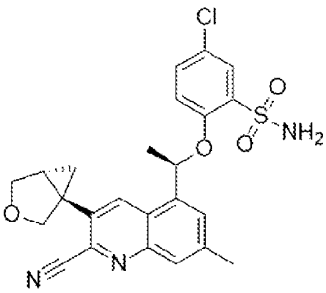
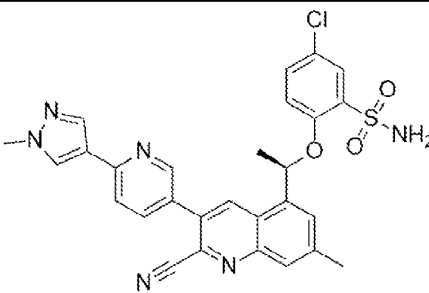
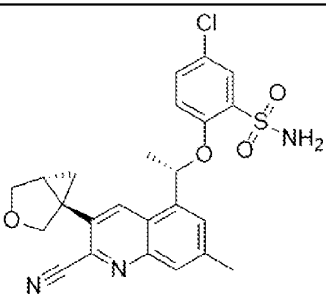
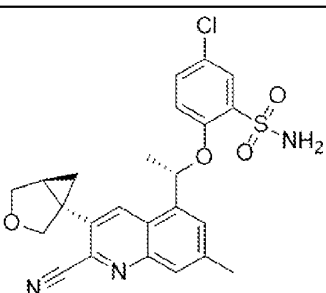
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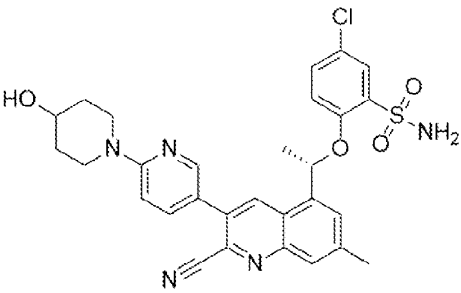
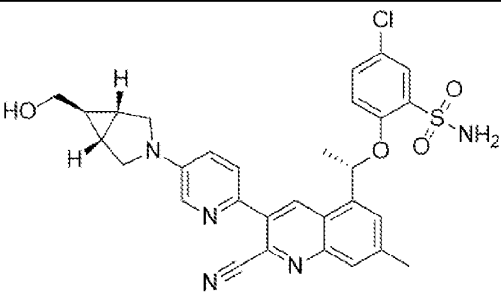
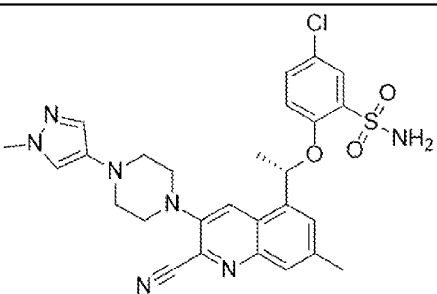
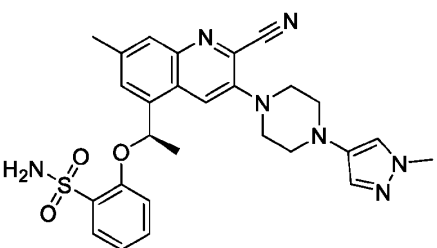
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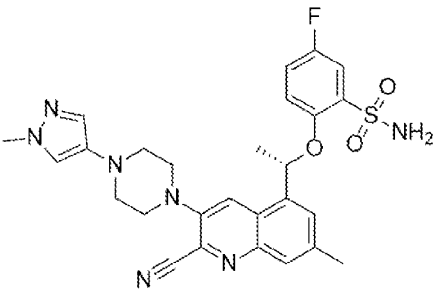
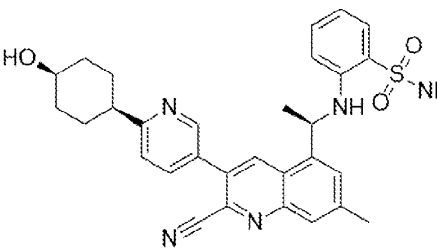
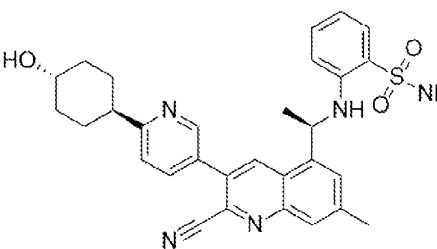
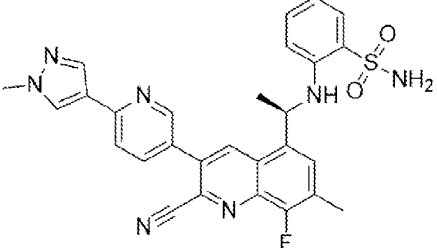
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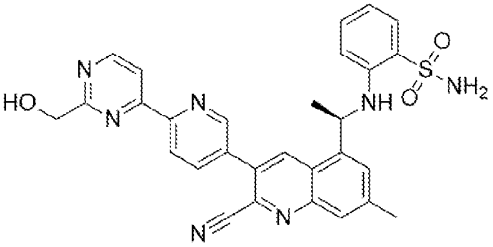
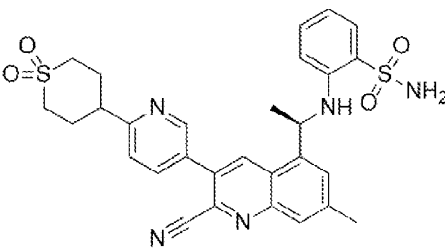
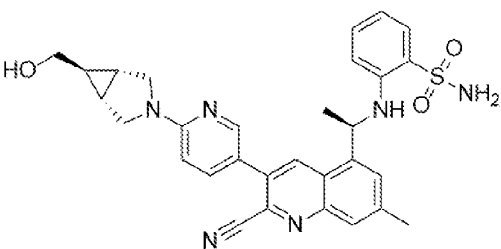
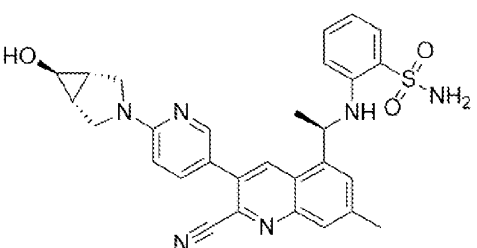
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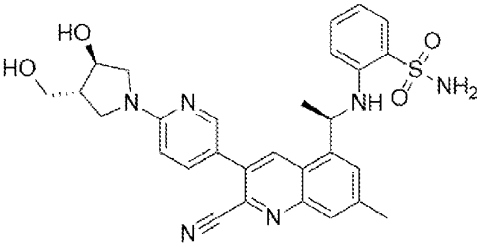
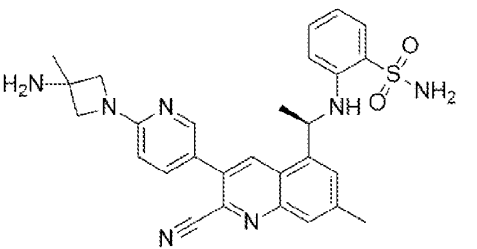
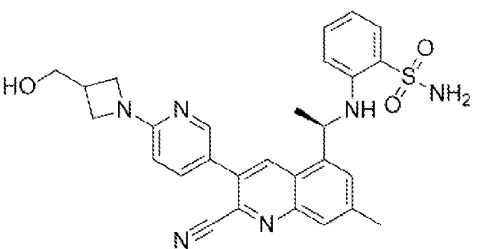
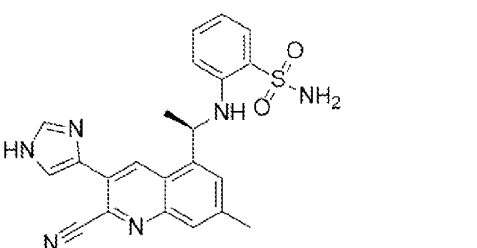
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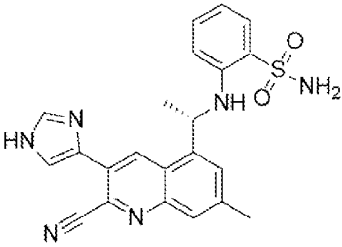
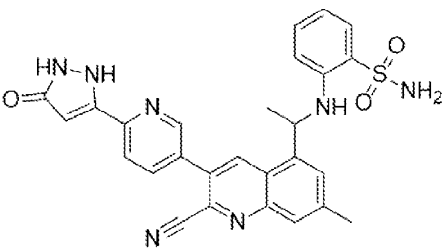
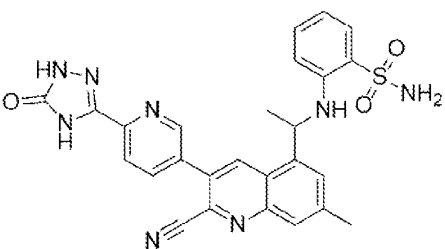
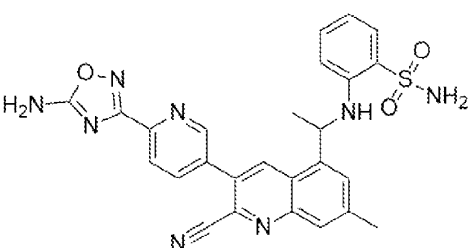
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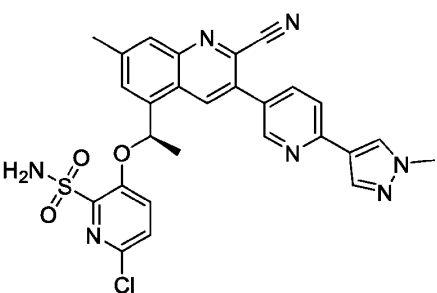
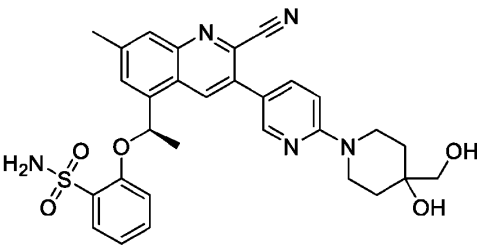
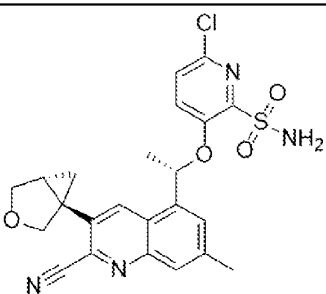
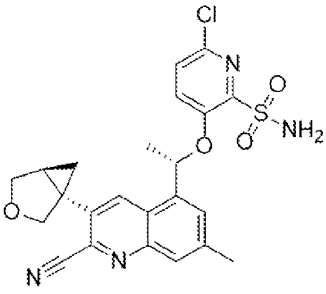
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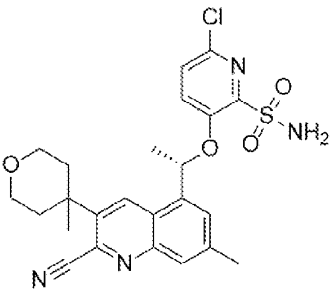
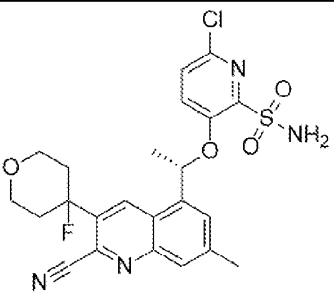
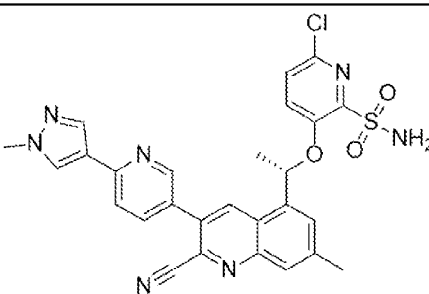
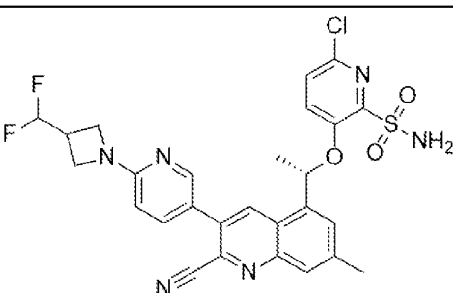
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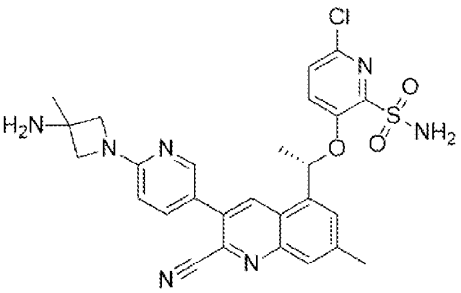
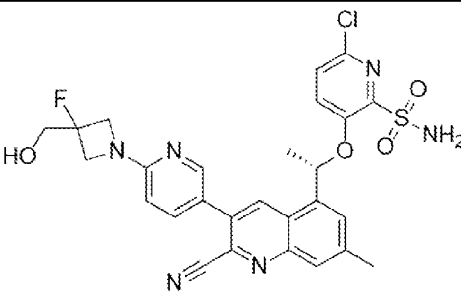
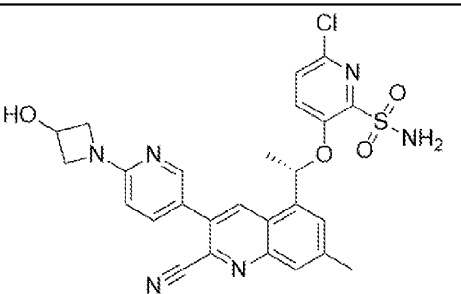
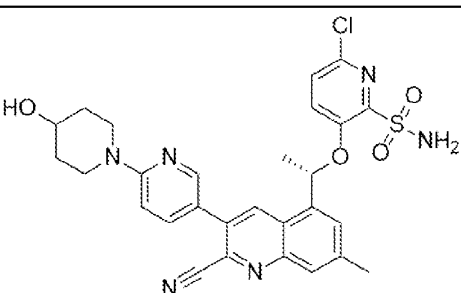
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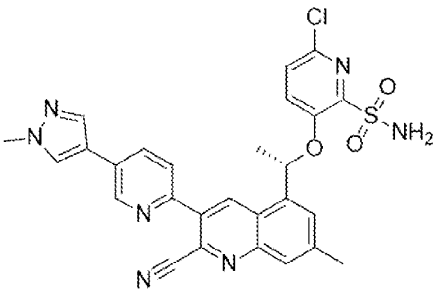
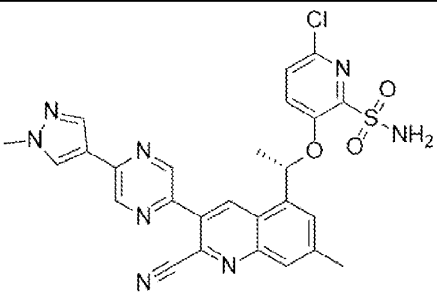
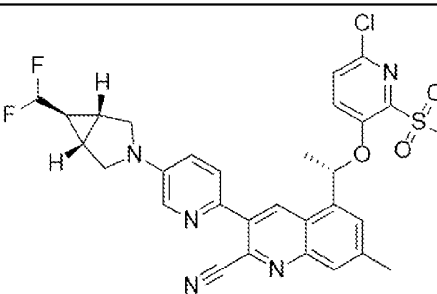
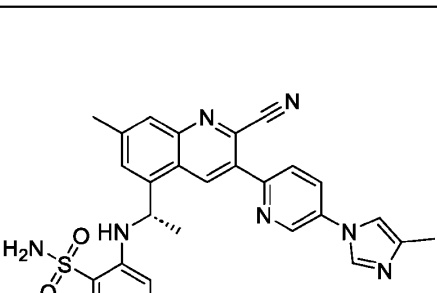
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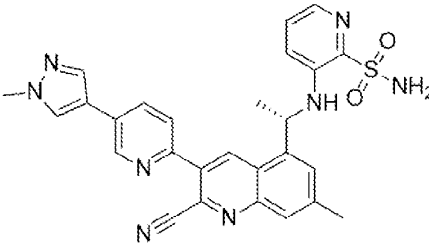
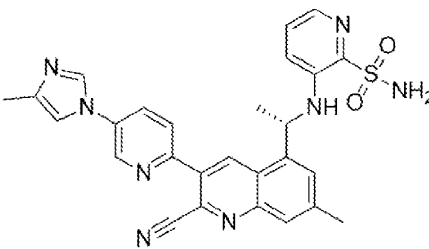
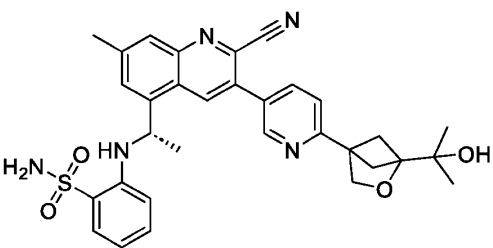
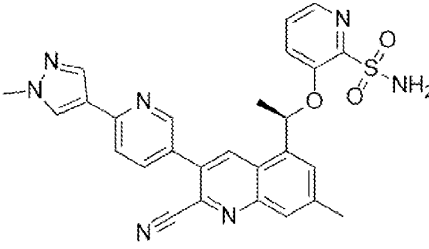
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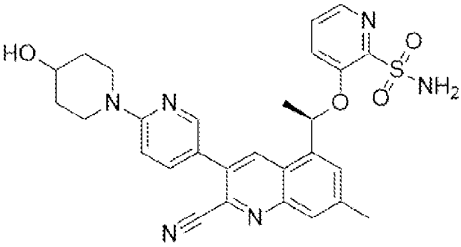
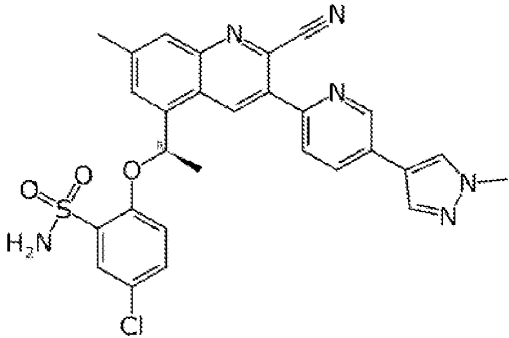
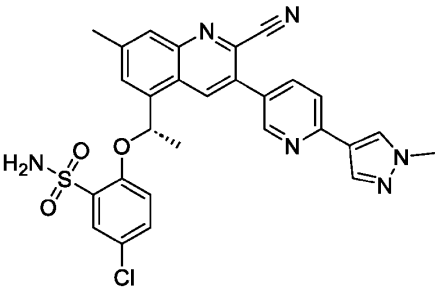
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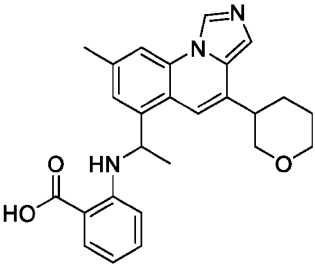
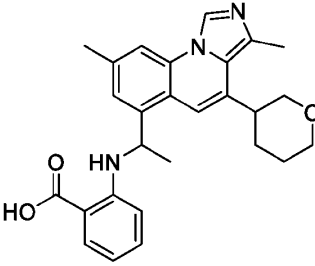
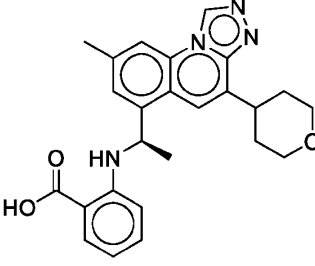
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In some embodiments, the compound is selected from the group consisting of the compounds in Table B, or a pharmaceutically acceptable salt thereof. Stereochemistry shown for the compounds in Table B has been arbitrarily assigned.

Table B

Compound Number	Structure
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Pharmaceutical Compositions

Some embodiments provide a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

Some embodiments provide a pharmaceutical composition comprising a compound of Formula (II), or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

Methods of Treatment

A “PI3K α inhibitor” as used herein (e.g., compounds of Formula (I) and pharmaceutically acceptable salts thereof and compounds of Formula (II) and pharmaceutically acceptable salts thereof) includes any compound exhibiting PI3K α inactivation activity (e.g., inhibiting or decreasing). In some embodiments, a PI3K α inhibitor can be selective for PI3K α over one or more other kinases. In some embodiments, a PI3K α inhibitor can be selective for a PI3K α having one or more mutations.

The ability of test compounds to act as inhibitors of PI3K α may be demonstrated by assays known in the art. The activity of the compounds and compositions provided herein as PI3K α inhibitors can be assayed *in vitro*, *in vivo*, or in a cell line. *In vitro* assays include assays that determine inhibition of the kinase. Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to the protein kinase and can be measured either by radio labeling the compound prior to binding, isolating the compound/kinase complex and determining the amount of radio label bound, or by running a competition experiment where new compounds are incubated with the kinase bound to known radioligands.

Potency of a PI3K α inhibitor as provided herein can be determined by EC₅₀ value. A compound with a lower EC₅₀ value, as determined under substantially similar conditions, is a more potent inhibitor relative to a compound with a higher EC₅₀ value.

Potency of a PI3K α inhibitor as provided herein can also be determined by IC₅₀ value. A compound with a lower IC₅₀ value, as determined under substantially similar conditions, is a more potent inhibitor relative to a compound with a higher IC₅₀ value. In some embodiments, the substantially similar conditions comprise determining a PI3K α -dependent phosphorylation level, *in vitro* or *in vivo*.

The selectivity between wild type PI3K α and PI3K α containing one or more mutations as described herein can also be measured using *in vitro* assays such as surface plasmon resonance and fluorescence-based binding assays, and cellular assays such as the levels of pAKT, a biomarker of PI3K α activity, and/or proliferation assays where cell proliferation is dependent on mutant PI3K α kinase activity.

In some embodiments, the compounds provided herein can exhibit potent and selective inhibition of PI3K α . For example, the compounds provided herein can bind to the helical phosphatidylinositol kinase homology domain catalytic domain of PI3K α . In some embodiments,

the compounds provided herein can exhibit nanomolar potency against a PI3K α kinase including one or more mutations, for example, the mutations in Table 1.

In some embodiments, the compounds of Formula (I), or a pharmaceutically acceptable salt thereof, can selectively target PI3K α . For example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can selectively target PI3K α over another kinase or non-kinase target.

In some embodiments, the compounds of Formula (II), or a pharmaceutically acceptable salt thereof, can selectively target PI3K α . For example, a compound of Formula (II), or a pharmaceutically acceptable salt thereof, can selectively target PI3K α over another kinase or non-kinase target.

In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, (or a compound of Formula (II), or a pharmaceutically acceptable salt thereof) can exhibit greater inhibition of PI3K α containing one or more mutations as described herein (e.g., one or more mutations as described in Table 1) relative to inhibition of wild type PI3K α . In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof can exhibit at least 2-fold, 3-fold, 5-fold, 10-fold, 25-fold, 50-fold or 100-fold greater inhibition of PI3K α containing one or more mutations as described herein relative to inhibition of wild type PI3K α . In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can exhibit up to 1,000-fold greater inhibition of PI3K α containing one or more mutations as described herein relative to inhibition of wild type PI3K α . In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can exhibit up to 10,000-fold greater inhibition of PI3K α having a combination of mutations described herein relative to inhibition of wild type PI3K α .

In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can exhibit from about 2-fold to about 10-fold greater inhibition of PI3K α containing one or more mutations as described herein relative to inhibition of wild type PI3K α . In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can exhibit from about 10-fold to about 100-fold greater inhibition of PI3K α containing one or more mutations as described herein relative to inhibition of wild type PI3K α . In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can exhibit from about 100-fold to about 1,000-fold greater inhibition of PI3K α containing one or more mutations as

described herein relative to inhibition of wild type PI3K α . In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can exhibit from about 1000-fold to about 10,000-fold greater inhibition of PI3K α containing one or more mutations as described herein relative to inhibition of wild type PI3K α .

5 Compounds of Formula (I), or pharmaceutically acceptable salts thereof, and compounds of Formula (II), or pharmaceutically acceptable salts thereof, are useful for treating diseases which can be treated with a PI3K α inhibitor, such as PI3K α -associated diseases, e.g., proliferative disorders such as cancers, including hematological cancers and solid tumors (e.g., advanced or metastatic solid tumors).

10 In some embodiments, the subject has been identified or diagnosed as having a cancer with a dysregulation of a *PIK3CA* gene, a PI3K α protein, or expression or activity, or level of any of the same (a PI3K α -associated cancer), for example, as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit. In some embodiments, the subject has a tumor that is positive for a dysregulation of a *PIK3CA* gene, a PI3K α protein, or expression or activity, or level
15 of any of the same (e.g., as determined using a regulatory agency-approved assay or kit). For example, the subject has a tumor that is positive for a mutation as described in Table 1. The subject can be a subject with a tumor(s) that is positive for a dysregulation of a *PIK3CA* gene, a PI3K α protein, or expression or activity, or level of any of the same (e.g., identified as positive using a regulatory agency-approved, e.g., FDA-approved, assay or kit). The subject can be a subject whose
20 tumors have a dysregulation of a *PIK3CA* gene, a PI3K α protein, or expression or activity, or a level of the same (e.g., where the tumor is identified as such using a regulatory agency-approved, e.g., FDA-approved, kit or assay). In some embodiments, the subject is suspected of having a PI3K α -associated cancer. In some embodiments, the subject has a clinical record indicating that the subject has a tumor that has a dysregulation of a *PIK3CA* gene, a PI3K α protein, or expression
25 or activity, or level of any of the same (and optionally the clinical record indicates that the subject should be treated with any of the compositions provided herein).

 In certain embodiments, compounds of Formula (I), or pharmaceutically acceptable salt thereof, and compounds of Formula (II), or a pharmaceutically acceptable salt thereof, are useful for preventing diseases as defined herein such as cancer. The term “preventing” as used herein
30 means to delay the onset, recurrence or spread, in whole or in part, of the disease as described herein, or a symptom thereof.

The term “PI3K α -associated disease” as used herein refers to diseases associated with or having a dysregulation of a *PIK3CA* gene, a PI3K α protein, or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a *PIK3CA* gene, or a PI3K α protein, or the expression or activity or level of any of the same described herein). Non-limiting examples of a PI3K α -associated disease include, for example, proliferative disorders such as cancer (e.g., PI3K α -associated cancer).

The term “PI3K α -associated cancer” as used herein refers to cancers associated with or having a dysregulation of a *PIK3CA* gene, a PI3K α protein, or expression or activity, or level of any of the same. Non-limiting examples of PI3K α -associated cancer are described herein.

The phrase “dysregulation of a *PIK3CA* gene, a PI3K α protein, or the expression or activity or level of any of the same” refers to a genetic mutation (e.g., a mutation in a *PIK3CA* gene that results in the expression of a PI3K α that includes a deletion of at least one amino acid as compared to a wild type PI3K α , a mutation in a *PIK3CA* gene that results in the expression of PI3K α with one or more point mutations as compared to a wild type PI3K α , a mutation in a *PIK3CA* gene that results in the expression of PI3K α with at least one inserted amino acid as compared to a wild type PI3K α , a gene duplication that results in an increased level of PI3K α in a cell, or a mutation in a regulatory sequence (e.g., a promoter and/or enhancer) that results in an increased level of PI3K α in a cell), an alternative spliced version of PI3K α mRNA that results in PI3K α having a deletion of at least one amino acid in the PI3K α as compared to the wild type PI3K α), or increased expression (e.g., increased levels) of a wild type PI3K α in a mammalian cell due to aberrant cell signaling and/or dysregulated autocrine/paracrine signaling (e.g., as compared to a control non-cancerous cell). As another example, a dysregulation of a *PIK3CA* gene, a PI3K α protein, or expression or activity, or level of any of the same, can be a mutation in a *PIK3CA* gene that encodes a PI3K α that is constitutively active or has increased activity as compared to a protein encoded by a *PIK3CA* gene that does not include the mutation. Non-limiting examples of PI3K α point mutations/substitutions/insertions/deletions are described in Table 1.

The term “wild type” describes a nucleic acid (e.g., a *PIK3CA* gene or a PI3K α mRNA) or protein (e.g., a PI3K α) sequence that is typically found in a subject that does not have a disease related to the reference nucleic acid or protein.

The term “wild type PI3K α ” or “wild-type PI3K α ” describes a normal PI3K α nucleic acid (e.g., a *PIK3CA* or PI3K α mRNA) or protein that is found in a subject that does not have a PI3K α -

associated disease, e.g., a PI3K α -associated cancer (and optionally also does not have an increased risk of developing a PI3K α -associated disease and/or is not suspected of having a PI3K α -associated disease), or is found in a cell or tissue from a subject that does not have a PI3K α -associated disease, e.g., a PI3K α -associated cancer (and optionally also does not have an increased risk of developing a PI3K α -associated disease and/or is not suspected of having a PI3K α -associated disease).

Provided herein is a method of treating cancer (e.g., a PI3K α -associated cancer) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. For example, provided herein are methods for treating PI3K α -associated cancer in a subject in need thereof, comprising a) detecting a dysregulation of *PIK3CA* gene, a PI3K α protein, or the expression or activity or level of any of the same in a sample from the subject; and b) administering a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. Some embodiments provide a method of treating cancer in a subject previously determined to have a PI3K α -associated cancer, the method comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. Some embodiments provide a method of treating cancer in a subject identified or diagnosed with a PI3K α -associated cancer, the method comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

Provided herein is a method of treating cancer (e.g., a PI3K α -associated cancer) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (II), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. For example, provided herein are methods for treating PI3K α -associated cancer in a subject in need thereof, comprising a) detecting a dysregulation of *PIK3CA* gene, a PI3K α protein, or the expression or activity or level of any of the same in a sample from the subject; and b) administering a therapeutically effective amount of a compound of Formula (II), or a pharmaceutically acceptable salt thereof. Some embodiments provide a method of treating cancer in a subject previously determined to have a PI3K α -associated cancer, the method comprising administering to the subject a therapeutically effective amount of a compound of Formula (II), or

a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. Some embodiments provide a method of treating cancer in a subject identified or diagnosed with a PI3K α -associated cancer, the method comprising administering to the subject a therapeutically effective amount of a compound of Formula (II), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

In some embodiments, the dysregulation of a *PIK3CA* gene, a PI3K α protein, or the expression or activity or level of any of the same includes one or more a PI3K α protein substitutions/point mutations/insertions. Non-limiting examples of PI3K α protein substitutions/insertions/deletions are described in Table 1.

In some embodiments, the PI3K α protein substitution/insertion/deletion is selected from the group consisting of E542A, E542G, E542K, E542Q, E542V, E545A, E545D, E545G, E545K, E545Q, M1043I, M1043L, M1043T, M1043V, H1047L, H1047Q, H1047R, H1047Y, G1049R, and combinations thereof. In some embodiments, the PI3K α protein substitution / insertion / deletion is H1047X, where X is any amino acid other than H. In some embodiments, the PI3K α protein substitution / insertion / deletion is E542X, where X is any amino acid other than E. In some embodiments, the PI3K α protein substitution / insertion / deletion is E545X, where X is any amino acid other than E. In some embodiments, the PI3K α protein substitution / insertion / deletion is H1047R. In some embodiments, the PI3K α protein substitution / insertion / deletion is E545K.

In some embodiments, the dysregulation of a *PIK3CA* gene, a PI3K α protein, or expression or activity or level of any of the same, includes a splice variation in a PI3K α mRNA which results in an expressed protein that is an alternatively spliced variant of PI3K α having at least one residue deleted (as compared to the wild type PI3K α protein) resulting in a constitutive activity of a PI3K α protein domain.

In some embodiments, the dysregulation of a *PIK3CA* gene, a PI3K α protein, or expression or activity or level of any of the same, includes at least one point mutation in a *PIK3CA* gene that results in the production of a PI3K α protein that has one or more amino acid substitutions or insertions or deletions in a *PIK3CA* gene that results in the production of a PI3K α protein that has one or more amino acids inserted or removed, as compared to the wild type PI3K α protein. In some cases, the resulting mutant PI3K α protein has increased activity, as compared to a wild type PI3K α protein or a PI3K α protein not including the same mutation. In some embodiments, the compounds

described herein selectively inhibit the resulting mutant PI3K α protein relative to a wild type PI3K α protein or a PI3K α protein not including the same mutation.

In some embodiments of any of the methods or uses described herein, the cancer (e.g., PI3K α -associated cancer) is selected from a hematological cancer and a solid tumor.

5 In some embodiments of any of the methods or uses described herein, the cancer (e.g., PI3K α -associated cancer) is selected from breast cancer (including both HER2⁺ and HER2⁻ breast cancer, ER⁺ breast cancer, and triple negative breast cancer), uterine cancer (including endometrial cancer), lung cancer (including small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC, including adenocarcinoma lung cancer and squamous cell lung carcinoma)), esophageal
10 squamous cell carcinoma, ovarian cancer, colorectal cancer, esophagastic adenocarcinoma, bladder cancer, head and neck cancer (including head and neck squamous cell cancers such as oropharyngeal squamous cell carcinoma), thyroid cancer, glioma, cervical cancer, lymphangioma, meningioma, melanoma (including uveal melanoma), kidney cancer, pancreatic neuroendocrine neoplasms (pNETs), stomach cancer, esophageal cancer, acute myeloid leukemia, relapsed and
15 refractory multiple myeloma, hepatocellular carcinoma, prostate cancer, Malignant Peripheral Nerve Sheath Tumor (MPNST), glioblastoma, cholangiocarcinoma, and pancreatic cancer.

In some embodiments of any of the methods or uses described herein, the cancer (e.g., PI3K α -associated cancer) is selected from breast cancer (including both HER2⁺ and HER2⁻ breast cancer, ER⁺ breast cancer, and triple negative breast cancer), colon cancer, rectal cancer, colorectal
20 cancer, ovarian cancer, lymphangioma, meningioma, head and neck squamous cell cancer (including oropharyngeal squamous cell carcinoma), melanoma (including uveal melanoma), kidney cancer, pancreatic neuroendocrine neoplasms (pNETs), stomach cancer, esophageal cancer, acute myeloid leukemia, relapsed and refractory multiple myeloma, pancreatic cancer, lung cancer (including adenocarcinoma lung cancer and squamous cell lung carcinoma), and endometrial
25 cancer.

In some embodiments of any of the methods or uses described herein, the cancer (e.g., PI3K α -associated cancer) is selected from breast cancer, SCLC, NSCLC, endometrial cancer, esophageal squamous cell carcinoma, ovarian cancer, colorectal cancer, esophagastic adenocarcinoma, bladder cancer, head and neck cancer, thyroid cancer, glioma, and cervical
30 cancer.

In some embodiments of any of the methods or uses described herein, the PI3K α -associated cancer is breast cancer. In some embodiments of any of the methods or uses described herein, the PI3K α -associated cancer is colorectal cancer. In some embodiments of any of the methods or uses described herein, the PI3K α -associated cancer is endometrial cancer. In some embodiments of any of the methods or uses described herein, the PI3K α -associated cancer is lung cancer.

In some embodiments of any of the methods or uses described herein, the PI3K α -associated cancer is selected from the cancers described in Table 1.

Table 1. PI3K α Protein Amino Acid Substitutions/Insertions/Deletions^A

Amino Acid Position	Non-Limiting Exemplary Mutations	Non-Limiting Exemplary PI3K α Associated Cancer(s)
1043	M1043I, M1043L, M1043T, M1043V	Breast Invasive Lobular Carcinoma Tubular Stomach Adenocarcinoma Uterine Endometrioid Carcinoma Mucinous Adenocarcinoma of the Colon and Rectum Papillary Thyroid Cancer Esophageal Squamous Cell Carcinoma Colon Adenocarcinoma Breast Invasive Ductal Carcinoma Bladder Urothelial Carcinoma Pancreatic Adenocarcinoma Oligodendroglioma Uterine Serous Carcinoma/Uterine Papillary Serous Carcinoma Glioblastoma Multiforme Head and Neck Squamous Cell Carcinoma
1044	N1044I, N1044K, N1044Y	Uterine Endometrioid Carcinoma Breast Invasive Ductal Carcinoma
1045	D1045A, D1045V	Uterine Endometrioid Carcinoma Lung Squamous Cell Carcinoma
1047	H1047L, H1047Q, H1047R, H1047Y	Esophageal Squamous Cell Carcinoma Uterine Endometrioid Carcinoma Hepatocellular Carcinoma Cutaneous Melanoma Mucinous Adenocarcinoma of the Colon and Rectum Bladder Urothelial Carcinoma

		Cervical Squamous Cell Carcinoma Intrahepatic Cholangiocarcinoma Uterine Mixed Endometrial Carcinoma Breast Invasive Ductal Carcinoma Renal Clear Cell Carcinoma Uterine Serous Carcinoma/Uterine Papillary Serous Carcinoma Head and Neck Squamous Cell Carcinoma Lung Squamous Cell Carcinoma Breast Invasive Lobular Carcinoma Breast Invasive Carcinoma (NOS) Astrocytoma Colon Adenocarcinoma Leiomyosarcoma Uterine Carcinosarcoma/Uterine Malignant Mixed Mullerian Tumor Oligodendroglioma Serous Ovarian Cancer Mucinous Stomach Adenocarcinoma Rectal Adenocarcinoma Intestinal Type Stomach Adenocarcinoma Diffuse Type Stomach Adenocarcinoma Prostate Adenocarcinoma Lung Adenocarcinoma Stomach Adenocarcinoma Tubular Stomach Adenocarcinoma Adrenocortical Carcinoma Undifferentiated Pleomorphic Sarcoma/Malignant Fibrous Histiocytoma/High-Grade Spindle Cell Sarcoma Glioblastoma Multiforme Oligoastrocytoma
1048	H1048R	Colon Adenocarcinoma Renal Clear Cell Carcinoma
1049	G1049R	Intestinal Type Stomach Adenocarcinoma Bladder Urothelial Carcinoma Renal Clear Cell Carcinoma Breast Invasive Ductal Carcinoma Breast Invasive Lobular Carcinoma Uterine Endometrioid Carcinoma Colon Adenocarcinoma

1052	T1052K	Hepatocellular Carcinoma Colon Adenocarcinoma
1055	M1055I	Uterine Mixed Endometrial Carcinoma
1058	I1058M	Uterine Carcinosarcoma/Uterine Malignant Mixed Mullerian Tumor
1065	H1065L	Breast Invasive Lobular Carcinoma
1066	A1066V	Uterine Mixed Endometrial Carcinoma
1068	N1068Y, N1068fs*5 (Frame Shift Insertion)	Pleural Mesothelioma, Epithelioid Type Dedifferentiated Liposarcoma Head and Neck Squamous Cell Carcinoma

^A Unless noted otherwise, the mutations of Table 1 are found in cBioPortal database derived from Cerami et al. *The cBio Cancer Genomics Portal: An Open Platform for Exploring Multidimensional Cancer Genomics Data*. Cancer Discovery. May 2012 2; 401; and Gao et al. *Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal*. Sci. Signal. 6, pl1 (2013).

† Velho S, Oliveira C, Ferreira A, Ferreira AC, Suriano G, Schwartz S Jr, Duval A, Carneiro F, Machado JC, Hamelin R, Seruca R. The prevalence of PIK3CA mutations in gastric and colon cancer. Eur J Cancer. 2005 Jul;41(11):1649-54. doi: 10.1016/j.ejca.2005.04.022. PMID: 15994075.

Exemplary Sequence of Human Phosphatidylinositol 4,5-bisphosphate 3-kinase isoform alpha (UniProtKB entry P42336) (SEQ ID NO: 1)

MPPRPSSGEL WGIHLMPPRI LVECLLPNGM IVTLECLREA TLITIKHELF KEARKYPLHQ
LLQDESSYIF VSVTQEAERE EFFEDETRRLC DLRLFPFLK
VIEPVG NREE KILNREIGFA IGMPVCEFD M VKDPEVQDFR RNILNVCKEA
VDLRDLNSPH SRAMYVYPPN VESPELPKH IYNKLDKGQI IVVIWVIVSP
NNDKQKYTLK INHDCVPEQV IAEAIRKKTR SMLLSSEQLK LCVLEYQGKY
ILKVCGCDEY FLEKYPLSQY KYIRSCIMLG RMPNLMMLAK ESLYSQLPMD
CFTMPSYSRR ISTATPYMNG ETSTKSLWVI NSALRIKILC ATYVNVNIRD
IDKIYVRTGI YHGGEPLCDN VNTQRVPCSN PRWNEWLN YD IYIPDLPRAA
RLCLSICSVK GRKGAKEEHC PLAWGNINLF DYTDTLVSGK MALNLWPVPH
GLEDLLNPIG VTGSNPNKET PCLELEFDWF SSVVKFPDMS VIEEHANWSV
SREAGFSYSH AGLSNRLARD NELRENDKEQ LKAISTRDPL SEITEQEKDF
LWSHRHYCVT IPEILPKLLL SVKWSNRDEV AQMYCLVKDW PPIKPEQAME
LLDCNYPDPM VRGFAVRCLE KYLTDDKLSQ YLIQLVQVLK YEQYLDNLLV

RFLKKALTN QRIGFFFWH LKSEMHNKTV SQRFGLLLES YCRACGMYLK
HLNRQVEAME KLINLTDILK QEKKDETQKV QMKFLVEQMR RPDFMDALQG
FLSPLNPAHQ LGNLRLEECR IMSSAKRPLW LNWENPDIMS ELLFQNEII
FKNGDDLQRD MLTLQIRIM ENIWQNQGLD LRMLPYGCLS IGDCVGLIEV
5 VRNSHTIMQI QCKGGLKGAL QFNSHTLHQW LKDKNKGEIY DAAIDLFTRS
CAGYCVATFI LGIGDRHNSN IMVKDDGQLF HIDFGHFLDH KKKKFGYKRE
RVPFVLTQDF LIVISKGAQE CTKTREFERF QEMCYKAYLA IRQHANLFIN
LFSMMLGSGM PELQSFDIA YIRKTLALDK TEQEALYFM KQMNDAAHHGG
WTTKMDWIFH TIKQHALN

10 Also provided is a method for inhibiting PI3K α activity in a cell, comprising contacting the cell with a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the contacting is *in vitro*. In some embodiments, the contacting is *in vivo*. In some embodiments, the contacting is *in vivo*, wherein the method comprises administering an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, to a subject
15 having a cell having aberrant PI3K α activity. In some embodiments, the cell is a cancer cell. In some embodiments, the cancer cell is any cancer as described herein. In some embodiments, the cancer cell is a PI3K α -associated cancer cell. As used herein, the term "contacting" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" a PI3K α protein with a compound provided herein includes the administration of a
20 compound provided herein to an individual or subject, such as a human, having a PI3K α protein, as well as, for example, introducing a compound provided herein into a sample containing a cellular or purified preparation containing the PI3K α protein.

Also provided herein is a method of inhibiting cell proliferation, *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound of Formula (I), or a
25 pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein.

Further provided herein is a method of increase cell death, *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein. Also provided
30 herein is a method of increasing tumor cell death in a subject, comprising administering to the

subject an effective compound of Formula (I), or a pharmaceutically acceptable salt thereof, in an amount effective to increase tumor cell death.

Also provided is a method for inhibiting PI3K α activity in a cell, comprising contacting the cell with a compound of Formula (II), or a pharmaceutically acceptable salt thereof. In some embodiments, the contacting is *in vitro*. In some embodiments, the contacting is *in vivo*. In some embodiments, the contacting is *in vivo*, wherein the method comprises administering an effective amount of a compound of Formula (II), or a pharmaceutically acceptable salt thereof, to a subject having a cell having aberrant PI3K α activity. In some embodiments, the cell is a cancer cell. In some embodiments, the cancer cell is any cancer as described herein. In some embodiments, the cancer cell is a PI3K α -associated cancer cell. As used herein, the term "contacting" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" a PI3K α protein with a compound provided herein includes the administration of a compound provided herein to an individual or subject, such as a human, having a PI3K α protein, as well as, for example, introducing a compound provided herein into a sample containing a cellular or purified preparation containing the PI3K α protein.

Also provided herein is a method of inhibiting cell proliferation, *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound of Formula (II), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein.

Further provided herein is a method of increase cell death, *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound of Formula (II), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein. Also provided herein is a method of increasing tumor cell death in a subject, comprising administering to the subject an effective compound of Formula (II), or a pharmaceutically acceptable salt thereof, in an amount effective to increase tumor cell death.

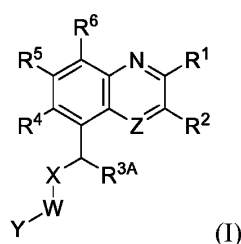
In some embodiments, the PI3K α is human PI3K α . In some embodiments, the PI3K α has one or more point mutations in the *PIK3CA* gene. In some embodiments, the point mutations include a substitution at amino acid position 1047 of a human PI3K α protein. In some embodiments, the substitution is H1047R.

When employed as pharmaceuticals, the compounds of Formula (I), including pharmaceutically acceptable salts thereof, can be administered in the form of pharmaceutical compositions as described herein.

5

NUMBERED EMBODIMENTS

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

Z is N or CH;

10

R¹ is hydrogen, halogen, cyano, C3-C6 cycloalkyl, C1-C6 thioalkyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 alkoxyalkyl, 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl; or C1-C6 alkyl optionally substituted with (i) C3-C6 cycloalkyl or (ii) 4-10 membered heterocyclyl;

15

R² is C6-C10 aryl optionally substituted with 1-4 independently selected R^{2A}, 5-10 membered heteroaryl optionally substituted with 1-4 independently selected R^{2A}, 4-10 membered heterocyclyl optionally substituted with 1-4 independently selected R^{2A}, C4-C10 cycloalkyl optionally substituted with 1-4 independently selected R^{2A}, 4-10 membered heterocycloxy optionally substituted with 1-4 independently selected R^{2A}, 5-10 heteroaryloxy optionally substituted with 1-4 independently selected R^{2A}, C1-C6 alkoxyalkyl optionally substituted with -C(=O)NR^AR^C, or C1-C6 alkoxy optionally substituted with -C(=O)NR^AR^C, C4-C10 cycloalkyl, 4-10 membered heterocyclyl, 5-10 membered heteroaryl, or phenyl;

20

each R^{2A} is independently selected from:

(i) halogen;

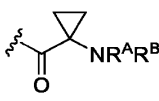
25

(ii) cyano;

(iii) hydroxyl;

(iv) -NR^AR^B;

(v) $-C(=O)NR^A R^B$;

(vi)  ;

(vii) $-NHC(=O)R^C$;

(viii) $-C(=O)OR^D$;

5 (ix) $-SO_2R^D$;

(x) $-NHSO_2R^D$;

(xi) $-SO_2NR^D R^E$;

(xii) $-NHC(=O)C1-C6$ alkyl optionally substituted with $NR^A R^B$;

(xiii) C1-C6 haloalkyl;

10 (xiv) C1-C6 hydroxyalkyl;

(xv) 5-10 membered heteroaryl optionally substituted with 1-3 substituents independently selected from hydroxyl, cyano, halogen, $-C(=O)NR^A R^B$, $-NR^A R^B$, C1-C6 alkyl optionally substituted with hydroxyl; and 4-10 membered heterocyclyl optionally substituted with hydroxyl or C1-C6 alkyl;

15 (xvi) 4-10 membered heterocyclyl optionally substituted with 1-3 substituents independently selected from hydroxyl, cyano, halogen, C1-C6 haloalkyl, $-C(=O)C1-C6$ alkyl, $-SO_2(C1-C6$ alkyl), $-SO_2NR^D R^E$, C1-C6 alkoxy, $-C(=O)NR^A R^B$, $-NR^A R^B$, $-NHC(=O)C1-C6$ alkyl optionally substituted with $-NR^A R^B$, and C1-C6 alkyl optionally substituted with C1-C6 alkoxy or hydroxyl;

20 (xvii) C1-C6 alkyl optionally substituted with 1-3 substituents independently selected from hydroxyl, oxo, $-NR^A R^B$, $-C(=O)NR^A R^B$, C1-C6 alkoxy, and 4-10 membered heterocyclyl optionally substituted with hydroxyl, C1-C6 alkyl, aralkyl, heteroaralkyl, $-C(=O)NR^A R^B$, or $-C(=O)C3-C6$ cycloalkyl;

25 (xviii) C1-C6 alkoxy optionally substituted with $-NR^A R^B$ or 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl, aralkyl, heteroaralkyl, or $-C(=O)C3-C6$ cycloalkyl;

(xix) C3-C6 cycloalkyl optionally substituted with hydroxyl, $-C(=O)NR^A R^B$, $-C(=N)OR^D$, or 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl; and

(xx) 4-10 membered heterocyclyloxy optionally substituted with hydroxyl, cyano, halogen, or C1-C6 alkyl optionally substituted with hydroxyl;

each R^A and R^B is independently selected from hydrogen, hydroxyl, C1-C6 alkoxy, C3-C6 cycloalkyl, C2-C6 alkenyl, and C1-C6 alkyl optionally substituted with hydroxyl or C1-C6 alkoxy, or R^A and R^B together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclyl optionally substituted with 1-2 substituents independently selected from halogen, C1-C6 alkyl, and $-C(=O)C1-C6$ alkyl;

each R^C is independently selected from C3-C6 cycloalkyl, $-C(=O)NHR^{Y1}$, and a C1-C6 alkyl optionally substituted with $-NR^A R^B$ or with 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl or with C1-C6 hydroxyalkyl;

each R^D and R^E is independently selected from hydrogen, hydroxyl, phenyl, C1-C6 alkoxy, and C1-C6 alkyl optionally substituted with oxo or $-NR^A R^B$;

each R^{3A} and R^{3B} is independently selected from hydrogen, C1-C6 alkyl, C1-C6 alkoxy, and C1-C6 haloalkyl, or R^{3A} and R^{3B} , together with the carbon and nitrogen atoms, respectively, to which they are attached together form a 4-8 membered heterocyclyl group;

R^4 is hydrogen, halogen, C1-C6 alkyl, or acrylamido;

R^5 is hydrogen, halogen, C1-C6 alkyl, cyano, $-NR^{5A}R^{5B}$, $-NR^{5A}C(=O)R^{5B}$, or $-C(=O)NR^{5A}R^{5B}$;

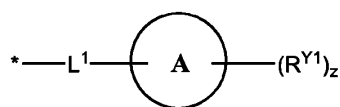
R^{5A} and R^{5B} are independently selected from hydrogen, C1-C6 alkyl, C2-C6 alkenyl, and C1-C6 hydroxyalkyl;

R^6 is hydrogen, halogen, or C1-C6 alkyl;

X is a bond, CH_2 , $CH(CH_3)$, $C(CH_3)_2$, or ;

W is NR^{3B} or O;

Y is phenyl, naphthyl, or 5-10 membered heteroaryl, wherein the phenyl, naphthyl, and 5-10 membered heteroaryl are optionally and independently substituted with 1-3 independently



selected R^Y or , wherein * represents the connection of L^1 to the remainder of the compound of Formula (I);

each R^Y is independently selected from: halogen, cyano, hydroxyl, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkoxy, C1-C6 hydroxyalkyl, $-(CH_2)_n-C(=O)R^F$, $-(CH_2)_n-NHC(=O)R^F$, $-(CH_2)_n-NHC(=O)OR^F$, $-C(=O)C(=O)NHR^F$, $-CO_2R^G$, $-(CH_2)_n-SO_2NR^H R^I$, $-(CH_2)_n-NHSO_2R^J$,

$-(\text{CH}_2)_n-\text{S}(=\text{O})(=\text{NR}^{\text{H}})\text{R}^{\text{J}}$, $-(\text{CH}_2)_n-\text{SO}_2\text{R}^{\text{J}}$, $-(\text{CH}_2)_n-\text{C}(=\text{O})\text{NR}^{\text{H}}\text{R}^{\text{I}}$, $-(\text{CH}_2)_n-\text{C}(=\text{O})\text{NR}^{\text{H}}\text{OR}^{\text{I}}$, and C1-C6 haloalkyl optionally substituted with hydroxyl;

each R^{F} is independently selected from: C3-C6 cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocyclyl optionally substituted with C1-C6 alkyl; and C1-C6 alkyl optionally substituted with hydroxyl or $-\text{SO}_2(\text{C1-C6 alkyl})$;

each R^{G} is independently selected from: hydrogen, C3-C6 cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocyclyl, and C1-C6 alkyl optionally substituted with hydroxyl or $-\text{SO}_2(\text{C1-C6 alkyl})$;

each R^{H} and R^{I} is independently selected from: hydrogen, C1-C6 alkoxy, C3-C6 cycloalkyl, C2-C6 alkenyl, $-(\text{CH}_2)_n-\text{C}(=\text{O})\text{NH}_2$, $-(\text{CH}_2)_n-\text{SO}_2\text{NH}_2$, $-(\text{CH}_2)_n-\text{SO}_2(\text{C1-C6 alkyl})$, C1-C6 alkyl optionally substituted with 1-2 substituents independently selected from hydroxyl, $-\text{SO}_2(\text{C1-C6 alkyl})$, C1-C6 alkoxy, 5-6 membered heteroaryl, C3-C6 cycloalkyl, and $-\text{C}(=\text{O})\text{NR}^{\text{K1}}\text{R}^{\text{K2}}$; or R^{H} and R^{I} together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclyl optionally substituted with 1-2 substituents independently selected from halogen, C1-C6 alkyl, and $-\text{C}(=\text{O})\text{C1-C6 alkyl}$;

R^{J} is C1-C6 alkyl, C3-C6 cycloalkyl, or C1-C6 alkoxy;

each R^{K1} and R^{K2} is independently hydrogen or C1-C6 alkyl;

Ring A is phenyl, 4-10 membered heteroaryl, 4-10 membered heterocyclyl, or C4-C10 cycloalkyl;

L^1 is a bond, C1-C6 alkoxy, $-(\text{CH}_2)_n-\text{NHC}(=\text{O})-$, $-\text{C}(=\text{O})\text{NH}-(\text{CH}_2)_n-$, $-\text{CO}_2-$, $-\text{SO}_2-$, $-\text{NHSO}_2-$, $-\text{SO}_2\text{NH}-$, $-\text{S}(=\text{O})(=\text{NR}^{\text{G}})-$, $-\text{SO}_2(\text{C1-C6 alkylene})-$, $-\text{C}(=\text{O})\text{C}(=\text{O})\text{NH}-$, or C1-C6 alkylene optionally substituted with oxo;

each R^{Y1} is independently selected from: cyano, hydroxyl, halogen, $-\text{C}(=\text{O})\text{R}^{\text{F}}$, $-\text{NHC}(=\text{O})\text{R}^{\text{F}}$, $-\text{CO}_2\text{R}^{\text{G}}$, $-\text{SO}_2\text{NR}^{\text{H}}\text{R}^{\text{I}}$, $-\text{NHSO}_2\text{R}^{\text{J}}$, $-\text{S}(=\text{O})(=\text{NR}^{\text{H}})\text{R}^{\text{J}}$, $-\text{SO}_2(\text{C1-C6 alkyl})$, $-\text{C}(=\text{O})\text{NR}^{\text{H}}\text{R}^{\text{I}}$, 4-6 membered heteroaryl, C1-C6 alkoxy optionally substituted with R^{Y2} , C1-C6 haloalkyl, C1-C6 alkyl optionally substituted with R^{Y2} , and 4-6 membered heterocyclyl optionally substituted with hydroxyl or C1-C6 alkyl;

R^{Y2} is hydroxyl, $-\text{NR}^{\text{H}}\text{R}^{\text{I}}$, $-\text{C}(=\text{O})\text{NR}^{\text{H}}\text{R}^{\text{I}}$, or $-\text{SO}_2\text{NR}^{\text{H}}\text{R}^{\text{I}}$;

n is 0, 1, or 2; and

z is 0, 1, 2, or 3.

2. The compound of Embodiment 1, wherein Z is CH.

3. The compound of Embodiment 1, wherein Z is N.
4. The compound of any one of Embodiments 1-3, wherein R¹ is hydrogen.
5. The compound of any one of Embodiments 1-3, wherein R¹ is halogen.
6. The compound of any one of Embodiments 1-3, wherein R¹ is cyano.
- 5 7. The compound of any one of Embodiments 1-3, wherein R¹ is C3-C6 cycloalkyl.
8. The compound of any one of Embodiments 1-3, wherein R¹ is C1-C6 alkyl optionally substituted with C3-C6 cycloalkyl, or 4-10 membered heterocyclyl.
9. The compound of any one of Embodiments 1-3 or 8, wherein R¹ is C1-C6 alkyl substituted with C3-C6 cycloalkyl, or 4-10 membered heterocyclyl.
- 10 10. The compound of any one of Embodiments 1-3 or 8, wherein R¹ is C1-C6 alkyl
11. The compound of any one of Embodiments 1-3, 8, or 10, wherein R¹ is methyl.
12. The compound of any one of Embodiments 1-3, wherein R¹ is 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl.
13. The compound of any one of Embodiments 1-3, wherein R¹ is C1-C6 thioalkyl.
- 15 14. The compound of any one of Embodiments 1-3, wherein R¹ is C1-C6 haloalkyl.
15. The compound of any one of Embodiments 1-3, wherein R¹ is C1-C6 alkoxy.
16. The compound of any one of Embodiments 1-3, wherein R¹ is C1-C6 alkoxyalkyl.
17. The compound of any one of Embodiments 1-16, wherein R² is C6-C10 aryl optionally substituted with 1-4 independently selected R^{2A}.
- 20 18. The compound of any one of Embodiments 1-16 or 17, wherein R² is C6-C10 aryl substituted with 1-4 independently selected R^{2A}.
19. The compound of any one of Embodiments 1-16 or 17, wherein R² is C6-C10 aryl.
20. The compound of any one of Embodiments 1-18, wherein R² is phenyl optionally substituted with 1-4 independently selected R^{2A}.
- 25 21. The compound of any one of Embodiments 1-18 or 20, wherein R² is phenyl substituted with 1-4 independently selected R^{2A}.
22. The compound of any one of Embodiments 1-16 or 20, wherein R² is phenyl.
23. The compound of any one of Embodiments 1-16, wherein R² is 5-10 membered heteroaryl optionally substituted with 1-4 independently selected R^{2A}.
- 30 24. The compound of any one of Embodiments 1-16, wherein R² is 5-10 membered heteroaryl substituted with 1-4 independently selected R^{2A}.

25. The compound of any one of Embodiments 1-16, wherein R^2 is 5-10 membered heteroaryl.
26. The compound of any one of Embodiments 1-16, wherein R^2 is 4-10 membered heterocyclyl optionally substituted with 1-3 independently selected R^{2A} .
- 5 27. The compound of any one of Embodiments 1-16, wherein R^2 is 4-10 membered heterocyclyl substituted with 1-3 independently selected R^{2A} .
28. The compound of any one of Embodiments 1-16, wherein R^2 is 4-10 membered heterocyclyl.
29. The compound of any one of Embodiments 1-16, wherein R^2 is C4-C10 cycloalkyl
10 optionally substituted with 1-3 independently selected R^{2A} .
30. The compound of any one of Embodiments 1-16, wherein R^2 is C4-C10 cycloalkyl substituted with 1-3 independently selected R^{2A} .
31. The compound of any one of Embodiments 1-16, wherein R^2 is C4-C10 cycloalkyl.
32. The compound of any one of Embodiments 1-16, wherein R^2 is 4-10 membered
15 heterocycloxyloxy optionally substituted with 1-4 independently selected R^{2A} .
33. The compound of any one of Embodiments 1-16, wherein R^2 is 4-10 membered heterocycloxyloxy substituted with 1-4 independently selected R^{2A} .
34. The compound of any one of Embodiments 1-16, wherein R^2 is 4-10 membered heterocycloxyloxy.
- 20 35. The compound of any one of Embodiments 1-16, wherein R^2 is 5-10 heteroaryloxy optionally substituted with 1-4 independently selected R^{2A} .
36. The compound of any one of Embodiments 1-16, wherein R^2 is 5-10 heteroaryloxy substituted with 1-4 independently selected R^{2A} .
37. The compound of any one of Embodiments 1-16, wherein R^2 is 5-10 heteroaryloxy.
- 25 38. The compound of any one of Embodiments 1-16, wherein R^2 is C1-C6 alkoxy optionally substituted with $-C(=O)NR^A R^C$, C4-C10 cycloalkyl, 4-10 membered heterocyclyl, 5-10 membered heteroaryl, or phenyl.
39. The compound of any one of Embodiments 1-16 or 38, wherein R^2 is C1-C6 alkoxy substituted with $-C(=O)NR^A R^C$, C4-C10 cycloalkyl, 4-10 membered heterocyclyl, 5-10
30 membered heteroaryl, or phenyl.
40. The compound of any one of Embodiments 1-16 or 38, wherein R^2 is C1-C6 alkoxy.

41. The compound of any one of Embodiments 1-16, R^2 is C1-C6 alkoxyalkyl optionally substituted with $-C(=O)NR^A R^C$.

42. The compound of any one of Embodiments 1-16, R^2 is C1-C6 alkoxyalkyl substituted with $-C(=O)NR^A R^C$.

5 43. The compound of any one of Embodiments 1-16, R^2 is C1-C6 alkoxyalkyl.

44. The compound of any one of Embodiments 1-43, wherein 1, 2, 3, or 4 of R^{2A} are independently halogen.

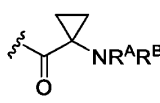
45. The compound of any one of Embodiments 1-44, wherein 1, 2, 3, or 4 of R^{2A} are independently cyano.

10 46. The compound of any one of Embodiments 1-45, wherein 1, 2, 3, or 4 of R^{2A} are independently hydroxyl.

47. The compound of any one of Embodiments 1-46, wherein 1, 2, 3, or 4 of R^{2A} are independently $-NR^A R^B$.

15 48. The compound of any one of Embodiments 1-47, wherein 1, 2, 3, or 4 of R^{2A} are independently $-C(=O)NR^A R^B$.

49. The compound of any one of Embodiments 1-48, wherein 1, 2, 3, or 4 of R^{2A} are

independently .

50. The compound of any one of Embodiments 1-49, wherein 1, 2, 3, or 4 of R^{2A} are independently $-NHC(=O)R^C$.

20 51. The compound of any one of Embodiments 1-50, wherein 1, 2, 3, or 4 of R^{2A} are independently $-C(=O)OR^D$.

52. The compound of any one of Embodiments 1-51, wherein 1, 2, 3, or 4 of R^{2A} are independently $-SO_2R^D$.

25 53. The compound of any one of Embodiments 1-52, wherein 1, 2, 3, or 4 of R^{2A} are independently $-NHSO_2R^D$.

54. The compound of any one of Embodiments 1-53, wherein 1, 2, 3, or 4 of R^{2A} are independently $-SO_2NR^D R^E$.

55. The compound of any one of Embodiments 1-54, wherein 1, 2, 3, or 4 of R^{2A} are independently $-NHC(=O)C1-C6$ alkyl optionally substituted with $NR^A R^B$.

56. The compound of any one of Embodiments 1-55, wherein 1, 2, 3, or 4 of R^{2A} are independently $-NHC(=O)C1-C6$ alkyl substituted with $NR^A R^B$.

57. The compound of any one of Embodiments 1-56, wherein 1, 2, 3, or 4 of R^{2A} are independently C1-C6 haloalkyl.

5 58. The compound of any one of Embodiments 1-57, wherein 1, 2, 3, or 4 of R^{2A} are independently C1-C6 hydroxyalkyl.

59. The compound of any one of Embodiments 1-58, wherein 1, 2, 3, or 4 of R^{2A} are independently 5-10 membered heteroaryl optionally substituted with 1-3 substituents independently selected from hydroxyl, cyano, C1-C6 alkyl optionally substituted with hydroxyl, 10 halogen, $-C(=O)NR^A R^B$, $-NR^A R^B$, and 4-10 membered heterocyclyl optionally substituted with hydroxyl or C1-C6 alkyl.

60. The compound of any one of Embodiments 1-59, wherein 1, 2, 3, or 4 of R^{2A} are independently 5-10 membered heteroaryl substituted with 1-3 substituents independently selected from hydroxyl, cyano, C1-C6 alkyl, halogen, $-C(=O)NR^A R^B$, $-NR^A R^B$, and 4-10 membered 15 heterocyclyl optionally substituted with hydroxyl or C1-C6 alkyl.

61. The compound of any one of Embodiments 1-60, wherein 1, 2, 3, or 4 of R^{2A} are independently 5-10 membered heteroaryl.

62. The compound of any one of Embodiments 1-61, wherein 1, 2, 3, or 4 of R^{2A} are independently 4-10 membered heterocyclyl optionally substituted with 1-3 substituents 20 independently selected from hydroxyl, cyano, halogen, C1-C6 haloalkyl, $-C(=O)C1-C6$ alkyl, $-SO_2(C1-C6$ alkyl), $-SO_2NR^D R^E$, C1-C6 alkoxy, $-C(=O)NR^A R^B$, $-NR^A R^B$, $-NHC(=O)C1-C6$ alkyl optionally substituted with $-NR^A R^B$, and C1-C6 alkyl optionally substituted with C1-C6 alkoxy or hydroxyl.

63. The compound of any one of Embodiments 1-62, wherein 1, 2, 3, or 4 of R^{2A} are independently 4-10 membered heterocyclyl substituted with 1-3 substituents independently 25 selected from hydroxyl, cyano, halogen, C1-C6 haloalkyl, $-C(=O)C1-C6$ alkyl, $-SO_2(C1-C6$ alkyl), $-SO_2NR^D R^E$, C1-C6 alkoxy, $-C(=O)NR^A R^B$, $-NR^A R^B$, $-NHC(=O)C1-C6$ alkyl optionally substituted with $-NR^A R^B$, and C1-C6 alkyl optionally substituted with C1-C6 alkoxy or hydroxyl.

64. The compound of any one of Embodiments 1-63, wherein 1, 2, 3, or 4 of R^{2A} are independently 4-10 membered heterocyclyl substituted with 1-3 substituents independently 30 selected from hydroxyl, cyano, halogen, C1-C6 haloalkyl, $-C(=O)C1-C6$ alkyl, $-SO_2(C1-C6$ alkyl),

-SO₂NR^{DR^E}, C1-C6 alkoxy, -C(=O)NR^{AR^B}, -NR^{AR^B}, -NHC(=O)C1-C6 alkyl substituted with -NR^{AR^B}, and C1-C6 alkyl substituted with C1-C6 alkoxy or hydroxyl.

65. The compound of any one of Embodiments 1-64, wherein 1, 2, 3, or 4 of R^{2A} are independently 4-10 membered heterocyclyl substituted with 1-3 substituents independently selected from hydroxyl, cyano, halogen, C1-C6 haloalkyl, -C(=O)C1-C6 alkyl, -SO₂(C1-C6 alkyl), -SO₂NR^{DR^E}, C1-C6 alkoxy, -C(=O)NR^{AR^B}, -NR^{AR^B}, -NHC(=O)C1-C6 alkyl, and C1-C6 alkyl.

66. The compound of any one of Embodiments 1-62, wherein 1, 2, 3, or 4 of R^{2A} are independently 4-10 membered heterocyclyl.

67. The compound of any one of Embodiments 1-66, wherein 1, 2, 3, or 4 of R^{2A} are independently C1-C6 alkyl optionally substituted with 1-3 substituents independently selected from hydroxyl, oxo, -NR^{AR^B}, -C(=O)NR^{AR^B}, and 4-10 membered heterocyclyl optionally substituted with hydroxyl, C1-C6 alkyl, aralkyl, heteroaralkyl, -C(=O)NR^{AR^B}, or -C(=O)C3-C6 cycloalkyl.

68. The compound of any one of Embodiments 1-67, wherein 1, 2, 3, or 4 of R^{2A} are independently C1-C6 alkyl substituted with 1-3 substituents independently selected from hydroxyl, oxo, -NR^{AR^B}, -C(=O)NR^{AR^B}, C1-C6 alkoxy, and 4-10 membered heterocyclyl optionally substituted with hydroxyl, C1-C6 alkyl, aralkyl, heteroaralkyl, -C(=O)NR^{AR^B}, or -C(=O)C3-C6 cycloalkyl.

69. The compound of any one of Embodiments 1-68, wherein 1, 2, 3, or 4 of R^{2A} are independently C1-C6 alkyl substituted with 1-3 substituents independently selected from hydroxyl, oxo, -NR^{AR^B}, -C(=O)NR^{AR^B}, C1-C6 alkoxy, and 4-10 membered heterocyclyl substituted with hydroxyl, C1-C6 alkyl, aralkyl, heteroaralkyl, -C(=O)NR^{AR^B}, or -C(=O)C3-C6 cycloalkyl.

70. The compound of any one of Embodiments 1-69, wherein 1, 2, 3, or 4 of R^{2A} are independently C1-C6 alkyl substituted with 1-3 substituents independently selected from hydroxyl, oxo, -NR^{AR^B}, -C(=O)NR^{AR^B}, and 4-10 membered heterocyclyl.

71. The compound of any one of Embodiments 1-67, wherein 1, 2, 3, or 4 of R^{2A} are independently C1-C6 alkyl.

72. The compound of any one of Embodiments 1-71, wherein 1, 2, 3, or 4 of R^{2A} are independently C1-C6 alkoxy optionally substituted with -NR^{AR^B} or 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl, aralkyl, heteroaralkyl, or -C(=O)C3-C6 cycloalkyl.

73. The compound of any one of Embodiments 1-72, wherein 1, 2, 3, or 4 of R^{2A} are independently C1-C6 alkoxy substituted with $-NR^A R^B$ or 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl, aralkyl, heteroaralkyl, or $-C(=O)C3-C6$ cycloalkyl.

74. The compound of any one of Embodiments 1-73, wherein 1, 2, 3, or 4 of R^{2A} are independently C1-C6 alkoxy substituted with $-NR^A R^B$ or 4-10 membered heterocyclyl substituted with C1-C6 alkyl, aralkyl, heteroaralkyl, or $-C(=O)C3-C6$ cycloalkyl.

75. The compound of any one of Embodiments 1-73, wherein 1, 2, 3, or 4 of R^{2A} are independently C1-C6 alkoxy substituted with $-NR^A R^B$ or 4-10 membered heterocyclyl.

76. The compound of any one of Embodiments 1-72, wherein 1, 2, 3, or 4 of R^{2A} are independently C1-C6 alkoxy.

77. The compound of any one of Embodiments 1-76, wherein 1, 2, 3, or 4 of R^{2A} are independently C3-C6 cycloalkyl optionally substituted with hydroxyl, $-C(=O)NR^A R^B$, $-C(=N)OR^D$, or 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl.

78. The compound of any one of Embodiments 1-77, wherein 1, 2, 3, or 4 of R^{2A} are independently C3-C6 cycloalkyl substituted with hydroxyl, $-C(=O)NR^A R^B$, $-C(=N)OR^D$, or 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl.

79. The compound of any one of Embodiments 1-78, wherein 1, 2, 3, or 4 of R^{2A} are independently C3-C6 cycloalkyl substituted with hydroxyl, $-C(=O)NR^A R^B$, $-C(=N)OR^D$, or 4-10 membered heterocyclyl substituted with C1-C6 alkyl.

80. The compound of any one of Embodiments 1-79, wherein 1, 2, 3, or 4 of R^{2A} are independently C3-C6 cycloalkyl substituted with hydroxyl, $-C(=O)NR^A R^B$, $-C(=N)OR^D$, or 4-10 membered heterocyclyl.

81. The compound of any one of Embodiments 1-77, wherein 1, 2, 3, or 4 of R^{2A} are independently C3-C6 cycloalkyl.

82. The compound of any one of Embodiments 1-81, wherein X is a bond.

83. The compound of any one of Embodiments 1-81, wherein X is CH_2 .

84. The compound of any one of Embodiments 1-81, wherein X is $CH(CH_3)$.

85. The compound of any one of Embodiments 1-81, wherein X is $C(CH_3)_2$.

86. The compound of any one of Embodiments 1-81, wherein X is .

87. The compound of any one of Embodiments 1-86, wherein W is O.

88. The compound of any one of Embodiments 1-87, wherein R^{3A} is hydrogen.
89. The compound of any one of Embodiments 1-87, wherein R^{3A} is C1-C6 alkyl.
90. The compound of any one of Embodiments 1-87 or 89, wherein R^{3A} is methyl.
91. The compound of any one of Embodiments 1-87, wherein R^{3A} is C1-C6 alkoxy.
- 5 92. The compound of any one of Embodiments 1-87, wherein R^{3A} is C1-C6 haloalkyl.
93. The compound of any one of Embodiments 1-86, wherein W is NR^{3B} .
94. The compound of any one of Embodiments 1-86 or 93, wherein one of R^{3A} and R^{3B} is hydrogen and the other of R^{3A} and R^{3B} is C1-C6 alkyl.
95. The compound of any one of Embodiments 1-86 or 93, wherein one of R^{3A} and R^{3B} is hydrogen and the other of R^{3A} and R^{3B} is methyl.
- 10 96. The compound of any one of Embodiments 1-86 or 93, wherein each of R^{3A} and R^{3B} is hydrogen.
97. The compound of any one of Embodiments 1-86 or 93, wherein each of R^{3A} and R^{3B} is an independently selected C1-C6 alkyl.
- 15 98. The compound of any one of Embodiments 1-86, 93, or 97, wherein each of R^{3A} and R^{3B} is methyl.
99. The compound of any one of Embodiments 1-86 or 93, wherein one of R^{3A} and R^{3B} is hydrogen and the other of R^{3A} and R^{3B} is C1-C6 alkoxy.
100. The compound of any one of Embodiments 1-86 or 93, wherein one of R^{3A} and R^{3B} is C1-C6 alkyl and the other of R^{3A} and R^{3B} is C1-C6 alkoxy.
- 20 101. The compound of any one of Embodiments 1-86 or 93, wherein each of R^{3A} and R^{3B} is C1-C6 alkoxy.
102. The compound of any one of Embodiments 1-86 or 93, wherein one of R^{3A} and R^{3B} is hydrogen and the other of R^{3A} and R^{3B} is C1-C6 haloalkyl.
- 25 103. The compound of any one of Embodiments 1-86 or 93, wherein one of R^{3A} and R^{3B} is C1-C6 alkyl and the other of R^{3A} and R^{3B} is C1-C6 haloalkyl.
104. The compound of any one of Embodiments 1-86 or 93, wherein each of R^{3A} and R^{3B} is C1-C6 haloalkyl.
- 30 105. The compound of any one of Embodiments 1-86 or 93, wherein R^{3A} and R^{3B} , together with the carbon and nitrogen atoms, respectively, to which they are attached together form a 4-8 membered heterocyclyl group.

106. The compound of any one of Embodiments 1-105, wherein Y is unsubstituted phenyl.

107. The compound of any one of Embodiments 1-105, wherein Y is unsubstituted naphthyl.

5 108. The compound of any one of Embodiments 1-105, wherein Y is unsubstituted 5-10 membered heteroaryl.

109. The compound of any one of Embodiments 1-105, wherein Y is phenyl optionally substituted with 1-3 independently selected R^Y .

10 110. The compound of any one of Embodiments 1-105, wherein Y is naphthyl optionally substituted with 1-3 independently selected R^Y .

111. The compound of any one of Embodiments 1-105, wherein Y is 5-10 membered heteroaryl optionally substituted with 1-3 independently selected R^Y .

112. The compound of any one of Embodiments 1-105 or 109-111, wherein 1, 2, or 3 of R^Y is independently halogen.

15 113. The compound of any one of Embodiments 1-105 or 109-111, wherein 1, 2, or 3 of R^Y is hydroxyl.

114. The compound of any one of Embodiments 1-105 or 109-113, wherein 1, 2, or 3 of R^Y is cyano.

20 115. The compound of any one of Embodiments 1-105 or 109-114, wherein 1, 2, or 3 of R^Y is C1-C6 alkyl.

116. The compound of any one of Embodiments 1-105 or 109-115, wherein 1, 2, or 3 of R^Y is independently C1-C6 haloalkyl optionally substituted with hydroxyl.

117. The compound of any one of Embodiments 1-105 or 109-116, wherein 1, 2, or 3 of R^Y is independently C1-C6 alkoxy.

25 118. The compound of any one of Embodiments 1-105 or 109-117, wherein 1, 2, or 3 of R^Y is independently C1-C6 haloalkoxy.

119. The compound of any one of Embodiments 1-105 or 109-118, wherein 1, 2, or 3 of R^Y is independently C1-C6 hydroxyalkyl.

30 120. The compound of any one of Embodiments 1-105 or 109-119, wherein 1, 2, or 3 of R^Y is independently $-(CH_2)_n-NHC(=O)R^F$.

121. The compound of any one of Embodiments 1-105 or 109-120, wherein 1, 2, or 3 of R^Y is independently $-(CH_2)_n-C(=O)R^F$.

122. The compound of any one of Embodiments 1-105 or 109-121, wherein 1, 2, or 3 of R^Y is independently $-CO_2R^G$.

5 123. The compound of any one of Embodiments 1-105 or 109-122, wherein 1, 2, or 3 of R^Y is independently $-(CH_2)_n-SO_2NR^HR^I$.

124. The compound of any one of Embodiments 1-105 or 109-123, wherein 1, 2, or 3 of R^Y is independently $-(CH_2)_n-NHSO_2R^J$.

10 125. The compound of any one of Embodiments 1-105 or 109-124, wherein 1, 2, or 3 of R^Y is independently $-(CH_2)_n-S(=O)(=NR^H)R^J$.

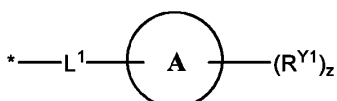
126. The compound of any one of Embodiments 1-105 or 109-125, wherein 1, 2, or 3 of R^Y is independently $-(CH_2)_n-SO_2R^J$.

127. The compound of any one of Embodiments 1-105 or 109-126, wherein 1, 2, or 3 of R^Y is independently $-(CH_2)_n-C(=O)NR^HR^I$.

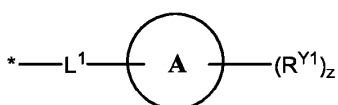
15 128. The compound of any one of Embodiments 1-105 or 109-126, wherein 1, 2, or 3 of R^Y is independently $-(CH_2)_n-C(=O)NR^HOR^I$.

129. The compound of any one of Embodiments 1-105 or 109-127, wherein 1, 2, or 3 of R^Y is independently C1-C6 alkyl.

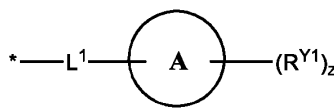
130. The compound of any one of Embodiments 1-105, wherein Y is phenyl substituted

20 with , wherein * represents the connection of L^1 to the remainder of the compound of Formula (I).

131. The compound of any one of Embodiments 1-105, wherein Y is naphthyl

substituted with , wherein * represents the connection of L^1 to the remainder of the compound of Formula (I).

132. The compound of any one of Embodiments 1-105, wherein Y is 5-10 membered

heteroaryl substituted with , wherein * represents the connection of L¹ to the remainder of the compound of Formula (I).

133. The compound of any one of Embodiments 1-105 or 130-132, wherein L¹ is a bond.

5 134. The compound of any one of Embodiments 1-105 or 130-132, wherein L¹ is C1-C6 alkoxylenes.

135. The compound of any one of Embodiments 1-105 or 130-132, wherein L¹ is - (CH₂)_n-NHC(=O)-.

136. The compound of any one of Embodiments 1-105 or 130-132, wherein L¹ is - C(=O)NH-(CH₂)_n-.
10

137. The compound of any one of Embodiments 1-105 or 130-132, wherein L¹ is -CO₂-

138. The compound of any one of Embodiments 1-105 or 130-132, wherein L¹ is -SO₂-

15 139. The compound of any one of Embodiments 1-105 or 130-132, wherein L¹ is - NHSO₂- or -SO₂NH-.

140. The compound of any one of Embodiments 1-105 or 130-132, wherein L¹ is - S(=O)(=NR^G)-.

141. The compound of any one of Embodiments 1-105 or 130-132, wherein L¹ is - SO₂(C1-C6 alkylene)-.
20

142. The compound of any one of Embodiments 1-105 or 130-132, wherein L¹ is -C(=O)C(=O)NH-.

143. The compound of any one of Embodiments 1-105 or 130-132, wherein L¹ is C1-C6 alkylene optionally substituted with oxo.

25 144. The compound of any one of Embodiments 1-105 or 130-143, wherein 1, 2, or 3 of R^{Y1} is independently cyano.

145. The compound of any one of Embodiments 1-105 or 130-143, wherein 1, 2, or 3 of R^{Y1} is independently hydroxyl.

146. The compound of any one of Embodiments 1-105 or 130-143, wherein 1, 2, or 3 of R^{Y1} is independently halogen.

147. The compound of any one of Embodiments 1-105 or 130-143, wherein 1, 2, or 3 of R^{Y1} is independently $-C(=O)R^F$.

5 148. The compound of any one of Embodiments 1-105 or 130-143, wherein 1, 2, or 3 of R^{Y1} is independently $-NHC(=O)R^F$.

149. The compound of any one of Embodiments 1-105 or 130-143, wherein 1, 2, or 3 of R^{Y1} is independently $-CO_2R^G$.

10 150. The compound of any one of Embodiments 1-105 or 130-143, wherein 1, 2, or 3 of R^{Y1} is independently $-SO_2NR^HR^I$.

151. The compound of any one of Embodiments 1-105 or 130-143, wherein 1, 2, or 3 of R^{Y1} is independently $-NHSO_2R^J$.

152. The compound of any one of Embodiments 1-105 or 130-143, wherein 1, 2, or 3 of R^{Y1} is independently $-S(=O)(=NR^H)R^F$.

15 153. The compound of any one of Embodiments 1-105 or 130-143, wherein 1, 2, or 3 of R^{Y1} is independently $-SO_2(C1-C6 \text{ alkyl})$.

154. The compound of any one of Embodiments 1-105 or 130-143, wherein 1, 2, or 3 of R^{Y1} is independently $-C(=O)NR^HR^I$.

20 155. The compound of any one of Embodiments 1-105 or 130-143, wherein 1, 2, or 3 of R^{Y1} is independently 4-6 membered heteroaryl.

156. The compound of any one of Embodiments 1-105 or 130-143, wherein 1, 2, or 3 of R^{Y1} is independently C1-C6 alkoxy optionally substituted with R^{Y2} .

157. The compound of any one of Embodiments 1-105 or 130-143, wherein 1, 2, or 3 of R^{Y1} is independently C1-C6 haloalkyl.

25 158. The compound of any one of Embodiments 1-105 or 130-143, wherein 1, 2, or 3 of R^{Y1} is independently C1-C6 alkyl optionally substituted with R^{Y2} .

159. The compound of any one of Embodiments 1-105 or 130-143, wherein 1, 2, or 3 of R^{Y1} is independently 4-6 membered heterocyclyl optionally substituted with hydroxyl or C1-C6 alkyl.

30 160. The compound of any one of Embodiments 1-105 or 130-159, wherein Ring A is phenyl.

161. The compound of any one of Embodiments 1-105 or 130-159, wherein Ring A is 4-10 membered heteroaryl.

162. The compound of any one of Embodiments 1-105 or 130-159, wherein Ring A is 4-10 membered heterocyclyl.

5 163. The compound of any one of Embodiments 1-105 or 130-159, wherein Ring A is C4-C10 cycloalkyl.

164. The compound of any one of Embodiments 1-163, wherein R^4 is hydrogen.

165. The compound of any one of Embodiments 1-163, wherein R^4 is halogen.

166. The compound of any one of Embodiments 1-163, wherein R^4 is C1-C6 alkyl.

10 167. The compound of any one of Embodiments 1-163, wherein R^4 is acrylamido.

168. The compound of any one of Embodiments 1-167, wherein R^5 is hydrogen.

169. The compound of any one of Embodiments 1-167, wherein R^5 is halogen.

170. The compound of any one of Embodiments 1-167, wherein R^5 is C1-C6 alkyl.

171. The compound of any one of Embodiments 1-167, wherein R^5 is cyano.

15 172. The compound of any one of Embodiments 1-167, wherein R^5 is $-NR^{5A}R^{5B}$.

173. The compound of any one of Embodiments 1-167, wherein R^5 is $-C(=O)NR^{5A}R^{5B}$.

174. The compound of any one of Embodiments 1-167, wherein R^5 is $-NR^{5A}C(=O)R^{5B}$.

20 175. The compound of any one of Embodiments 1-167 or 172-174, wherein one of R^{5A} and R^{5B} is hydrogen and the other of R^{5A} and R^{5B} is C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 hydroxyalkyl.

176. The compound of any one of Embodiments 1-167 or 172-174, wherein one of R^{5A} and R^{5B} is C1-C6 alkyl and the other of R^{5A} and R^{5B} is C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 hydroxyalkyl.

25 177. The compound of any one of Embodiments 1-167 or 172-174, wherein each of R^{5A} and R^{5B} is hydrogen.

178. The compound of any one of Embodiments 1-167 or 172-174, wherein each of R^{5A} and R^{5B} is an independently selected C1-C6 alkyl.

179. The compound of any one of Embodiments 1-178, wherein R^6 is hydrogen.

30 180. The compound of any one of Embodiments 1-178, wherein R^6 is halogen.

181. The compound of any one of Embodiments 1-178, wherein R^6 is C1-C6 alkyl.

182. The compound of any one of Embodiments 1-181, wherein each of R^A and R^B are independently selected from hydrogen, hydroxyl, C1-C6 alkoxy, C3-C6 cycloalkyl, C2-C6 alkenyl, or C1-C6 alkyl optionally substituted with hydroxyl or C1-C6 alkoxy.

183. The compound of any one of Embodiments 1-182, wherein one of R^A and R^B is hydrogen and the other of R^A and R^B is hydroxyl, C1-C6 alkoxy, C3-C6 cycloalkyl, C2-C6 alkenyl, or C1-C6 alkyl optionally substituted with hydroxyl or C1-C6 alkoxy.

184. The compound of any one of Embodiments 1-182, wherein one of R^A and R^B is hydrogen and the other of R^A and R^B is hydroxyl, C1-C6 alkoxy, C3-C6 cycloalkyl, C2-C6 alkenyl, or C1-C6 alkyl substituted with hydroxyl or C1-C6 alkoxy.

185. The compound of any one of Embodiments 1-182, wherein one of R^A and R^B is hydrogen and the other of R^A and R^B is hydroxyl, C1-C6 alkoxy, C3-C6 cycloalkyl, C2-C6 alkenyl, or C1-C6 alkyl.

186. The compound of any one of Embodiments 1-182, wherein R^A and R^B together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclyl optionally substituted with 1-2 substituents independently selected from halogen, C1-C6 alkyl, or $-C(=O)C1-C6$ alkyl.

187. The compound of any one of Embodiments 1-182 or 186, wherein R^A and R^B together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclyl substituted with 1-2 substituents independently selected from halogen, C1-C6 alkyl, or $-C(=O)C1-C6$ alkyl.

188. The compound of any one of Embodiments 1-182 or 186, wherein R^A and R^B together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclyl.

189. The compound of any one of Embodiments 1-188, wherein each R^C is independently C3-C6 cycloalkyl, $-C(=O)NHR^{Y1}$, or a C1-C6 alkyl substituted with $-NR^A R^B$ or with 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl or with C1-C6 hydroxylalkyl.

190. The compound of any one of Embodiments 1-188, wherein each R^C is independently C3-C6 cycloalkyl, $-C(=O)NHR^{Y1}$, or a C1-C6 alkyl substituted with $-NR^A R^B$ or with 4-10 membered heterocyclyl substituted with C1-C6 alkyl or with C1-C6 hydroxylalkyl.

191. The compound of any one of Embodiments 1-188, wherein each R^C is independently C3-C6 cycloalkyl, $-C(=O)NHR^{Y1}$, or a C1-C6 alkyl substituted with $-NR^A R^B$ or with 4-10 membered heterocyclyl.

192. The compound of any one of Embodiments 1-188, wherein each R^C is
5 independently C3-C6 cycloalkyl, $-C(=O)NHR^{Y1}$, or a C1-C6 alkyl.

193. The compound of any one of Embodiments 1-192, wherein each R^D is hydrogen, hydroxyl, or C1-C6 alkoxy.

194. The compound of any one of Embodiments 1-192, wherein each R^D is phenyl or C1-C6 alkyl optionally substituted with oxo.

10 195. The compound of any one of Embodiments 1-194, wherein each R^E is hydrogen, hydroxyl, or C1-C6 alkoxy.

196. The compound of any one of Embodiments 1-194, wherein each R^E is phenyl or C1-C6 alkyl optionally substituted with oxo.

15 197. The compound of any one of Embodiments 1-196, wherein each R^F is C1-C6 alkyl optionally substituted with hydroxyl or $-SO_2(C1-C6 \text{ alkyl})$.

198. The compound of any one of Embodiments 1-196, wherein each R^F is C3-C6 cycloalkyl, 5-6 membered heteroaryl, or 4-6 membered heterocyclyl.

199. The compound of any one of Embodiments 1-198, wherein each R^G is hydrogen, C3-C6 cycloalkyl, or C1-C6 alkyl optionally substituted with hydroxyl or $-SO_2(C1-C6 \text{ alkyl})$.

20 200. The compound of any one of Embodiments 1-198, wherein each R^G is 5-6 membered heteroaryl or 4-6 membered heterocyclyl.

201. The compound of any one of Embodiments 1-200, wherein one of R^H and R^I is hydrogen and the other of R^H and R^I is C1-C6 alkyl optionally substituted with C1-C6 alkyl optionally substituted with 1-2 substituents independently selected from hydroxyl, $-SO_2(C1-C6 \text{ alkyl})$, C1-C6 alkoxy, 5-6 membered heteroaryl, C3-C6 cycloalkyl, and $-C(=O)NR^{K1}R^{K2}$.
25

202. The compound of any one of Embodiments 1-200, wherein one of R^H and R^I is hydrogen and the other of R^H and R^I is C1-C6 alkoxy, C3-C6 cycloalkyl, or C2-C6 alkenyl.

203. The compound of any one of Embodiments 1-200, wherein each of R^H and R^I is hydrogen.

30 204. The compound of any one of Embodiments 1-200, wherein each of R^H and R^I is an independently selected C1-C6 alkyl optionally substituted with C1-C6 alkyl optionally substituted

with 1-2 substituents independently selected from hydroxyl, $-\text{SO}_2(\text{C}1\text{-C}6 \text{ alkyl})$, $\text{C}1\text{-C}6$ alkoxy, 5-6 membered heteroaryl, $\text{C}3\text{-C}6$ cycloalkyl, and $-\text{C}(=\text{O})\text{NR}^{\text{K}1}\text{R}^{\text{K}2}$.

205. The compound of any one of Embodiments 1-200, wherein one of R^{H} and R^{I} is hydrogen and the other of R^{H} and R^{I} is $-(\text{CH}_2)_n\text{-C}(=\text{O})\text{NH}_2$, $-(\text{CH}_2)_n\text{-SO}_2\text{NH}_2$, or $-(\text{CH}_2)_n\text{-SO}_2(\text{C}1\text{-C}6 \text{ alkyl})$.

206. The compound of any one of Embodiments 1-200, wherein R^{H} and R^{I} together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclyl optionally substituted with 1-2 substituents independently selected from halogen, $\text{C}1\text{-C}6$ alkyl, and $-\text{C}(=\text{O})\text{C}1\text{-C}6 \text{ alkyl}$.

207. The compound of any one of Embodiments 1-206, wherein R^{J} is $\text{C}1\text{-C}6$ alkyl.

208. The compound of any one of Embodiments 1-206, wherein R^{J} is $\text{C}1\text{-C}6$ alkoxy.

209. The compound of any one of Embodiments 1-206, wherein R^{J} is $\text{C}3\text{-C}6$ cycloalkyl.

210. A compound selected from the group consisting of the compounds in Table A, or a pharmaceutically acceptable salt thereof and the compounds in Table B, or a pharmaceutically acceptable salt thereof.

211. A pharmaceutical composition comprising a compound of any one of Embodiments 1-210, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

212. A method for treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of Embodiments 1-210, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Embodiment 211.

213. A method for treating cancer in a subject in need thereof, the method comprising (a) determining that the cancer is associated with a dysregulation of a *PIK3CA* gene, a $\text{PI}3\text{K}\alpha$ protein, or expression or activity or level of any of the same; and (b) administering to the subject a therapeutically effective amount of a compound of any one of Embodiments 1-210, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Embodiment 211.

214. A method of treating a $\text{PI}3\text{K}\alpha$ -associated cancer in a subject, comprising administering to a subject identified or diagnosed as having a $\text{PI}3\text{K}\alpha$ -associated cancer a therapeutically effective amount of a compound of any one of Embodiments 1-210 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Embodiment 211.

215. A method for inhibiting mutant PI3K α activity in a mammalian cell, the method comprising contacting the mammalian cell with an effective amount of a compound of any one of Embodiments 1-210, or a pharmaceutically acceptable salt thereof.

EXAMPLES

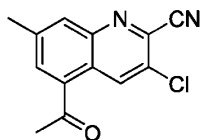
Example 1: Compound Preparation

The general methods for the preparation of the compounds of Formula (I) have been described in an illustrative manner and is intended to be description, rather than of limitation. Thus, it will be appreciated that conditions such as choice of solvent, temperature of reaction, volumes, reaction time may vary while still producing the desired compounds. In addition, it will be appreciated that many of the reagents provided in the following examples may be substituted with other suitable reagents. *See, e.g.*, Smith & March, Advanced Organic Chemistry, 7th Ed. (2013). Such changes and modifications, including without limitation, those relating to the chemical structures, substituents, derivatives, intermediates, syntheses, formulations and / or methods of use provided herein, may be made without departing from the spirit and scope thereof.

The starting materials used for the syntheses are either synthesized or obtained from commercial sources, such as, but not limited to, Sigma-Aldrich, Fluka, Acros Organics, Alfa Aesar, Enamine, Strem, VWR Scientific, and the like. Nuclear Magnetic Resonance (NMR) analysis was conducted using a Bruker AVANCE III HD (300 or 400) MHz spectrometer or Bruker AVANCE NEO 400 MHz spectrometer with an appropriate deuterated solvent. LCMS spectra were obtained on a Shimadzu LCMS-2020 with electrospray ionization in positive ion detection mode with 20ADXR pump, SIL-20ACXR autosampler, CTO-20AC column oven, M20A PDA Detector and LCMS 2020 MS detector.

Intermediate Preparation:

Intermediate: 5-acetyl-3-chloro-7-methylquinoline-2-carbonitrile



Step 1: Synthesis of 5-bromo-3-chloro-7-methylquinolin-2(1H)-one.

In a three necked flask provided with a stir bar, a condenser and a nitrogen inlet, ethyl-2-chloroacetate (32 mL, 42 mmol) and 3-amino-5-bromo-4-tolualdehyde (3 g, 14 mmol) in tetrahydrofuran (32 mL) were charged. The solution was cooled at -78 °C, and 1.3 M THF solution of lithium bis(trimethylsilyl)azanide (3 eq., 393 mmol) was added portion wise under nitrogen atmosphere. The reaction was allowed to warm up to room temperature until deemed complete. The mixture was poured into ice/water and the resulting slurry was extracted with ethyl acetate (2 x 30 mL) and the suspension was washed with water (2 x 30 mL) and concentrated under vacuum using ethyl acetate (50 mL) to dry the solids by azeotropic distillation. The slurry was resuspended in ethyl acetate (30 mL) and heated to 50 °C in a water bath. The solids were cooled while sonicating and filtered using MTBE to transfer and rinse the cake to give the title compound as a white solid (1.7 g, 44%). MS: 273.1 m/z (M+H⁺). ¹H NMR (400 MHz, DMSO) δ 12.49 (s, 1H), 8.17 (s, 1H), 7.42 (s, 1H), 7.14 (s, 1H), 2.38 (s, 3H).

Step 2: Synthesis of 5-acetyl-3-chloro-7-methylquinolin-2(1H)-one.

To a suspension of 5-bromo-3-chloro-7-methyl-2-quinolinol (2 g, 7.34 mmol) in 1,4-dioxane (120 mL, 1.41 mol), 1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (537 mg, 0.1 eq., 734 μmol) and tributyl(1-ethoxyethenyl)stannane (2.98 mL, 1.2 eq., 8.81 mmol) were charged. The suspension was sparged with nitrogen for 3 min and the reaction was heated in a heating block to 110 °C for 2 h. The crude reaction mixture was filtered, the filtrate concentrated, and the resulting solids resuspended in MTBE/heptane (1:1, 100 mL). The resulting thin slurry was concentrated under vacuum to approx 40 mL and the solids obtained were filtered using heptane to transfer and rinse the solids to give the intermediate 3-chloro-5-(1-ethoxyvinyl)-7-methylquinolin-2(1H)-one (1.4 g, 72%). MS: 264.1 m/z (M+H⁺).

The intermediate 3-chloro-5-(1-ethoxyvinyl)-7-methylquinolin-2(1H)-one (1.4 g, 5.3 mmol) was resuspended in THF (30 mL) and a 3N aqueous HCl solution (30 mL, 90 mmol) was charged. The slurry was stirred at room temperature until the reaction was deemed complete (~1 h). The solvent was concentrated, and the aqueous residue was extracted with ethyl acetate (2 x 200 mL). The resulting slurry was concentrated to ~100 mL and a solution of potassium fluoride (1.28 g, 22 mmol) in water (100 mL) was charged. The slurry was stirred at room temperature for 1 h. The layers were allowed to settle and the organic layer containing the slurry was separated and washed with water (2 x 50 mL). The solvent was concentrated to dryness under vacuum, then ethyl acetate (3 x 100 mL) was charged and evaporated to remove water by azeotropic distillation.

To the resulting solids, ethyl acetate (30 mL) was charged and the mixture heated to 60 °C in a water bath until a homogeneous slurry was obtained. The solids were cooled to room temp while sonicating and were filtered using ethyl acetate to wash the cake to give the title compound as a light brown solid. (1.2 g, 69%). MS: 236.1 m/z (M+H⁺). ¹H NMR (400 MHz, DMSO) δ 12.44 (s, 1H), 8.71 (s, 1H), 7.71 (s, 1H), 7.33 (s, 1H), 2.61 (s, 3H), 2.45 (s, 3H).

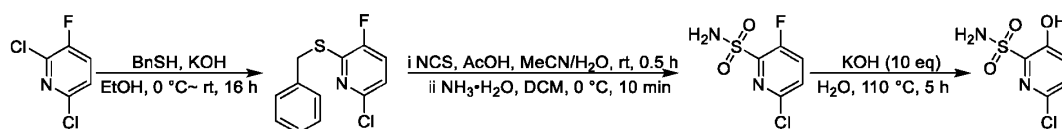
Step 3: 5-acetyl-3-chloro-7-methylquinolin-2-yl trifluoromethanesulfonate.

In a 40 mL vial provided with a stir bar and a septum cap, a suspension of 5-acetyl-3-chloro-7-methylquinolin-2(1H)-one (0.3 g, 1.27 mmol) and pyridine (309 μL, 3.82 mmol) in DCM (12 mL) was charged. The mixture was cooled to 0 °C and trifluoro(trifluoromethylsulfonyl)methane (641 μL, 3 eq., 3.82 mmol) was charged portion wise via needle. The initial slurry dissolved after the addition was completed. The reaction was stirred for another 10 min and the reaction was poured over an ice/sat NaHCO₃ mixture. The mixture was poured into a separatory funnel, and the organic layer was separated. The aqueous layer was extracted with DCM (10 mL) and the organic layers combined, dried over sodium sulfate, filtered and concentrated to dryness to give the title product as a light purple solid (460 g, 98% yield). MS: 367.1 m/z (M+H⁺). ¹H NMR (400 MHz, CDCl₃) δ 9.52 (s, 1H), 8.01 (s, 1H), 7.98 (s, 1H), 2.77 (s, 3H), 2.63 (s, 3H).

Step 4: 5-acetyl-3-chloro-7-methylquinoline-2-carbonitrile.

In a 40 mL vial provided with a stir bar and a septum cap, 1-[3-chloro-7-methyl-(trifluoromethoxy)-5-quinolyl]-1-ethanone (1 g, 2.45 mmol), zinc bis(cyanide) (345 mg, 1.2 eq., 2.94 mmol), Tetrakis(triphenylphosphine)palladium(0) (283 mg, 0.1 eq., 245 μmol) and dimethylformamide (15 mL, 194 mmol) were charged. The mixture was sparged with nitrogen for 3 min and the vial was capped and heated to 90 °C for 1 h. The reaction was cooled to room temperature and stirred for 1 h. The solids obtained were filtered and washed with MTBE (10 mL) and air dried to give the title compound as a light brown solid (556 mg, 92%). MS: 245.1 m/z (M+H⁺). ¹H NMR (400 MHz, DMSO) δ 9.29 (s, 1H), 8.42 (s, 1H), 8.17 (s, 1H), 2.77 (s, 3H), 2.63 (s, 3H).

Intermediate: 6-chloro-3-hydroxypyridine-2-sulfonamide



Step1 – Synthesis of 2-(benzylthio)-6-chloro-3-fluoropyridine:

To a solution of KOH (4.11 g, 73.25 mmol, 1.2 eq) in EtOH (50 mL) was added dropwise BnSH (8.49 mL, 72.30 mmol, 1.2 eq) at 0 °C. After addition, 2,6-dichloro-3-fluoro-pyridine (10 g, 60.25 mmol, 1 eq) in EtOH (50 mL) was added dropwise at 0 °C. The resulting mixture was stirred at room temperature for 16 h. Then the mixture was quenched with water (100 mL), extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The crude product was purified by silica gel chromatography (solvent gradient: 100% petroleum ether) to give the title compound (14 g, 91%) as pink oil, which was further confirmed by ¹³C-NMR (2D-NMR). ¹H NMR (400 MHz, CDCl₃) δ 7.48 - 7.44 (m, 2H), 7.37 - 7.29 (m, 2H), 7.29 - 7.24 (m, 1H), 7.22 - 7.17 (m, 1H), 7.02 - 6.98 (m, 1H), 4.44 (s, 2H).

Step 2 – Synthesis of 6-chloro-3-fluoropyridine-2-sulfonamide:

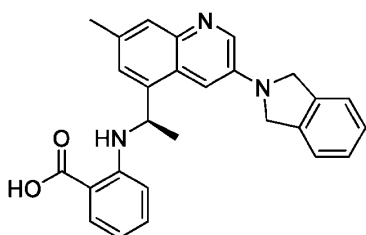
To a solution of 2-benzylsulfanyl-6-chloro-3-fluoro-pyridine (20 g, 78.83 mmol, 1 eq) in water (20 mL) and acetonitrile (200 mL) was added AcOH (36.10 mL, 630.61 mmol, 8 eq) at 0 °C. After addition, then NCS (42.10 g, 315.30 mmol, 4 eq) was added slowly at 0 °C. The resulting mixture was stirred at 0 °C for 0.5 h. The mixture was added water (50 mL), then extracted with DCM (3 x 100 mL). The combined organic layers were washed with brine (100 mL x 3) and dried over Na₂SO₄. The organic mixture was added to ammonium hydroxide (80 mL, 623.19 mmol, 29 wt%, 8 eq) in THF (80 mL) at 0 °C. After the addition, the reaction mixture was stirred at 0 °C for 10 min. Then the mixture was quenched with water (100 mL), extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The crude product was triturated with DCM (50 mL), then filtered and the filter cake was concentrated in vacuo to give the title compound (11 g, 66%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.14 - 8.09 (m, 1H), 7.97 (s, 2H), 7.92 - 7.88 (m, 1H).

Step 3 – Synthesis of 6-chloro-3-hydroxypyridine-2-sulfonamide:

To a solution of 6-chloro-3-fluoro-pyridine-2-sulfonamide (10 g, 47.48 mmol, 1 eq) in water (250 mL) was added KOH (26.64 g, 474.80 mmol, 10 eq) at room temperature. After the addition, the reaction mixture was stirred at 110 °C for 5 h. After cooling to 0 °C, the pH was adjusted to ~ 4 - 5 with concentrated HCl (12M). The mixture was extracted with DCM: *i*-PrOH = 3:1 (100 mL x 5), then the combined organic layers were washed with brine (200 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by

silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (2.9 g, 29%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.23 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.35 (s, 2H).

5 **Example 1: (*R*)-2-((1-(3-(isoindolin-2-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid (Compound 1)**



Step 1 – Synthesis of 3-(benzyloxy)-5-bromo-7-methylquinoline:

10 To a mixture of 2-amino-6-bromo-4-methylbenzaldehyde (2.0 g, 9.36 mmol) (prepared according to the procedure in WO202192525) and 2-benzyloxyacetaldehyde (1.68 g, 11.20 mmol, 1.56 mL) in EtOH (40 mL) was added aqueous NaOH (748 mg, 18.68 mmol, dissolved in 2 mL H₂O). The reaction vessel was sealed and stirred at 110 °C under microwave for 30 min. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo. The
 15 crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (2.53 g, 83%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.72 (d, *J* = 2.4 Hz, 1H), 7.79 (s, 2H), 7.75 (d, *J* = 2.4 Hz, 1H), 7.57 - 7.51 (m, 2H), 7.46 - 7.40 (m, 2H), 7.34 - 7.28 (m, 1H), 5.33 (s, 2H), 2.47 (s, 3H). MS: *m/z* 328.0 (M+H⁺).

Step 2 – Synthesis of 1-(3-(benzyloxy)-7-methylquinolin-5-yl)ethan-1-one:

20 A mixture of 3-(benzyloxy)-5-bromo-7-methylquinoline (2.53 g, 7.71 mmol), tributyl(1-ethoxyvinyl)stannane (5.57 g, 15.42 mmol), Pd(dppf)Cl₂ (305 mg, 416 μmol) in dioxane (20 mL) was stirred at 90 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the mixture was quenched with 50 mL of 10% KF aqueous solution and stirred for 30 min. The mixture was extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (50 mL),
 25 dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product (2.55 g) as a yellow solid. The crude product was dissolved in dioxane (20 mL), then added 1M HCl (10 mL). The mixture was stirred at room temperature for 1 h. The reaction mixture was filtered and

the filter cake was dried in vacuo to give the title compound (1.34 g, 60%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.73 (d, *J* = 2.8 Hz, 1H), 8.61 (d, *J* = 2.8 Hz, 1H), 8.14 (s, 1H), 7.98 (s, 1H), 7.57 - 7.51 (m, 2H), 7.47 - 7.33 (m, 3H), 5.24 (s, 2H), 2.73 (s, 3H), 2.54 (s, 3H). MS: *m/z* 292.2 (M+H⁺).

5 **Step 3 – Synthesis of 1-(3-(benzyloxy)-7-methylquinolin-5-yl)ethan-1-amine:**

To a solution of 1-(3-(benzyloxy)-7-methylquinolin-5-yl)ethan-1-one (1.25 g, 4.29 mmol), NH₄OAc (4.96 g, 64.35 mmol) and AcOH (257 mg, 4.29 mmol, 236 μL) in MeOH (40 mL) was added NaBH₃CN (808 mg, 12.87 mmol). The reaction was heated to 60 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was diluted with DCM (100
10 mL). The mixture was washed with saturated NaHCO₃ solution (50 mL x 3), brine (100 mL), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated to give the title compound (1.15 g, crude) as a yellow solid that required no further purification. MS: *m/z* 293.2 (M+H⁺).

Step 4 – Synthesis of methyl 2-((1-(3-(benzyloxy)-7-methylquinolin-5-yl)ethyl)amino)benzoate:

15 A mixture of methyl 2-iodobenzoate (909 mg, 3.47 mmol), 1-(3-(benzyloxy)-7-methylquinolin-5-yl)ethan-1-amine (676 mg, 5.30 mmol), Pd₂(dba)₃ (113 mg, 123 μmol), Xantphos (143 mg, 247 μmol) and Cs₂CO₃ (2.26 g, 6.61 mmol) in dioxane (10 mL) under N₂ atmosphere. The mixture was heated to 110 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction was filtered and concentrated in vacuo. The crude residue was
20 purified by silica gel chromatography (solvent gradient: 0 - 20% EtOAc in petroleum ether) to give the title compound (820 mg, 83%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.70 (d, *J* = 2.4 Hz, 1H), 8.27 (d, *J* = 6.0 Hz, 1H), 8.05 (d, *J* = 2.4 Hz, 1H), 7.88 - 7.79 (m, 1H), 7.64 (s, 1H), 7.54 (d, *J* = 7.2 Hz, 2H), 7.43 - 7.31 (m, 4H), 7.22 - 7.16 (m, 1H), 6.59 - 6.51 (m, 1H), 6.40 (d, *J* = 8.4 Hz, 1H), 5.50 - 5.41 (m, 1H), 5.39 - 5.30 (m, 2H), 3.85 (s, 3H), 2.37 (s, 3H), 1.54 (d, *J* = 6.8
25 Hz, 3H). MS: *m/z* 427.2 (M+H⁺).

Step 5 – Synthesis of methyl 2-((1-(3-hydroxy-7-methylquinolin-5-yl)ethyl)amino)benzoate:

To a solution of methyl 2-((1-(3-(benzyloxy)-7-methylquinolin-5-yl)ethyl)amino)benzoate (815 mg, 1.91 mmol) in MeOH (10 mL) was added Pd(OH)₂ on carbon (400 mg, 20% Pd, 50%
30 wet with water). The reaction was stirred at room temperature for 1 h under H₂ atmosphere (15

psi). The reaction was filtered through diatomaceous earth and the filtrate was concentrated in vacuo to give the title compound (160 mg, 25%) as a yellow solid that required no further purification. MS: m/z 337.2 ($M+H^+$).

**Step 6 – Synthesis of methyl 2-((1-(7-methyl-3-
5 (((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)ethyl)amino)benzoate:**

To a solution of methyl 2-((1-(3-hydroxy-7-methylquinolin-5-yl)ethyl)amino)benzoate (160 mg, 476 μ mol) in DCM (4 mL) was added pyridine (115 μ L, 1.43 mmol) and Tf_2O (201 mg, 713 μ mol, 118 μ L). The reaction was stirred at 0 °C for 1 h. The reaction mixture was diluted with DCM 20 mL and washed with 1M HCl (10 mL), and then the organic layer was washed with
10 $NaHCO_3$ (10 mL x 2), dried over anhydrous Na_2SO_4 and filtered and concentrated in vacuo to give the title compound (198 mg, 89%) as a yellow solid that required no further purification. 1H NMR (400 MHz, $DMSO-d_6$) δ 9.06 (s, 1H), 9.02 (s, 1H), 8.26 (d, J = 6.4 Hz, 1H), 7.92 - 7.78 (m, 2H), 7.56 (s, 1H), 7.26 - 7.16 (m, 1H), 6.64 - 6.52 (m, 1H), 6.43 (d, J = 8.4 Hz, 1H), 5.64 - 5.46 (m, 1H), 3.86 (s, 3H), 2.49 (s, 3H), 1.59 (d, J = 6.4 Hz, 3H). MS: m/z 469.1 ($M+H^+$).

**Step 7 – Synthesis of methyl 2-((1-(3-(isoindolin-2-yl)-7-methylquinolin-5-
15 yl)ethyl)amino)benzoate:**

A mixture of methyl 2-((1-(7-methyl-3-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)ethyl)amino)benzoate (198 mg, 423 μ mol), isoindoline (76 mg, 634 μ mol), $Pd_2(dba)_3$ (38 mg, 42 μ mol), Xantphos (49 mg, 85 μ mol) and Cs_2CO_3 (413 mg, 1.27 mmol) in dioxane (4 mL). The
20 mixture was heated to 110 °C for 8 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to give the title compound (76 mg, 41%) as a white solid. MS: m/z 438.1 ($M+H^+$).

**Step 8 – Synthesis of 2-((1-(3-(isoindolin-2-yl)-7-methylquinolin-5-
25 yl)ethyl)amino)benzoic acid:**

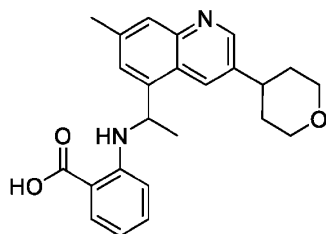
A solution of methyl 2-((1-(3-(isoindolin-2-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoate (76 mg, 174 μ mol) in MeOH (2 mL) and THF (0.2 mL) was added LiOH (42 mg, 1.75 mmol, dissolved in 0.2 mL H_2O). The mixture was stirred at 60 °C for 16 h. After
30 cooling to room temperature, the reaction mixture was adjusted to pH 6 with formic acid. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography

(acetonitrile 45% - 75% / 0.225% formic acid in water) to give the title compound (50 mg, 68%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.66 (d, *J* = 2.4 Hz, 1H), 8.59 - 8.49 (m, 1H), 7.84 - 7.75 (m, 1H), 7.56 (s, 1H), 7.49 - 7.40 (m, 3H), 7.38 - 7.32 (m, 2H), 7.29 (d, *J* = 1.2 Hz, 1H), 7.21 - 7.12 (m, 1H), 6.54 - 6.48 (m, 1H), 6.44 (d, *J* = 8.4 Hz, 1H), 5.48 - 5.31 (m, 1H), 4.87 - 4.75 (m, 4H), 2.37 (s, 3H), 1.63 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 424.2 (M+H⁺).

Step 9 – Synthesis of (*R*)-2-((1-(3-(isoindolin-2-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid and (*S*)-2-((1-(3-(isoindolin-2-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid:

2-((1-(3-(isoindolin-2-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid (50 mg, 118 μmol) was separated by using chiral SFC (DAICEL CHIRALPAK AD (250mm*30mm,10um); Supercritical CO₂ / EtOH + 0.1% NH₃•H₂O = 60/40; 70 mL/min) to afford (*R*)-2-((1-(3-(isoindolin-2-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid (4 mg, first peak) and (*S*)-2-((1-(3-(isoindolin-2-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid (5 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. (first peak): ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.76 (s, 1H), 8.66 (d, *J* = 2.4 Hz, 1H), 8.58 - 8.47 (m, 1H), 7.85 - 7.76 (m, 1H), 7.56 (s, 1H), 7.47 - 7.40 (m, 3H), 7.38 - 7.33 (m, 2H), 7.29 (s, 1H), 7.20 - 7.13 (m, 1H), 6.56 - 6.49 (m, 1H), 6.45 (d, *J* = 8.4 Hz, 1H), 5.47 - 5.34 (m, 1H), 4.88 - 4.73 (m, 4H), 2.37 (s, 3H), 1.64 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 424.1 (M+H⁺).

Example 2: 2-((1-(7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoic acid (Compound 2)



Step 1 – Synthesis of methyl 2-((1-(3-(3,6-dihydro-2*H*-pyran-4-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoate:

A mixture of methyl 2-((1-(7-methyl-3-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)ethyl)amino)benzoate (270 mg, 576 μmol), 2-(3,6-dihydro-2*H*-pyran-4-yl)-4,4,5,5-tetramethyl-

1,3,2-dioxaborolane (242 mg, 1.15 mmol), Pd(PPh₃)₄ (66 mg, 58 μmol) and K₂CO₃ (239 mg, 1.41 mmol) in dioxane (4 mL) and H₂O (0.1 mL). The mixture was stirred at 110 °C for 8 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 33% EtOAc in petroleum ether) to give the title compound (231 mg, 98%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.09 (d, *J* = 2.0 Hz, 1H), 8.52 (s, 1H), 8.25 (d, *J* = 6.0 Hz, 1H), 7.87 - 7.79 (m, 1H), 7.69 (s, 1H), 7.40 (d, *J* = 1.2 Hz, 1H), 7.25 - 7.14 (m, 1H), 6.65 - 6.52 (m, 2H), 6.47 (d, *J* = 8.4 Hz, 1H), 5.63 - 5.51 (m, 1H), 4.30 (d, *J* = 2.8 Hz, 2H), 3.91 - 3.87 (m, 2H), 3.86 (s, 3H), 2.68 - 2.58 (m, 2H), 2.43 (s, 3H), 1.62 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 403.1 (M+H⁺).

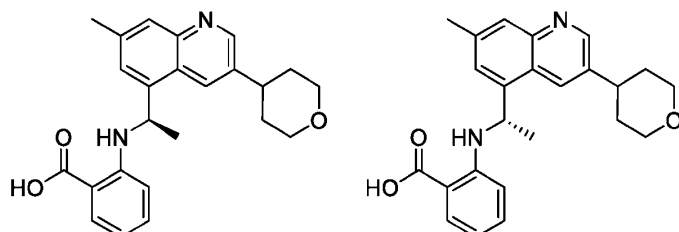
Step 2 – Synthesis of methyl 2-((1-(7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoate:

To a solution of methyl 2-((1-(3-(3,6-dihydro-2*H*-pyran-4-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoate (231 mg, 547 μmol) in MeOH (10 mL) was added Pd(OH)₂ on carbon (115 mg, 20% Pd, 50% wet with water). The reaction was stirred at room temperature for 1 h under H₂ atmosphere (15 psi). The reaction was filtered through diatomaceous earth and the filtrate was concentrated in vacuo to give the title compound (196 mg, 83%) as a yellow solid that required no further purification. MS: *m/z* 405.1 (M+H⁺).

Step 3 – Synthesis of 2-((1-(7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoic acid:

A solution of methyl 2-((1-(7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoate (196 mg, 470 μmol) in MeOH (4 mL) and THF (0.4 mL) was added LiOH (99 mg, 2.35 mmol, dissolved in H₂O). The mixture was stirred at 60 °C for 16 h. After cooling to room temperature, the reaction mixture was adjusted to pH 6 with formic acid. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 25% - 55% / 0.225% formic acid in water) to give the title compound (84 mg, 45%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.79 (s, 1H), 8.84 (d, *J* = 2.0 Hz, 1H), 8.55 (s, 1H), 8.45 (d, *J* = 1.2 Hz, 1H), 7.84 - 7.76 (m, 1H), 7.66 (s, 1H), 7.38 (d, *J* = 1.2 Hz, 1H), 7.20 - 7.10 (m, 1H), 6.56 - 6.47 (m, 1H), 6.41 (d, *J* = 8.4 Hz, 1H), 5.54 - 5.44 (m, 1H), 4.04 - 3.97 (m, 2H), 3.54 - 3.45 (m, 2H), 3.09 - 2.99 (m, 1H), 2.42 (s, 3H), 1.92 - 1.79 (m, 4H), 1.59 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 391.1 (M+H⁺).

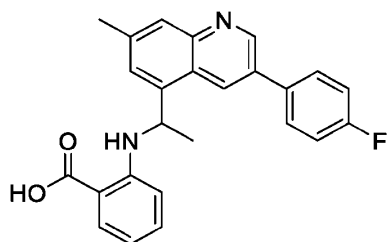
Example 3A and Example 3B: (*R*)-2-((1-(7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoic acid (Compound 3) & (*S*)-2-((1-(7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino) benzoic acid (Compound 4):



Step 1 – Synthesis of (*R*)-2-((1-(7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoic acid & (*S*)-2-((1-(7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoic acid:

2-((1-(7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoic acid (80 mg, 197.78 μ mol) was separated by using chiral SFC (DAICEL CHIRALCEL OJ (250mm*30mm,10 μ m); Supercritical CO₂ / EtOH+0.1% NH₃•H₂O = 60/40; 70 mL/min) to afford (*R*)-2-((1-(7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoic acid (21 mg, first peak) and (*S*)-2-((1-(7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoic acid (16 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. Example 3A (first peak): ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.80 (s, 1H), 8.84 (d, *J* = 2.0 Hz, 1H), 8.57 - 8.40 (m, 2H), 7.88 - 7.74 (m, 1H), 7.67 (s, 1H), 7.38 (s, 1H), 7.22 - 7.11 (m, 1H), 6.60 - 6.47 (m, 1H), 6.42 (d, *J* = 8.4 Hz, 1H), 5.49 (s, 1H), 4.09 - 3.93 (m, 2H), 3.58 - 3.44 (m, 2H), 3.10 - 2.97 (m, 1H), 2.42 (s, 3H), 1.91 - 1.77 (m, 4H), 1.59 (d, *J* = 6.8 Hz, 3H). MS: *m/z* 391.1 (M+H⁺). Example 3B (second peak): ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.77 (s, 1H), 8.84 (d, *J* = 2.0 Hz, 1H), 8.58 - 8.37 (m, 2H), 7.86 - 7.76 (m, 1H), 7.67 (s, 1H), 7.38 (s, 1H), 7.21 - 7.09 (m, 1H), 6.58 - 6.47 (m, 1H), 6.42 (d, *J* = 8.4 Hz, 1H), 5.49 (s, 1H), 4.06 - 3.94 (m, 2H), 3.56 - 3.42 (m, 2H), 3.10 - 2.99 (m, 1H), 2.42 (s, 3H), 1.93 - 1.78 (m, 4H), 1.59 (d, *J* = 6.8 Hz, 3H). MS: *m/z* 391.1 (M+H⁺).

Example 4: 2-((1-(3-(4-fluorophenyl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid (Compound 5)



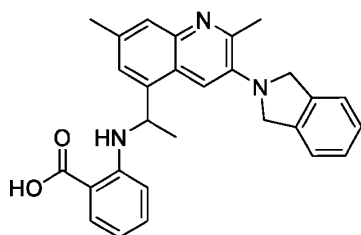
Step 1 – Synthesis of methyl 2-((1-(3-(4-fluorophenyl)-7-methylquinolin-5-yl)ethyl)amino)benzoate:

A mixture of methyl 2-((1-(7-methyl-3-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)ethyl)amino)benzoate (139 mg, 297 μ mol), (4-fluorophenyl)boronic acid (83 mg, 593 μ mol), Pd(PPh₃)₄ (34 mg, 30 μ mol) and K₂CO₃ (123 mg, 890 mmol) in dioxane (3 mL) and H₂O (0.1 mL). The mixture was stirred at 110 °C for 2 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 33% EtOAc in petroleum ether) to give the title compound (122 mg, 99%) as a white solid. MS: m/z 415.1 (M+H⁺).

Step 2 – Synthesis of 2-((1-(3-(4-fluorophenyl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid:

A solution of methyl 2-((1-(3-(4-fluorophenyl)-7-methylquinolin-5-yl)ethyl)amino)benzoate (122 mg, 294 μ mol) in MeOH (4 mL) and THF (0.4 mL) was added LiOH (35 mg, 1.47 mmol, dissolved in 0.4 mL H₂O). The mixture was stirred at 60 °C for 16 h. After cooling to room temperature, the reaction mixture was adjusted to pH 6 with formic acid. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 50% - 80% / 0.225% formic acid in water) to give the title compound (21 mg, 18%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.78 (s, 1H), 9.21 (d, *J* = 2.0 Hz, 1H), 8.87 (d, *J* = 1.6 Hz, 1H), 8.50 (s, 1H), 8.03 - 7.95 (m, 2H), 7.86 - 7.79 (m, 1H), 7.74 (s, 1H), 7.46 - 7.36 (m, 3H), 7.22 - 7.12 (m, 1H), 6.57 - 6.44 (m, 2H), 5.73 - 5.59 (m, 1H), 2.45 (s, 3H), 1.62 (d, *J* = 6.8 Hz, 3H). MS: m/z 401.2 (M+H⁺).

Example 5: 2-((1-(3-(isoindolin-2-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid (Compound 6)



Step 1 – Synthesis of 3-(benzyloxy)-5-bromo-2,7-dimethylquinoline:

To a solution of 2-amino-6-bromo-4-methyl-benzaldehyde (550 mg, 2.54 mmol) and 1-benzyloxypropan-2-one (506 mg, 3.08 mmol) in EtOH (15 mL) and H₂O (1 mL) was added NaOH (206 mg, 5.14 mmol). The reaction vessel was sealed and stirred at 110 °C under microwave for 30 min. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (880 mg, 78%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.72 (s, 2H), 7.66 (s, 1H), 7.59 - 7.53 (m, 2H), 7.47 - 7.41 (m, 2H), 7.39 - 7.35 (m, 1H), 5.34 (s, 2H), 2.61 (s, 3H), 2.46 (s, 3H). MS: m/z 342.0 (M+H⁺).

Step 2 – Synthesis of 1-(3-(benzyloxy)-2,7-dimethylquinolin-5-yl)ethan-1-one:

A mixture of 3-(benzyloxy)-5-bromo-2,7-dimethylquinoline (880 mg, 2.38 mmol), tributyl(1-ethoxyvinyl)stannane (1.72 g, 4.77 mmol), Pd(dppf)Cl₂ (174 mg, 238 μmol) in dioxane (10 mL) was stirred at 90 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the mixture was quenched with 30 mL of 10% KF aqueous solution and stirred for 30 min. The mixture was extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude product (790 mg) as a yellow solid. The crude product was dissolved in dioxane (10 mL), then added aqueous HCl (1M, 40 mL). The mixture was stirred at room temperature for 2 h. The reaction mixture was filtered and the filter cake was dried in vacuo to give the title compound (560 mg, 69%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.56 (s, 1H), 8.08 (d, *J* = 1.6 Hz, 1H), 7.91 (s, 1H), 7.59 - 7.52 (m, 2H), 7.47 - 7.40 (m, 2H), 7.39 - 7.35 (m, 1H), 5.24 (s, 2H), 2.72 (s, 3H), 2.58 (s, 3H), 2.53 (s, 3H). MS: m/z 306.1 (M+H⁺).

Step 3 – Synthesis of 1-(3-(benzyloxy)-2,7-dimethylquinolin-5-yl)ethan-1-amine:

To a solution of 1-(3-(benzyloxy)-2,7-dimethylquinolin-5-yl)ethan-1-one (560 mg, 1.67 mmol), NH₄OAc (1.93 g, 25.05 mmol) and AcOH (100 mg, 1.67 mmol, 96 μL) in MeOH (10 mL)

was added NaBH₃CN (808 mg, 5.01 mmol). The reaction was heated to 60 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was diluted with DCM (100 mL). The mixture was washed with saturated NaHCO₃ solution (50 mL) and brine (50 mL), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated in vacuo to give the title compound (960 mg, crude) as a yellow solid that required no further purification. MS: m/z 307.1 (M+H⁺).

Step 4 – Synthesis of methyl 2-((1-(3-(benzyloxy)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate:

A mixture of methyl 2-iodobenzoate (638 mg, 2.44 mmol), 1-(3-(benzyloxy)-2,7-dimethylquinolin-5-yl)ethan-1-amine (676 mg, 5.30 mmol), Pd₂(dba)₃ (84 mg, 92 μmol), Xantphos (188 mg, 324 μmol) and Cs₂CO₃ (1.58 g, 4.87 mmol) in dioxane (2 mL). The mixture was stirred at 110 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction was filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% EtOAc in petroleum ether) to give the title compound (330 mg, 40%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.25 (d, *J* = 6.0 Hz, 1H), 7.92 (s, 1H), 7.84 - 7.80 (m, 1H), 7.56 - 7.51 (m, 4H), 7.43 - 7.39 (m, 2H), 7.36 - 7.32 (m, 1H), 7.27 (d, *J* = 1.2 Hz, 1H), 7.21 - 7.15 (m, 1H), 6.60 - 6.49 (m, 1H), 6.39 (d, *J* = 8.4 Hz, 1H), 5.38 - 5.30 (m, 2H), 3.85 (s, 3H), 2.58 (s, 3H), 2.36 (s, 3H), 1.52 (d, *J* = 6.4 Hz, 3H). MS: m/z 441.3 (M+H⁺).

Step 5 – Synthesis of methyl 2-((1-(3-hydroxy-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate:

To a solution of methyl 2-((1-(3-(benzyloxy)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (330 mg, 749 μmol) in MeOH (10 mL) was added Pd(OH)₂ on carbon (200 mg, 20% Pd, 50% wet with water). The reaction was stirred at room temperature for 1 h under H₂ atmosphere (15 psi). The reaction was filtered through diatomaceous earth and the filtrate was concentrated in vacuo to give the title compound (209 mg, 80%) as a yellow solid that required no further purification. MS: m/z 351.2 (M+H⁺).

Step 6 – Synthesis of methyl 2-((1-(2,7-dimethyl-3-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)ethyl)amino)benzoate:

To a solution of methyl 2-((1-(3-hydroxy-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (209 mg, 596 μmol), pyridine (144 μL, 1.79 mmol) in DCM (4 mL) was added Tf₂O (252 mg, 895

μmol). The reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with DCM (30 mL) and washed with 1M HCl (10 mL), and then the organic layer was washed with NaHCO₃ (10 mL x 2), dried over anhydrous Na₂SO₄ and filtered and concentrated in vacuo to give the title compound (280 mg, 97%) as a yellow solid that required no further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.79 (s, 1H), 8.23 (d, *J* = 6.0 Hz, 1H), 7.85 - 7.78 (m, 1H), 7.74 (s, 1H), 7.49 (s, 1H), 7.23 - 7.17 (m, 1H), 6.60 - 6.54 (m, 1H), 6.46 (d, *J* = 8.4 Hz, 1H), 5.56 - 5.42 (m, 1H), 3.85 (s, 3H), 3.31 (s, 3H), 2.70 (s, 3H), 1.59 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 483.2 (M+H⁺).

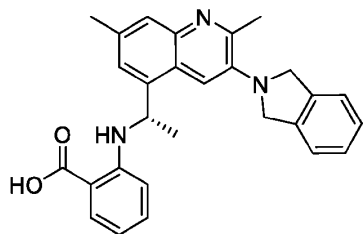
Step 7 – Synthesis of methyl 2-((1-(3-(isoindolin-2-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate:

A mixture of methyl 2-((1-(2,7-dimethyl-3-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)ethyl)amino)benzoate (280 mg, 746 μmol), isoindoline (133 mg, 1.12 mmol), Pd₂(dba)₃ (68 mg, 75 μmol), Xantphos (86 mg, 149 μmol) and Cs₂CO₃ (729 mg, 2.24 mmol) in dioxane (4 mL). The mixture was stirred at 110 °C for 3 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 33% EtOAc in Petroleum ether) to give the title compound (187 mg, 56%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.25 (d, *J* = 6.0 Hz, 1H), 8.15 - 7.98 (m, 1H), 7.90 - 7.77 (m, 2H), 7.52 (s, 1H), 7.42 - 7.36 (m, 2H), 7.34 - 7.29 (m, 2H), 7.27 (s, 1H), 6.57 - 6.44 (m, 2H), 5.50 - 5.36 (m, 1H), 4.86 - 4.62 (m, 4H), 3.83 (s, 3H), 2.80 (s, 3H), 2.37 (s, 3H), 1.63 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 452.3 (M+H⁺).

Step 8 – Synthesis of 2-((1-(3-(isoindolin-2-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid:

To a solution of methyl 2-((1-(3-(isoindolin-2-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (90 mg, 199 μmol) in MeOH (2 mL) and THF (0.2 mL) was added LiOH monohydrate (42 mg, 997 μmol, dissolved in 0.2 mL H₂O). The mixture was stirred at 60 °C for 16 h. After cooling to room temperature, the reaction mixture was adjusted to pH 6 with formic acid. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 35% - 65% / 0.225% formic acid in water) to give the title compound (60 mg, 69%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.70 (s, 1H), 8.44 (s, 1H), 7.88 - 7.72 (m, 2H), 7.51 (s, 1H), 7.42 - 7.37 (m, 2H), 7.34 - 7.29 (m, 2H), 7.27 (s, 1H), 7.22 - 7.16 (m, 1H), 6.57 - 6.45 (m, 2H), 5.45 - 5.35 (m, 1H), 4.78 - 4.68 (m, 4H), 2.80 (s, 3H), 2.38 (s, 3H), 1.62 (d, *J* = 6.8 Hz, 3H). MS: *m/z* 438.3 (M+H⁺).

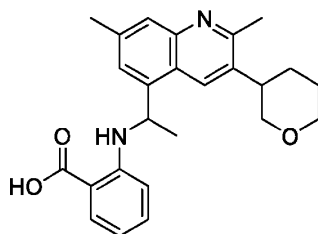
Example 6: **(*S*)-2-((1-(3-(isoindolin-2-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid (Compound 7)**



Step 1 – Synthesis of (*R*)-2-((1-(3-(isoindolin-2-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid & (*S*)-2-((1-(3-(isoindolin-2-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid:

2-((1-(3-(isoindolin-2-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid (50 mg, 114 μmol) was separated by using chiral SFC (DAICEL CHIRALPAK AD (250mm*30mm,10 μm); Supercritical CO_2 / EtOH + 0.1% $\text{NH}_3 \cdot \text{H}_2\text{O}$ = 60/40; 60 mL/min) to afford (*R*)-2-((1-(3-(isoindolin-2-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid (5 mg, first peak) and (*S*)-2-((1-(3-(isoindolin-2-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid (6 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. Example 6 (second peak): ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.72 (s, 1H), 8.42 (d, J = 6.0 Hz, 1H), 7.84 - 7.75 (m, 2H), 7.51 (s, 1H), 7.44 - 7.36 (m, 2H), 7.34 - 7.29 (m, 2H), 7.27 (s, 1H), 7.22 - 7.16 (m, 1H), 6.55 - 6.46 (m, 2H), 5.48 - 5.34 (m, 1H), 4.79 - 4.67 (m, 4H), 2.80 (s, 3H), 2.38 (s, 3H), 1.62 (d, J = 6.4 Hz, 3H). MS: m/z 438.1 ($\text{M}+\text{H}^+$).

Example 7A: **2-((1-(2,7-dimethyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (Compound 79)**



Step 1 – Synthesis of methyl 2-((1-(3-(5,6-dihydro-2*H*-pyran-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate:

A mixture of methyl 2-((1-(2,7-dimethyl-3-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)ethyl)amino)benzoate (310 mg, 643 μ mol), 2-(5,6-dihydro-2*H*-pyran-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (202 mg, 964 μ mol), Pd₂(dba)₃ (59 mg, 64 μ mol), Xantphos (74 mg, 129 μ mol) and Cs₂CO₃ (628 mg, 1.93 mmol) in dioxane (5 mL). The mixture was stirred at 110 °C for 3 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 33% EtOAc in petroleum ether) to give the title compound (200 mg, 75%) as a white solid. MS: m/z 417.2 (M+H⁺).

Step 2 – Synthesis of methyl 2-((1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate:

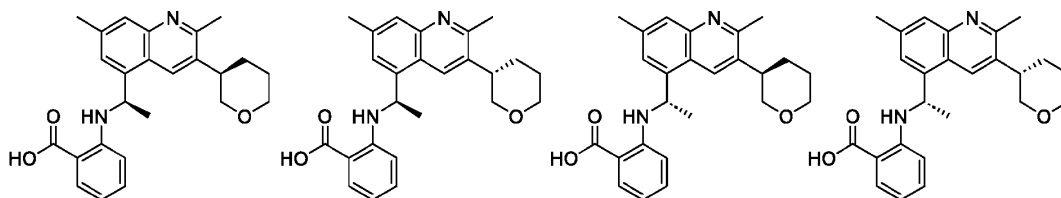
To a solution of methyl 2-((1-(3-(5,6-dihydro-2*H*-pyran-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (200 mg, 480 μ mol) in MeOH (10 mL) was added wet Pd(OH)₂ on carbon (100 mg, 20% Pd, 50% wet with water). The reaction was stirred at room temperature for 4 h under H₂ atmosphere (15 psi). The reaction was filtered through diatomaceous earth and the filtrate was concentrated to afford the title compound (100 mg, 50%) as a yellow solid that required no further purification. MS: m/z 419.3 (M+H⁺).

Step 3 – Synthesis of 2-((1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid:

A mixture of methyl 2-((1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate (50 mg, 119 μ mol) in MeOH (0.3 mL) and THF (3 mL) was added LiOH (29 mg, 1.19 mmol, dissolved in 0.3 mL H₂O). The mixture was stirred at 60 °C for 16 h. After cooling to room temperature, the reaction mixture was adjusted to pH 6 with formic acid. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 20% - 50% / 0.225% formic acid in water) to give the title compound (10 mg, 21%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.74 (s, 1H), 8.51 - 8.38 (m, 1H), 8.36 - 8.30 (m, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.56 (s, 1H), 7.38 - 7.28 (m, 1H), 7.24 - 7.13 (m, 1H), 6.56 - 6.44 (m, 2H), 5.51 - 5.35 (m, 1H), 3.95 - 3.81 (m, 2H), 3.48 - 3.34 (m, 2H), 3.14 - 3.01 (m, 1H),

2.68 (s, 3H), 2.41 (s, 3H), 1.99 - 1.89 (m, 1H), 1.87 - 1.77 (m, 1H), 1.76 - 1.65 (m, 2H), 1.60 (d, J = 6.4 Hz, 3H). MS: m/z 405.1 ($M+H^+$).

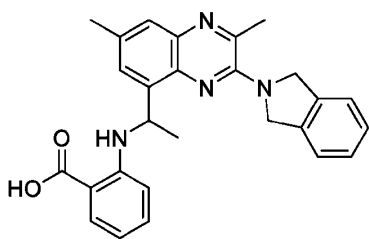
Example 7B: 2-((1-(2,7-dimethyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid; 2-(((*R*)-1-(2,7-dimethyl-3-((*R*)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid; 2-(((*R*)-1-(2,7-dimethyl-3-((*S*)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid; 2-(((*S*)-1-(2,7-dimethyl-3-((*R*)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid; and 2-(((*S*)-1-(2,7-dimethyl-3-((*S*)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (Compounds 8A-8D)



2-((1-(2,7-dimethyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (60 mg, 148 μ mol) was separated by using chiral SFC (DAICEL CHIRALCEL OD (250mm*30mm,10 μ m); Supercritical CO₂ / EtOH+0.1% NH₃•H₂O = 60/40; 70 mL/min) to afford 2-(((*R*)-1-(2,7-dimethyl-3-((*R*)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid and 2-(((*R*)-1-(2,7-dimethyl-3-((*S*)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (20 mg, peak 2 and peak 4, inseparable), 2-(((*S*)-1-(2,7-dimethyl-3-((*R*)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (4 mg, first peak) and 2-(((*S*)-1-(2,7-dimethyl-3-((*S*)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (7 mg, third peak) both as white solid. The mixture of peak 2 and peak 4 (20 mg, 48 μ mol) was separated by using chiral SFC (DAICEL CHIRALCEL IG (250mm*30mm,10 μ m); Supercritical CO₂ / EtOH+0.1% NH₃•H₂O = 65/35; 70 mL/min) to afford 2-(((*R*)-1-(2,7-dimethyl-3-((*R*)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (4 mg, second peak) and 2-(((*R*)-1-(2,7-dimethyl-3-((*S*)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (5 mg, fourth peak). Absolute configuration was arbitrarily assigned to each enantiomer. (The retention times of these four peaks are sorted according to this method: OJ_3_EtOH_DEA_5_40_25ML_6MIN).

Second peak (Compound 8A): ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.76 (s, 1H), 8.67 – 8.27 (m, 2H), 7.80 (d, $J = 7.2$ Hz, 1H), 7.57 (s, 1H), 7.34 (s, 1H), 7.23 – 7.12 (m, 1H), 6.58 – 6.41 (m, 2H), 5.44 – 5.40 (m, 1H), 3.89 – 3.87 (m, 1H), 3.45 – 3.40 (m, 2H), 3.09 – 3.05 (m, 1H), 2.68 (s, 3H), 2.41 (s, 3H), 1.96 – 1.91 (m, 1H), 1.85 – 1.78 (m, 1H), 1.74 – 1.66 (m, 2H), 1.60 (d, $J = 6.0$ Hz, 3H), 1.58 – 1.57 (m, 1H). MS: m/z 405.1 ($\text{M}+\text{H}^+$). Fourth peak (Compound 8B): ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.46 (s, 1H), 8.33 (s, 1H), 7.87 – 7.76 (m, 1H), 7.57 (s, 1H), 7.32 (s, 1H), 7.25 – 7.11 (m, 1H), 6.58 – 6.42 (m, 2H), 5.51 – 5.36 (m, 1H), 3.95 – 3.84 (m, 2H), 3.48 – 3.42 (m, 2H), 3.12 – 3.02 (m, 1H), 2.68 (s, 3H), 2.41 (s, 3H), 1.97 – 1.89 (m, 1H), 1.89 – 1.79 (m, 1H), 1.75 – 1.65 (m, 2H), 1.60 (d, $J = 6.4$ Hz, 3H). MS: m/z 405.1 ($\text{M}+\text{H}^+$). First peak (Compound 8C): ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.46 (s, 1H), 8.34 (s, 1H), 7.88 – 7.74 (m, 1H), 7.56 (s, 1H), 7.34 (s, 1H), 7.24 – 7.09 (m, 1H), 6.61 – 6.41 (m, 2H), 5.47 – 5.32 (m, 1H), 3.96 – 3.79 (m, 2H), 3.47 – 3.40 (m, 2H), 3.13 – 3.00 (m, 1H), 2.68 (s, 3H), 2.41 (s, 3H), 2.00 – 1.89 (m, 1H), 1.87 – 1.77 (m, 1H), 1.77 – 1.64 (m, 2H), 1.60 (d, $J = 6.4$ Hz, 3H). MS: m/z 405.1 ($\text{M}+\text{H}^+$). Third peak (Compound 8D): ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.53 (s, 1H), 8.33 (s, 1H), 7.91 – 7.72 (m, 1H), 7.56 (s, 1H), 7.32 (s, 1H), 7.23 – 7.09 (m, 1H), 6.62 – 6.38 (m, 2H), 5.44 (s, 1H), 3.96 – 3.84 (m, 2H), 3.47 – 3.43 (m, 2H), 3.11 – 3.04 (m, 1H), 2.68 (s, 3H), 2.40 (s, 3H), 1.98 – 1.89 (m, 1H), 1.89 – 1.79 (m, 1H), 1.75 – 1.66 (m, 2H), 1.60 (d, $J = 6.4$ Hz, 3H). MS: m/z 405.0 ($\text{M}+\text{H}^+$).

Example 8: 2-((1-(3-(isoindolin-2-yl)-2,7-dimethylquinoxalin-5-yl)ethyl)amino)benzoic acid (Compound 9)



Step 1 – Synthesis of *N*-(2-bromo-4-methyl-6-nitrophenyl)-2-oxopropanamide:

To a solution of 2-oxopropanoic acid (0.5 g, 5.68 mmol) in THF (5 mL) was added DMF (54 mg, 738 μmol) and oxalyl chloride (721 mg, 5.7 mmol) at 0 $^{\circ}\text{C}$. The mixture was stirred at 0 $^{\circ}\text{C}$ for 1 h under N_2 atmosphere. Then 2-bromo-4-methyl-6-nitro-aniline (0.7 g, 3 mmol) dissolved in THF (10 mL) and TEA (919 mg, 9.09 mmol) was added to the mixture. The mixture was stirred at room temperature for 2 h. The mixture was quenched with H_2O (20 mL), extracted with EtOAc

(60 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (600 mg, 66%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.63 (s, 1H), 7.96 (s, 1H), 7.88 (d, *J* = 1.2 Hz, 1H), 2.43 (s, 3H), 2.41 (s, 3H).

Step 2 – Synthesis of 8-bromo-3, 6-dimethylquinoxalin-2-ol:

To a solution of *N*-(2-bromo-4-methyl-6-nitro-phenyl)-2-oxo-propanamide (0.6 g, 2 mmol) in AcOH (6 mL) was added Fe (557 mg, 10 mmol, powder). The mixture was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the solution was filtered and concentrated in vacuo. The residue was dissolved in H₂O (20 mL) and stirred for 10 min. The suspension solution was filtered and the filter cake was dried in vacuo to give the title compound (350 mg, 70%) as a yellow solid that required no further purification. ¹H NMR (400MHz, DMSO-*d*₆) δ 7.63 (s, 1H), 7.54 (s, 1H), 2.42 (s, 3H), 2.37 (s, 3H).

Step 3 – Synthesis of 5-bromo-3-chloro-2, 7-dimethylquinoxaline:

A solution of 8-bromo-3,6-dimethyl-quinoxalin-2-ol (0.35 g, 1.38 mmol) in POCl₃ (2 mL, 21 mmol). The mixture was stirred at 120 °C for 5 h. After cooling to room temperature, POCl₃ was removed in vacuo, DCM (50 mL) was added, and the mixture was washed with sat. aq. NaHCO₃ (50 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to afford the crude product (72 g, 99%) as a white solid that required no further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.07 (d, *J* = 1.6 Hz, 1H), 7.86 (s, 1H), 2.77 (s, 3H), 2.54 (s, 3H).

Step 4 – Synthesis of 5-bromo-3-(isoindolin-2-yl)-2, 7-dimethylquinoxaline:

To a solution of 5-bromo-3-chloro-2,7-dimethyl-quinoxaline (0.47g, 1.73 mmol) and isoindoline (412 mg, 3.46 mmol) in MeCN (5 mL) was added K₂CO₃ (718 mg, 5.2 mmol). The reaction mixture was stirred at 90 °C for 16 h. After cooling to room temperature, the reaction was diluted with water (20 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with 1M HCl (20 mL) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give the title compound (600 mg, 97%) as a yellow solid that required no further purification. ¹H NMR (400MHz, DMSO-*d*₆) δ 7.75 (d, *J* = 1.6 Hz, 1H), 7.58 (s, 1H), 7.47 - 7.43 (m, 2H), 7.37 - 7.31 (m, 2H), 5.21 (s, 4H), 2.94 (s, 3H), 2.43 (s, 3H). MS: *m/z* 354.0 (M+H⁺).

Step 5 – Synthesis of 1-(3-(isoindolin-2-yl)-2,7-dimethylquinoxalin-5-yl)ethan-1-one:

A mixture of 5-bromo-3-(isoindolin-2-yl)-2,7-dimethylquinoxaline (880 mg, 2.48 mmol), tributyl(1-ethoxyvinyl)stannane (2.24 g, 6.21 mmol) and Pd(dppf)Cl₂ (182 mg, 0.25 mmol) in dioxane (10 mL) was degassed and purged with N₂ for 3 times. The reaction mixture was stirred at 90 °C for 16 h under N₂ atmosphere. After cooling to room temperature, HCl (1 mL, 1 M) was added. The mixture was stirred at room temperature for 0.5 h. The reaction mixture was added 50 mL 10% KF aqueous solution, stirred at room temperature for 2 h. The mixture was extracted with EtOAc (60 mL x 3). The combined organic layers were washed with brine (60 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to give the title compound (200 mg, 28%) as a yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ 7.78 - 7.76 (m, 1H), 7.68 (d, *J* = 2.0 Hz, 1H), 7.47 - 7.43 (m, 2H), 7.36 - 7.32 (m, 2H), 5.22 (s, 4H), 2.96 (s, 3H), 2.93 (s, 3H), 2.45 (s, 3H).

Step 6 – Synthesis of 1-(3-(isoindolin-2-yl)-2, 7-dimethylquinoxalin-5-yl)ethan-1-amine:

To a solution of 1-(3-(isoindolin-2-yl)-2, 7-dimethylquinoxalin-5-yl)ethan-1-one (170 mg, 0.53 mmol), NH₄OAc (619 mg, 8.03 mmol) in MeOH (4 mL), NaBH₃CN (101 mg, 1.61 mmol) was added. The reaction was heated to 60 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction was diluted with water (20 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give the title compound (160 mg, 94%) as yellow oil that required no further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.50 - 7.47 (m, 2H), 7.46 -7.42 (m, 2H), 7.35 - 7.30 (m, 2H), 5.23 - 5.12 (m, 4H), 4.97 – 4.92 (m, 1H), 2.91 (s, 3H), 2.44 (s, 3H), 1.49 (d, *J* = 6.8 Hz, 3H). MS: *m/z* 319.1 (M+H⁺).

Step 7 – Synthesis of *tert*-butyl 2-((1-(3-(isoindolin-2-yl)-2,7-dimethylquinoxalin-5-yl)ethyl)amino)benzoate:

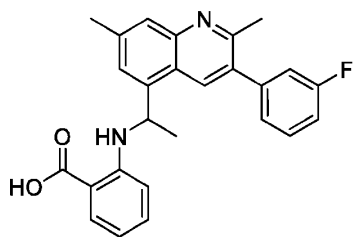
A mixture of 1-(3-(isoindolin-2-yl)-2,7-dimethylquinoxalin-5-yl)ethan-1-amine (160 mg, 502 μmol), *tert*-butyl 2-iodobenzoate (229 mg, 753 μmol), Pd₂(dba)₃ (46 mg, 50 μmol), Xantphos (58 mg, 100 μmol) and Cs₂CO₃ (491 mg, 1.51 mmol) in dioxane (4 mL). The mixture was heated to 100 °C for 4 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture

was filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (100 mg, 40%) as yellow oil. MS: m/z 495.2 (M+H⁺).

Step 8 – Synthesis of 2-((1-(3-(isoindolin-2-yl)-2,7-dimethylquinoxalin-5-yl)ethyl)amino)benzoic acid:

To a mixture of *tert*-butyl 2-((1-(3-(isoindolin-2-yl)-2,7-dimethylquinoxalin-5-yl)ethyl)amino)benzoate (100 mg, 202 μ mol) in DCM (3 mL) was added TFA (0.5 mL, 6.9 mmol). The reaction mixture was stirred at room temperature for 16 h. The mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 53% - 83% / 0.225% formic acid in water) to give the title compound (52 mg, 11%) as a yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ 12.65 (s, 1H), 8.53 (s, 1H), 7.79 - 7.75 (m, 1H), 7.50 - 7.40 (m, 3H), 7.37 - 7.28 (m, 3H), 7.18 - 7.11 (m, 1H), 6.56 - 6.41 (m, 2H), 5.63 - 5.56 (m, 1H), 5.32 - 5.14 (m, 4H), 2.94 (s, 3H), 2.36 (s, 3H), 1.65 (d, *J* = 6.8 Hz, 3H). MS: m/z 439.2 (M+H⁺).

Example 11A: 2-((1-(3-(3-fluorophenyl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid (Compound 10)



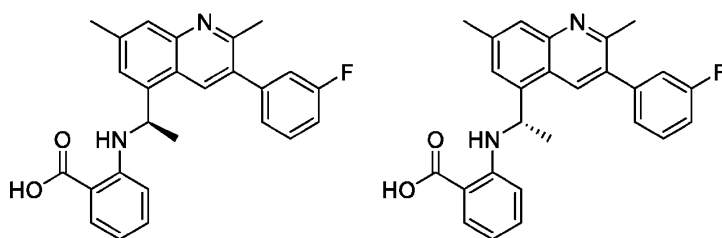
Step 1 – Synthesis of methyl 2-((1-(3-(3-fluorophenyl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate:

A mixture of methyl 2-((1-(2,7-dimethyl-3-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)ethyl)amino)benzoate (150 mg, 311 μ mol), (3-fluorophenyl)boronic acid (87 mg, 622 μ mol), Pd(PPh₃)₄ (36 mg, 31 μ mol) and K₂CO₃ (129 mg, 933 μ mol) in dioxane (3 mL) and H₂O (0.1 mL). The mixture was stirred at 100 °C for 2 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (106 mg, 80%) as a yellow solid. MS: m/z 429.1 (M+H⁺).

Step 2 – Synthesis of 2-((1-(3-(3-fluorophenyl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid:

A solution of methyl 2-((1-(3-(3-fluorophenyl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (20 mg, 47 μ mol) in EtOH (0.2 mL) was added KOH (26 mg, 467 μ mol, dissolved in 0.2 mL H₂O). The mixture was stirred at 100 °C for 2 h. After cooling to room temperature, the reaction mixture was adjusted to pH 6 with formic acid. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 32% - 62% / 0.225% formic acid in water) to give the title compound (15 mg, 78%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.58 - 8.41 (m, 2H), 7.85 - 7.77 (m, 1H), 7.66 (s, 1H), 7.60 - 7.51 (m, 1H), 7.48 - 7.42 (m, 1H), 7.41 - 7.34 (m, 2H), 7.33 - 7.24 (m, 1H), 7.18 - 7.08 (m, 1H), 6.55 - 6.46 (m, 1H), 6.40 (d, *J* = 8.0 Hz, 1H), 5.56 - 5.39 (m, 1H), 2.59 (s, 3H), 2.43 (s, 3H), 1.57 (d, *J* = 6.8 Hz, 3H). MS: *m/z* 414.9 (M+H⁺).

Example 11B: (R)-2-((1-(3-(3-fluorophenyl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid and (S)-2-((1-(3-(3-fluorophenyl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid (Compound 10A and Compound 10B)



Step 1 – Synthesis of methyl (R)-2-((1-(3-(3-fluorophenyl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate & methyl (S)-2-((1-(3-(3-fluorophenyl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate:

methyl 2-((1-(3-(3-fluorophenyl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (100 mg, 233 μ mol) was separated by using chiral SFC (DAICEL CHIRALCEL OD (250mm*30mm,10 μ m); Supercritical CO₂ / EtOH+0.1% NH₃•H₂O = 75/25; 70 mL/min) to afford methyl (R)-2-((1-(3-(3-fluorophenyl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (40 mg, first peak) and methyl (S)-2-((1-(3-(3-fluorophenyl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (40 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. MS: *m/z* 429.1 (M+H⁺).

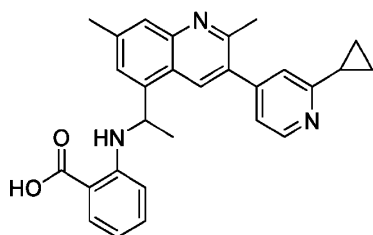
Step 2A – Synthesis of (*R*)-2-((1-(3-(3-fluorophenyl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid:

A solution of methyl (*R*)-2-((1-(3-(3-fluorophenyl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (40 mg, 93 μ mol) in EtOH (0.4 mL) was added KOH (52 mg, 934 μ mol, dissolved in 0.4 mL H₂O). The mixture was stirred at 100 °C for 2 h. After cooling to room temperature, the reaction mixture was adjusted to pH 6 with formic acid. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 37% - 67% / 0.225% formic acid in water) to give the title compound (11 mg, 28%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.63 - 8.51 (m, 1H), 8.46 (s, 1H), 7.84 - 7.77 (m, 1H), 7.66 (s, 1H), 7.60 - 7.50 (m, 1H), 7.45 (d, *J* = 9.6 Hz, 1H), 7.41 - 7.34 (m, 2H), 7.33 - 7.25 (m, 1H), 7.17 - 7.07 (m, 1H), 6.55 - 6.45 (m, 1H), 6.40 (d, *J* = 8.4 Hz, 1H), 5.49 - 5.43 (m, 1H), 2.59 (s, 3H), 2.43 (s, 3H), 1.57 (d, *J* = 6.8 Hz, 3H). MS: *m/z* 415.0 (M+H⁺).

Step 2B – Synthesis of (*S*)-2-((1-(3-(3-fluorophenyl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid:

A solution of methyl (*S*)-2-((1-(3-(3-fluorophenyl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (40 mg, 93 μ mol) in EtOH (0.4 mL) was added KOH (52 mg, 934 μ mol, dissolved in 0.4 mL H₂O). The mixture was stirred at 100 °C for 2 h. After cooling to room temperature, the reaction mixture was adjusted to pH 6 with formic acid. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 37% - 67% / 0.225% formic acid in water) to give the title compound (16 mg, 41%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.62 - 8.50 (m, 1H), 8.46 (s, 1H), 7.83 - 7.77 (m, 1H), 7.66 (s, 1H), 7.61 - 7.50 (m, 1H), 7.45 (d, *J* = 9.6 Hz, 1H), 7.41 - 7.34 (m, 2H), 7.33 - 7.24 (m, 1H), 7.18 - 7.07 (m, 1H), 6.56 - 6.44 (m, 1H), 6.40 (d, *J* = 8.4 Hz, 1H), 5.50 - 5.44 (m, 1H), 2.59 (s, 3H), 2.43 (s, 3H), 1.57 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 415.0 (M+H⁺).

Example 12A: 2-((1-(3-(2-cyclopropylpyridin-4-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid (Compound 11)



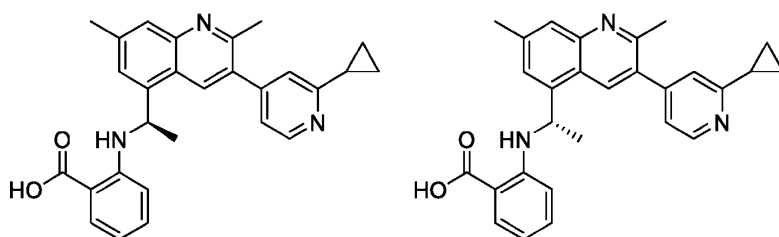
Step 1 – Synthesis of methyl 2-((1-(3-(2-cyclopropylpyridin-4-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate:

A mixture of methyl 2-((1-(2,7-dimethyl-3-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)ethyl)amino)benzoate (150 mg, 311 μ mol), 2-cyclopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (152 mg, 622 μ mol) (prepared according to the procedure in WO2019211463), Pd(PPh₃)₄ (36 mg, 31 μ mol) and K₂CO₃ (129 mg, 933 μ mol) in dioxane (3 mL) and H₂O (0.1 mL). The mixture was stirred at 100 °C for 2 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (126 mg, 85%) as a yellow solid. MS: m/z 452.2 (M+H⁺).

Step 2 – Synthesis of 2-((1-(3-(2-cyclopropylpyridin-4-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid:

To a solution of methyl 2-((1-(3-(2-cyclopropylpyridin-4-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (25 mg, 55 μ mol) in EtOH (0.4 mL) was added KOH (31 mg, 554 μ mol, dissolved in 0.4 mL H₂O). The mixture was stirred at 100 °C for 2 h. After cooling to room temperature, the reaction mixture was adjusted to pH 6 with formic acid. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 23% - 53% / 0.225% formic acid in water) to give the title compound (15 mg, 62%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.61 - 8.47 (m, 3H), 7.86 - 7.77 (m, 1H), 7.67 (s, 1H), 7.48 (s, 1H), 7.37 (s, 1H), 7.34 - 7.28 (m, 1H), 7.18 - 7.08 (m, 1H), 6.55 - 6.46 (m, 1H), 6.40 (d, *J* = 8.4 Hz, 1H), 5.57 - 5.38 (m, 1H), 2.60 (s, 3H), 2.44 (s, 3H), 2.23 - 2.13 (m, 1H), 1.57 (d, *J* = 6.8 Hz, 3H), 1.02 - 0.97 (m, 4H). MS: m/z 438.1 (M+H⁺).

Example 12B: (R)-2-((1-(3-(2-cyclopropylpyridin-4-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid and (S)-2-((1-(3-(2-cyclopropylpyridin-4-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid (Compound 11A and 11B)



Step 1 – Synthesis of methyl (*R*)-2-((1-(3-(2-cyclopropylpyridin-4-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate & methyl (*S*)-2-((1-(3-(2-cyclopropylpyridin-4-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate:

5 methyl 2-((1-(3-(2-cyclopropylpyridin-4-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (100 mg, 221 μmol) was separated by using chiral SFC (DAICEL CHIRALCEL OD (250mm*30mm,10 μm); Supercritical CO_2 / EtOH+0.1% $\text{NH}_3\cdot\text{H}_2\text{O}$ = 60/40; 70 mL/min) to afford methyl (*R*)-2-((1-(3-(2-cyclopropylpyridin-4-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (40 mg, first peak) and methyl (*S*)-2-((1-(3-(2-cyclopropylpyridin-4-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (40 mg, second peak) both as white solid. Absolute configuration was
10 arbitrarily assigned to each enantiomer. MS: m/z 452.2 ($\text{M}+\text{H}^+$).

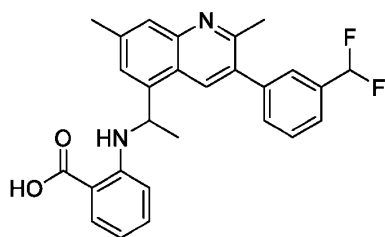
Step 2A – Synthesis of (*R*)-2-((1-(3-(2-cyclopropylpyridin-4-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid:

A solution of methyl (*R*)-2-((1-(3-(2-cyclopropylpyridin-4-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (40 mg, 89 μmol) in MeOH (0.1 mL) and THF (1 mL) was added LiOH (21 mg, 886 μmol , dissolved in 0.1 mL H_2O). The mixture was stirred at 60 $^\circ\text{C}$ for 16 h. After cooling to room temperature, the reaction mixture was adjusted to pH 6 with formic acid. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 21% - 51% / 0.225% formic acid in water) to give the title compound (16 mg, 42%)
15 as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.70 - 8.46 (m, 3H), 7.83 - 7.77 (m, 1H), 7.67 (s, 1H), 7.48 (s, 1H), 7.37 (s, 1H), 7.34 - 7.27 (m, 1H), 7.19 - 7.04 (m, 1H), 6.55 - 6.46 (m, 1H), 6.40 (d, J = 8.4 Hz, 1H), 5.60 - 5.34 (m, 1H), 2.60 (s, 3H), 2.44 (s, 3H), 2.23 - 2.14 (m, 1H), 1.57 (d, J = 6.8 Hz, 3H), 1.04 - 0.96 (m, 4H). MS: m/z 438.1 ($\text{M}+\text{H}^+$).

Step 2B – Synthesis of (*S*)-2-((1-(3-(2-cyclopropylpyridin-4-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid:
25

A solution of methyl (*S*)-2-((1-(3-(2-cyclopropylpyridin-4-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (40 mg, 89 μ mol) in MeOH (0.1 mL) and THF (1 mL) was added LiOH (21 mg, 886 μ mol, dissolved in 0.1 mL H₂O). The mixture was stirred at 60 °C for 16 h. After cooling to room temperature, the reaction mixture was adjusted to pH 6 with formic acid. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 21% - 51% / 0.225% formic acid in water) to give the title compound (14 mg, 37%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.66 - 8.47 (m, 3H), 7.83 - 7.77 (m, 1H), 7.67 (s, 1H), 7.48 (s, 1H), 7.37 (s, 1H), 7.34 - 7.28 (m, 1H), 7.18 - 7.06 (m, 1H), 6.59 - 6.45 (m, 1H), 6.39 (d, *J* = 8.4 Hz, 1H), 5.57 - 5.41 (m, 1H), 2.60 (s, 3H), 2.44 (s, 3H), 2.23 - 2.14 (m, 1H), 1.57 (d, *J* = 6.4 Hz, 3H), 1.02 - 0.96 (m, 4H). MS: *m/z* 438.1 (M+H⁺).

Example 13: methyl 2-((1-(3-(3-(difluoromethyl)phenyl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (Compound 29)



Step 1 – Synthesis of methyl 2-((1-(3-(3-(difluoromethyl)phenyl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate:

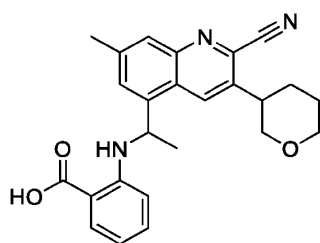
A mixture of methyl 2-((1-(2,7-dimethyl-3-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)ethyl)amino)benzoate (150 mg, 311 μ mol), (3-(difluoromethyl)phenyl)boronic acid (107 mg, 622 μ mol), Pd(PPh₃)₄ (36 mg, 31 μ mol) and K₂CO₃ (129 mg, 933 μ mol) in dioxane (3 mL) and H₂O (0.1 mL). The mixture was stirred at 100 °C for 2 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (100 mg, 70%) as a white solid. MS: *m/z* 461.1 (M+H⁺).

Step 2 – Synthesis of 2-((1-(3-(3-(difluoromethyl)phenyl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid:

A solution of methyl 2-((1-(3-(3-(difluoromethyl)phenyl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (20 mg, 43 μ mol) in EtOH (0.2 mL) was added KOH (24 mg, 434 μ mol,

dissolved in 0.2 mL H₂O). The reaction mixture was stirred at 100 °C for 2 h. After cooling to room temperature, the reaction mixture was adjusted to pH 6 with formic acid. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 30% - 60% / 0.225% formic acid in water) to give the title compound (15 mg, 77%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.52 - 8.38 (m, 2H), 7.84 - 7.78 (m, 1H), 7.77 - 7.70 (m, 2H), 7.69 - 7.65 (m, 3H), 7.36 (s, 1H), 7.27 - 6.96 (m, 2H), 6.60 - 6.47 (m, 1H), 6.41 (d, *J* = 8.0 Hz, 1H), 5.55 - 5.43 (m, 1H), 2.58 (s, 3H), 2.43 (s, 3H), 1.57 (d, *J* = 6.8 Hz, 3H). MS: *m/z* 447.0 (M+H⁺).

Example 14: 2-((1-(2-cyano-7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (Compound 30)



Step 1 – Synthesis of 3-(benzyloxy)-5-bromo-7-methylquinoline 1-oxide:

A mixture of 3-(benzyloxy)-5-bromo-7-methylquinoline (2.5 g, 7.61 mmol) and *m*-CPBA (3.09 g, 15.24 mmol, 85% purity) in DCM (25 mL) was stirred at room temperature for 16 h. The reaction mixture was quenched with sat. aq. Na₂S₂O₃ (20 mL) at room temperature, and then extracted with DCM (30 mL). The organic layer was washed with NaHCO₃ (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give the title compound (2.53 g, crude) as a black solid that required no further purification. MS: *m/z* 344.1 (M+H⁺).

Step 2 – Synthesis of 3-(benzyloxy)-5-bromo-7-methylquinoline-2-carbonitrile:

A mixture of 3-(benzyloxy)-5-bromo-7-methylquinoline 1-oxide (2.10 g, 6.10 mmol), TEA (1.23 g, 12.20 mmol), CCl₄ (1.88 g, 12.20 mmol), TMSCN (726 mg, 7.32 mmol) and diethyl phosphonate (1.69 g, 12.20 mmol) in CHCl₃ (40 mL) was stirred at room temperature for 16 h under N₂ atmosphere. The reaction mixture was diluted with DCM (20 mL). The mixture was washed with NaHCO₃ (30 mL x 2), brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent

gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (1.3 g, 60%) as a yellow solid. MS: m/z 353.0 (M+H⁺).

Step 3 – Synthesis of 5-(1-ethoxyvinyl)-3-hydroxy-7-methylquinoline-2-carbonitrile:

A mixture of tributyl(1-ethoxyvinyl)stannane (1.84 g, 5.10 mmol), 3-(benzyloxy)-5-bromo-7-methylquinoline-2-carbonitrile (900 mg, 2.55 mmol), Pd(dppf)Cl₂ (186 mg, 255 μmol) in dioxane (10 mL) was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the mixture was quenched with 30 mL of 10% KF aqueous solution and stirred for 30 min. The mixture was extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 33% EtOAc in petroleum ether) to give the title compound (400 mg, 62%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.55 (s, 1H), 7.97 (s, 1H), 7.75 (s, 1H), 7.50 (s, 1H), 4.63 - 4.52 (m, 1H), 4.46 - 4.33 (m, 1H), 3.98 (q, *J* = 6.8 Hz, 2H), 2.48 - 2.44 (m, 3H), 1.36 (t, *J* = 6.8 Hz, 3H). MS: m/z 255.1 (M+H⁺).

Step 4 – Synthesis of 5-acetyl-2-cyano-7-methylquinolin-3-yl trifluoromethanesulfonate:

A mixture of 5-(1-ethoxyvinyl)-3-hydroxy-7-methylquinoline-2-carbonitrile (100 mg, 393 μmol), pyridine (93 mg, 1.18 mmol), Tf₂O (166 mg, 590 μmol) in DCM (4 mL) was stirred at 0 °C for 1 h. The mixture was added to HCl (5 mL, 1M), and then stirred at room temperature for 0.5 h. The mixture was basified with sat. aq. NaHCO₃ to pH 7. Then the mixture was extracted with DCM (15 mL x 2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give the title compound (128 mg, crude) as a yellow solid that required no further purification. MS: m/z 359.0 (M+H⁺).

Step 5 – Synthesis of 5-acetyl-3-(5,6-dihydro-2H-pyran-3-yl)-7-methylquinoline-2-carbonitrile:

A mixture of 5-acetyl-2-cyano-7-methylquinolin-3-yl trifluoromethanesulfonate (128 mg, 357 μmol), 2-(5,6-dihydro-2H-pyran-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (113 mg, 536 μmol), Pd(PPh₃)₄ (41 mg, 36 μmol) and K₂CO₃ (148 mg, 1.07 mmol) in dioxane (2 mL) and H₂O (0.2 mL). The mixture was stirred at 100 °C for 2 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give

the title compound (73 mg, 70%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.98 (s, 1H), 8.34 (s, 1H), 8.12 (s, 1H), 6.36 - 6.24 (m, 1H), 4.41 - 4.38 (m, 2H), 3.86 - 3.81 (m, 2H), 2.76 (s, 3H), 2.62 (s, 3H), 2.35 - 2.31 (m, 2H). MS: m/z 293.4 ($\text{M}+\text{H}^+$).

Step 6 - Synthesis of 5-(1-aminoethyl)-3-(5,6-dihydro-2H-pyran-3-yl)-7-methylquinoline-2-carbonitrile:

A mixture of 5-acetyl-3-(5,6-dihydro-2H-pyran-3-yl)-7-methylquinoline-2-carbonitrile (65 mg, 222 μmol), NH_4OAc (257 mg, 3.34 mmol) and AcOH (13 mg, 222 μmol) in MeOH (1 mL) was stirred at room temperature for 1 h. Then NaBH_3CN (42 mg, 667 μmol) was added to the reaction mixture. After the addition, the reaction mixture was stirred at 60 $^\circ\text{C}$ for 16 h. After cooling to room temperature, the reaction mixture was diluted with DCM (20 mL). The mixture was washed with saturated NaHCO_3 solution (10 mL x 3), brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give the title compound (63 mg, crude) as a yellow solid that required no further purification. MS: m/z 294.2 ($\text{M}+\text{H}^+$).

Step 7 - Synthesis of *tert*-butyl 2-((1-(2-cyano-3-(5,6-dihydro-2H-pyran-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoate:

A mixture of 5-(1-aminoethyl)-3-(5,6-dihydro-2H-pyran-3-yl)-7-methylquinoline-2-carbonitrile (63 mg, 215 μmol), *tert*-butyl 2-iodobenzoate (98 mg, 322 μmol), Cs_2CO_3 (210 mg, 644 μmol), $\text{Pd}_2(\text{dba})_3$ (20 mg, 21 μmol) and Xantphos (25 mg, 43 μmol) in dioxane (2 mL), the reaction mixture was stirred at 100 $^\circ\text{C}$ for 2 h under N_2 atmosphere. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% EtOAc in petroleum ether) to give the title compound (50 mg, 50%) as a yellow solid. MS: m/z 470.3 ($\text{M}+\text{H}^+$).

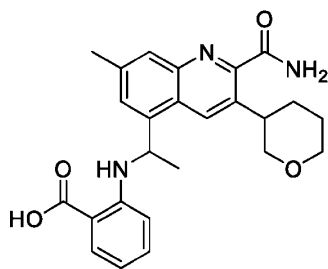
Step 8 - Synthesis of *tert*-butyl 2-((1-(2-cyano-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate:

To a solution of *tert*-butyl 2-((1-(2-cyano-3-(5,6-dihydro-2H-pyran-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoate (50 mg, 106 μmol) in MeOH (1 mL) was added $\text{Pd}(\text{OH})_2$ on carbon (16 mg, 20% Pd , 50% wet with water). The reaction was stirred at room temperature for 1 h under H_2 atmosphere (15 psi). The reaction was filtered through diatomaceous earth and the filtrate was concentrated in vacuo to give the title compound (49 mg, crude) as a yellow solid that required no further purification. MS: m/z 472.3 ($\text{M}+\text{H}^+$).

Step 9 – Synthesis of 2-((1-(2-cyano-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid:

To a solution of *tert*-butyl 2-((1-(2-cyano-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate (13 mg, 28 μ mol) in DCM (2 mL) was added TFA (154 mg, 1.36 mmol). The reaction mixture was stirred at 40 °C for 2 h. After cooling to room temperature, the reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 56% - 86% / 0.225% formic acid in water) to give the title compound (2.9 mg, 25%) as a white solid. ^1H NMR (400 MHz, DMSO-*d*₆) δ 12.78 (s, 1H), 8.76 (s, 1H), 8.62 - 8.40 (m, 1H), 7.91 - 7.71 (m, 2H), 7.60 - 7.57 (m, 1H), 7.26 - 7.10 (m, 1H), 6.57 - 6.53 (m, 1H), 6.50 - 6.41 (m, 1H), 5.68 - 5.46 (m, 1H), 4.02 - 3.85 (m, 2H), 3.57 - 3.43 (m, 3H), 2.48 - 2.45 (m, 3H), 2.13 - 1.91 (m, 2H), 1.78 - 1.67 (m, 2H), 1.61 (d, *J* = 5.6 Hz, 3H). MS: *m/z* 416.3 (*M*+*H*⁺).

Example 15: 2-((1-(2-carbamoyl-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino) benzoic acid (Compound 31)



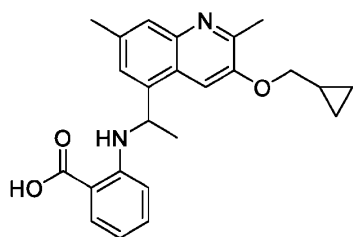
Step 1 – Synthesis of *tert*-butyl 2-((1-(2-carbamoyl-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate:

To a solution of *tert*-butyl 2-((1-(2-cyano-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate (40 mg, 85 μ mol) in THF (2 mL) and H₂O (0.5 mL) was added H₂O₂ (96 mg, 848 μ mol, 30% in water) and NaOH (14 mg, 339 μ mol). After the addition, the reaction mixture was stirred at room temperature for 16 h. The mixture was quenched with sat. aq. Na₂S₂O₃ solution (5 mL) and stirred for 30 min. The mixture was extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (38 mg, 64%) as a white solid. MS: *m/z* 490.1 (*M*+*H*⁺).

Step 2 – Synthesis of 2-((1-(2-carbamoyl-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid:

To a solution of *tert*-butyl 2-((1-(2-carbamoyl-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate (38 mg, 78 μ mol) in DCM (1 mL) was added TFA (0.3 mL, 37.9 mmol). The reaction mixture was stirred at room temperature for 16 h. The mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 45% - 75% / 0.225% formic acid in water) to give the title compound (4.9 mg, 14%) as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ 12.77 (s, 1H), 8.57 (d, J = 5.6 Hz, 1H), 8.05 (s, 1H), 7.85 - 7.79 (m, 1H), 7.72 - 7.65 (m, 2H), 7.45 (d, J = 8.0 Hz, 1H), 7.25 - 7.12 (m, 1H), 6.56 - 6.44 (m, 2H), 5.58 - 5.44 (m, 1H), 3.98 - 3.84 (m, 2H), 3.40 - 3.88 (m, 3H), 2.46 - 2.44 (m, 3H), 2.06 - 1.78 (m, 2H), 1.69 - 1.59 (m, 5H). MS: m/z 434.2 ($\text{M}+\text{H}^+$).

Example 16: 2-((1-(3-(cyclopropylmethoxy)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid (Compound 32)



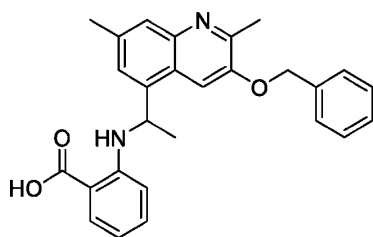
Step 1 – Synthesis of methyl 2-((1-(3-(cyclopropylmethoxy)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate:

A mixture of methyl 2-((1-(3-hydroxy-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (120 mg, 342 μ mol), bromomethylcyclopropane (120 mg, 888 μ mol), Cs_2CO_3 (335 mg, 1.03 mmol) in DMF (3 mL) was stirred at 80 $^\circ\text{C}$ for 2 h. After cooling to room temperature, the reaction mixture was quenched with water (15 mL), extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (30 mL x 3) and brine (30 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give the title compound (120 mg, crude) as a yellow solid that required no further purification. MS: m/z 405.1 ($\text{M}+\text{H}^+$).

Step 2 – Synthesis of 2-((1-(3-(cyclopropylmethoxy)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid:

To a solution of methyl 2-((1-(3-(cyclopropylmethoxy)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (120 mg, 297 μ mol) in EtOH (1 mL) was added KOH (194 mg, 3.46 mmol, dissolved in 1 mL H₂O). The reaction mixture was stirred at 100 °C for 2 h. After cooling to room temperature, the reaction mixture was adjusted to pH 6 with formic acid. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 26% - 56% / 0.225% formic acid in water) to give the title compound (100 mg, 86%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.54 - 8.34 (m, 1H), 7.82 - 7.74 (m, 2H), 7.53 (s, 1H), 7.28 (d, *J* = 1.2 Hz, 1H), 7.19 - 7.11 (m, 1H), 6.54 - 6.47 (m, 1H), 6.42 (d, *J* = 8.4 Hz, 1H), 5.50 - 5.29 (m, 1H), 3.99 (d, *J* = 6.8 Hz, 2H), 2.54 (s, 3H), 2.37 (s, 3H), 1.57 (d, *J* = 6.4 Hz, 3H), 1.34 - 1.22 (m, 1H), 0.65 - 0.55 (m, 2H), 0.45 - 0.34 (m, 2H). MS: *m/z* 391.1 (M+H⁺).

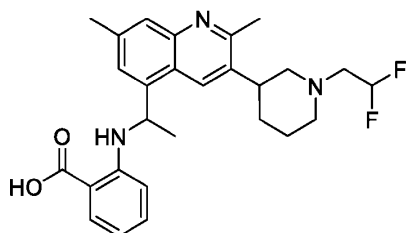
Example 17: 2-((1-(3-(benzyloxy)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid (Compound 33)



Step 1 – Synthesis of 2-((1-(3-(benzyloxy)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid:

To a solution of methyl 2-((1-(3-(benzyloxy)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (100 mg, 227 μ mol) in EtOH (1 mL) was added KOH (127 mg, 2.27 mmol, dissolved in 1 mL H₂O). The reaction mixture was stirred at 100 °C for 2 h. After cooling to room temperature, the reaction mixture was adjusted to pH 6 with formic acid. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 50% - 80% / 0.225% formic acid in water) to give the title compound (65 mg, 66%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.80 (s, 1H), 8.55 - 8.41 (m, 1H), 7.91 (s, 1H), 7.83 - 7.78 (m, 1H), 7.57 - 7.51 (m, 3H), 7.45 - 7.38 (m, 2H), 7.37 - 7.30 (m, 1H), 7.27 (d, *J* = 1.2 Hz, 1H), 7.17 - 7.09 (m, 1H), 6.55 - 6.48 (m, 1H), 6.37 (d, *J* = 8.4 Hz, 1H), 5.40 - 5.29 (m, 3H), 2.58 (s, 3H), 2.36 (s, 3H), 1.51 (d, *J* = 6.8 Hz, 3H). MS: *m/z* 427.2 (M+H⁺).

Example 18: 2-((1-(3-(1-(2,2-difluoroethyl)piperidin-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino) benzoic acid (Compound 34)



Step 1 - Synthesis of *tert*-butyl 5-(5-(1-((2-(methoxycarbonyl)phenyl)amino)ethyl)-2,7-dimethylquinolin-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate:

A mixture of methyl 2-((1-(2,7-dimethyl-3-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)ethyl)amino)benzoate (200 mg, 415 μ mol), *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (192 mg, 622 μ mol), Pd(PPh₃)₄ (48 mg, 42 μ mol) and K₂CO₃ (172 mg, 1.24 mmol) in dioxane (2 mL) and H₂O (0.2 mL). The mixture was heated to 100 °C for 2 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was quenched with water (5 mL), diluted with EtOAc (20 mL). The mixture was washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 15% EtOAc in petroleum ether) to give the title compound (200 mg, 95%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.36 (s, 1H), 8.23 (d, *J* = 6.0 Hz, 1H), 7.83 - 7.79 (m, 1H), 7.60 (s, 1H), 7.32 (s, 1H), 7.22 - 7.16 (m, 1H), 6.57 - 6.51 (m, 1H), 6.41 (d, *J* = 8.4 Hz, 1H), 5.91 - 5.87 (m, 1H), 5.48 - 5.44 (m, 1H), 4.09 - 4.06 (m, 2H), 3.85 (s, 3H), 3.57 - 3.52 (m, 2H), 2.62 (s, 3H), 2.40 (s, 3H), 2.30 - 2.26 (m, 2H), 1.58 (d, *J* = 6.8 Hz, 3H), 1.07 (s, 9H). MS: *m/z* 516.3 (M+H⁺).

Step 2 - Synthesis of *tert*-butyl 3-(5-(1-((2-(methoxycarbonyl)phenyl)amino)ethyl)-2,7-dimethylquinolin-3-yl)piperidine-1-carboxylate:

To a solution of *tert*-butyl 5-(5-(1-((2-(methoxycarbonyl)phenyl)amino)ethyl)-2,7-dimethylquinolin-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (200 mg, 388 μ mol) in MeOH (2 mL) was added Pd(OH)₂ on carbon (60 mg, 20% Pd, 50% wet with water). The reaction was stirred at room temperature for 1 h under H₂ atmosphere (15 psi). The reaction was filtered through diatomaceous earth and the filtrate was concentrated in vacuo to give the title compound (138 mg, crude) as a yellow solid that required no further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ

8.35 (s, 1H), 8.23 (d, $J = 6.0$ Hz, 1H), 7.83 - 7.81 (m, $J = 8.0$ Hz, 1H), 7.58 (s, 1H), 7.38 - 7.28 (m, 1H), 7.27 - 7.18 (m, 1H), 6.60 - 6.45 (m, 2H), 5.57 - 5.38 (m, 1H), 4.14 - 4.07 (m, 1H), 4.05 - 3.96 (m, 2H), 3.86 - 3.81 (m, 3H), 2.90 - 2.86 (m, 1H), 2.84 - 2.76 (m, 1H), 2.70 (s, 3H), 2.40 (s, 3H), 1.93 - 1.88 (m, 2H), 1.80 - 1.71 (m, 1H), 1.61 (d, $J = 6.8$ Hz, 3H), 1.52 - 1.48 (m, 1H), 1.42 (s, 9H). MS: m/z 518.3 ($M+H^+$).

Step 3 - Synthesis of methyl 2-((1-(2,7-dimethyl-3-(piperidin-3-yl)quinolin-5-yl)ethyl)amino)benzoate hydrochloride:

To a solution of *tert*-butyl 3-(5-(1-((2-(methoxycarbonyl)phenyl)amino)ethyl)-2,7-dimethylquinolin-3-yl)piperidine-1-carboxylate (138 mg, 267 μ mol) in DCM (2 mL) was added HCl (2 mL, 4M in EtOAc). After the addition, the reaction mixture was stirred at room temperature for 1 h. The mixture was concentrated to give the title compound (120 mg, crude) as a yellow solid that required no further purification. MS: m/z 418.3 ($M+H^+$).

Step 4 - Synthesis of methyl 2-((1-(3-(1-(2,2-difluoroethyl)piperidin-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate:

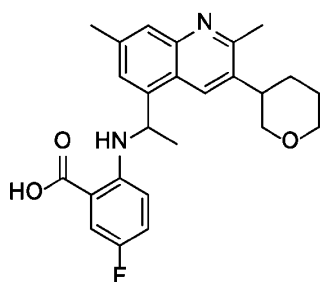
A mixture of methyl 2-((1-(2,7-dimethyl-3-(piperidin-3-yl)quinolin-5-yl)ethyl)amino)benzoate hydrochloride (120 mg, 263 μ mol), 2,2-difluoroethyl trifluoromethanesulfonate (85 mg, 395 μ mol) and TEA (110 μ L, 790 μ mol) in DCM (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 50 $^{\circ}$ C for 16 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was quenched by addition water (10 mL) and diluted with DCM (15 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 36% EtOAc in petroleum ether) to give the title compound (66 mg, 52%) as a white solid. 1H NMR (400 MHz, $DMSO-d_6$) δ 8.41 - 8.30 (m, 1H), 8.20 (d, $J = 6.0$ Hz, 1H), 7.83 - 7.80 (m, 1H), 7.57 (s, 1H), 7.37 - 7.30 (m, 1H), 7.29 - 7.20 (m, 1H), 6.61 - 6.49 (m, 2H), 6.35 - 5.98 (m, 1H), 5.49 - 5.38 (m, 1H), 3.86 - 3.77 (m, 3H), 3.10 - 3.01 (m, 1H), 2.97 - 2.86 (m, 2H), 2.81 - 2.72 (m, 2H), 2.67 (s, 3H), 2.41 (s, 3H), 2.27 - 2.23 (m, 2H), 1.84 - 1.77 (m, 1H), 1.76 - 1.65 (m, 2H), 1.62 (d, $J = 6.8$ Hz, 3H), 1.52 - 1.46 (m, 1H). MS: m/z 482.2 ($M+H^+$).

Step 5 - 2-((1-(3-(1-(2,2-difluoroethyl)piperidin-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid:

A solution of methyl 2-((1-(3-(1-(2,2-difluoroethyl)piperidin-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (66 mg, 137 μ mol) in EtOH (0.5 mL) was added KOH (19 mg, 342

μmol, dissolved in 0.5 mL H₂O). The mixture was stirred at 100 °C for 1 h. After cooling to room temperature, the reaction mixture was adjusted to pH 6 with formic acid. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 15 - 45% / 0.225% formic acid in water) to give the title compound (2.2 mg, 2%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.75 (s, 1H), 8.47 - 8.38 (m, 1H), 8.34 (s, 1H), 7.85 - 7.77 (m, 1H), 7.57 (s, 1H), 7.36 - 7.29 (m, 1H), 7.26 - 7.15 (m, 1H), 6.58 - 6.46 (m, 2H), 6.34 - 6.00 (m, 1H), 5.48 - 5.35 (m, 1H), 3.10 - 3.00 (m, 1H), 2.95 - 2.88 (m, 2H), 2.80 - 2.70 (m, 2H), 2.67 (s, 3H), 2.41 (s, 3H), 2.32 - 2.20 (m, 2H), 1.83 - 1.79 (m, 1H), 1.76 - 1.63 (m, 2H), 1.61 (d, *J* = 6.8 Hz, 3H), 1.57 - 1.47 (m, 1H). MS: *m/z* 468.3 (M+H⁺).

Example 19: 2-((1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)-5-fluorobenzoic acid (Compound 35)



Step 1 – Synthesis of methyl 2-((1-(3-(benzyloxy)-2,7-dimethylquinolin-5-yl)ethyl)amino)-5-fluorobenzoate:

A mixture of 1-(3-benzyloxy-2,7-dimethyl-5-quinolyl)ethanamine (2 g, 6.53 mmol), methyl 2-bromo-5-fluoro-benzoate (2.28 g, 9.79 mmol), Pd₂(dba)₃ (597 mg, 652 μmol), Xantphos (755 mg, 1.31 mmol) and Cs₂CO₃ (6.38 g, 19.58 mmol) in dioxane (40 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 110 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 25% EtOAc in petroleum ether) to give the title compound (1.1 g, 35%) as a white solid. MS: *m/z* 459.1 (M+H⁺).

Step 2 – Synthesis of methyl 5-fluoro-2-((1-(3-hydroxy-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate:

To a solution of methyl 2-((1-(3-(benzyloxy)-2,7-dimethylquinolin-5-yl)ethyl)amino)-5-fluorobenzoate (900 mg, 1.96 mmol) in MeOH (30 mL) was added wet Pd on carbon (835 mg, 10% Pd, 50% wet with water). The reaction was stirred at room temperature for 1h under H₂ atmosphere (15 psi). The reaction was filtered through diatomaceous earth and the filtrate was concentrated to afford the title compound (600 mg, 83%) as white solid that required no further purification. MS: m/z 369.1 (M+H⁺).

Step 3 – Synthesis of methyl 2-((1-(2,7-dimethyl-3-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)ethyl)amino)-5-fluorobenzoate:

To a solution of 5-fluoro-2-((1-(3-hydroxy-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (250 mg, 678 μmol) in DCM (5 mL) was added pyridine (161 mg, 2.04 mmol) and Tf₂O (287 mg, 1.02 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with DCM (30 mL) and washed with 1M HCl (10 mL), and then the organic layer was washed with NaHCO₃ (10 mL x 2), dried over anhydrous Na₂SO₄ and filtered and concentrated in vacuo to give the title compound (340 mg, 84%) as a white solid that required no further purification. MS: m/z 501.3 (M+H⁺).

Step 4 – Synthesis of methyl 2-((1-(3-(5,6-dihydro-2H-pyran-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)-5-fluorobenzoate:

A mixture of methyl 2-((1-(2,7-dimethyl-3-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)ethyl)amino)-5-fluorobenzoate (340 mg, 679 μmol), 2-(3,6-dihydro-2H-pyran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (171 mg, 815 μmol), Pd(PPh₃)₄ (78 mg, 67 μmol), K₂CO₃ (281 mg, 2.04 mmol) in dioxane (5 mL) and H₂O (0.5 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (270 mg, 86%) as a white solid. MS: m/z 435.1 (M+H⁺).

Step 5 – Synthesis of methyl 2-((1-(2,7-dimethyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)-5-fluorobenzoate:

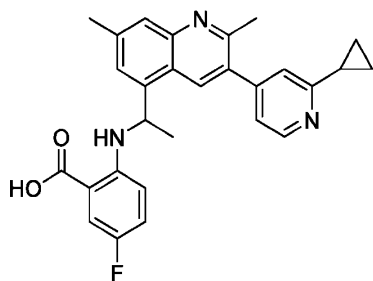
To a solution of methyl 2-((1-(3-(5,6-dihydro-2H-pyran-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)-5-fluorobenzoate (270 mg, 621 μmol) in MeOH (20 mL) was added wet Pd on carbon (264 mg, 10% Pd, 50% wet with water). The reaction was stirred at room temperature for 1.5 h under H₂ atmosphere (15 psi). The reaction was filtered through

diatomaceous earth and the filtrate was concentrated to afford the title compound (210 mg, 62%) as white solid that required no further purification. MS: m/z 437.1 ($M+H^+$).

Step 6 – Synthesis of 2-((1-(2,7-dimethyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)-5-fluorobenzoic acid:

To a solution of methyl 2-((1-(2,7-dimethyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)-5-fluorobenzoate (30 mg, 68 μ mol) in EtOH (1 mL) was added KOH (38 mg, 687 μ mol, dissolved in 1 mL H_2O). The mixture was stirred at 100 °C for 2 h. After cooling to room temperature, the reaction mixture was adjusted to pH 6 with formic acid. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 19 - 49% / 0.225% formic acid in water) to afford the title compound (4.22 mg, 14%) as a white solid. 1H NMR (400 MHz, $DMSO-d_6$) δ 13.07 (s, 1H), 8.33 (s, 1H), 8.23 (s, 1H), 7.57 (s, 1H), 7.54 - 7.49 (m, 1H), 7.33 - 7.29 (m, 1H), 7.17 - 7.10 (m, 1H), 6.52 - 6.44 (m, 1H), 5.48 - 5.37 (m, 1H), 3.95 - 3.85 (m, 2H), 3.45 - 3.37 (m, 2H), 3.12 - 3.03 (m, 1H), 2.68 (s, 3H), 2.42 - 2.39 (m, 3H), 1.99 - 1.90 (m, 1H), 1.88 - 1.78 (m, 1H), 1.75 - 1.66 (m, 2H), 1.60 (d, J = 6.4 Hz, 3H). MS: m/z 423.1 ($M+H^+$).

Example 20: 2-((1-(3-(2-cyclopropylpyridin-4-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)-5-fluorobenzoic acid (Compound 36)



Step 1 – Synthesis of methyl 2-((1-(3-(2-cyclopropylpyridin-4-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)-5-fluorobenzoate:

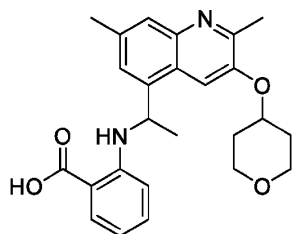
A mixture of methyl 2-((1-(2,7-dimethyl-3-(((trifluoromethyl)sulfonyl)oxy) quinolin-5-yl)ethyl)amino)-5-fluorobenzoate (40 mg, 80 μ mol), 2-cyclopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (39 mg, 160 μ mol), $Pd(PPh_3)_4$ (9 mg, 8 μ mol), K_2CO_3 (33 mg, 240 μ mol) in dioxane (2 mL) and H_2O (0.2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 16 h under N_2 atmosphere. After cooling to room temperature,

the reaction was filtered and the filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 25% EtOAc in petroleum ether) to give the title compound (11 mg, 29%) as a white solid. MS: m/z 470.1 ($M+H^+$).

Step 2 – Synthesis of 2-((1-(3-(2-cyclopropylpyridin-4-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)-5-fluorobenzoic acid

A solution of methyl 2-((1-(3-(2-cyclopropylpyridin-4-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)-5-fluorobenzoate (11 mg, 23 μ mol) and LiOH (6 mg, 251 μ mol) in THF (1 mL), MeOH (0.1 mL) and H₂O (0.1 mL) was stirred at 60 °C for 2 h. After cooling to room temperature, the reaction mixture was adjusted to pH 6 with formic acid. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 29 - 49% / 0.225% formic acid in water) to afford the title compound (4 mg, 38%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.52 - 8.49 (m, 2H), 7.67 (s, 1H), 7.55 - 7.50 (m, 1H), 7.50 - 7.48 (m, 1H), 7.36 (d, J = 1.2 Hz, 1H), 7.34 - 7.31 (m, 1H), 7.08 - 7.01 (m, 1H), 6.41 - 6.36 (m, 1H), 5.48 - 5.44 (m, 1H), 2.60 (s, 3H), 2.43 (s, 3H), 2.23 - 2.17 (m, 1H), 1.56 (d, J = 6.4 Hz, 3H), 1.01 - 0.97 (m, 4H). MS: m/z 456.1 ($M+H^+$).

Example 21: 2-((1-(2,7-dimethyl-3-((tetrahydro-2H-pyran-4-yl)oxy)quinolin-5-yl)ethyl)amino) benzoic acid (Compound 37)



Step 1 – Synthesis of methyl 2-((1-(2,7-dimethyl-3-((tetrahydro-2H-pyran-4-yl)oxy)quinolin-5-yl)ethyl)amino)benzoate:

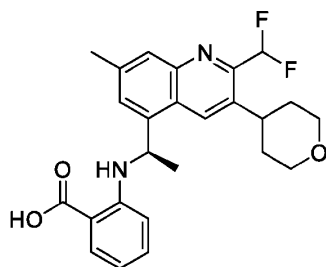
To a solution of methyl 2-((1-(3-hydroxy-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (140 mg, 399 μ mol) and 4-bromotetrahydropyran (131 mg, 799 μ mol) in DMF (8 mL) was added K₂CO₃ (165 mg, 1.20 mmol). The mixture was stirred at 100 °C for 16 h. After cooling to room temperature, the reaction was quenched with water (10 mL) and extracted with EtOAc (15 mL x 2). The combined organic layers were washed with brine (20 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel

chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (40 mg, 22%) as a white solid. MS: m/z 435.2 ($M+H^+$).

Step 2 – Synthesis of 2-((1-(2,7-dimethyl-3-((tetrahydro-2H-pyran-4-yl)oxy) quinoline-5-yl)ethyl)amino)benzoic acid:

To a solution of methyl 2-((1-(2,7-dimethyl-3-((tetrahydro-2H-pyran-4-yl)oxy) quinolin-5-yl)ethyl)amino)benzoate (40 mg, 92 μ mol) in EtOH (1 mL) was added KOH (51 mg, 920 μ mol, dissolved in 1 mL H₂O). The mixture was stirred at 100 °C for 2 h. The solution was adjusted to pH 6 with formic acid. The crude residue was purified by reverse phase chromatography (acetonitrile 23-53% / 0.225% formic acid in water) to afford the title compound (8.2 mg, 21%) as a white solid. ¹H NMR (400MHz, DMSO-*d*₆) δ 12.73 (s, 1H), 8.39 (s, 1H), 7.82 (s, 1H), 7.82 - 7.78 (m, 1H), 7.55 (s, 1H), 7.32 (d, J = 1.2 Hz, 1H), 7.23 - 7.17 (m, 1H), 6.55 - 6.49 (m, 2H), 5.43 - 5.39 (m, 1H), 4.84 - 4.76 (m, 1H), 3.88 - 3.79 (m, 2H), 3.56 - 3.43 (m, 2H), 2.53 (s, 3H), 2.39 (s, 3H), 2.03 - 1.92 (m, 2H), 1.70 - 1.62 (m, 2H), 1.58 (d, J = 6.4 Hz, 3H). MS: m/z 421.1 ($M+H^+$).

Example 22: (*R*)-2-((1-(2-(difluoromethyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoic acid (Compound 38)



Step 1 – Synthesis of 5-bromo-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline:

To a solution of 2-(tetrahydro-2H-pyran-4-yl)acetaldehyde (5.03 g, 39.24 mmol) and 2-amino-6-bromo-4-methyl-benzaldehyde (7 g, 32.70 mmol) in *n*-BuOH (100 mL) and H₂O (10 mL) was added NaOH (2.62 g, 65.40 mmol). The reaction mixture was stirred at 110 °C for 1 h. After cooling to room temperature, the mixture was adjusted pH to 5 with HCl (1M), then was added water (50 mL) and extracted with EtOAc (200 mL x 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 16% EtOAc in petroleum ether) to give the title compound (9.6 g, 96%) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ

8.90 (d, $J = 2.0$ Hz, 1H), 8.16 (d, $J = 1.6$ Hz, 1H), 7.83 (s, 2H), 4.05 - 3.96 (m, 2H), 3.55 - 3.45 (m, 2H), 3.16 - 3.03 (m, 1H), 2.51 (s, 3H), 1.88 - 1.76 (m, 4H). MS: m/z 305.9 ($M+H^+$).

Step 2 – Synthesis of 5-bromo-2-(difluoromethyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline:

5 A mixture of 5-bromo-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline (2 g, 6.53 mmol), bis(difluoromethylsulfonyloxy)zinc (4.28 g, 13.06 mmol) in DCM (2 mL) and H₂O (0.6 mL) was added TFA (744 mg, 6.53 mmol) and 2-hydroperoxy-2-methyl-propane (1.77 g, 19.60 mmol). The reaction mixture was stirred at room temperature for 16 h under N₂ atmosphere. The mixture was quenched with sat. aq. NaHCO₃ (20 mL) and extracted with EtOAc (50 mL x 2). The combined
10 organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (160 mg, 7%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.43 (s, 1H), 7.96 (s, 1H), 7.92 (s, 1H), 7.47 - 7.17 (m, 1H), 4.06 - 3.96 (m, 2H), 3.56 - 3.47 (m, 2H), 3.46 - 3.37 (m, 1H), 2.53 (s, 3H), 2.04 - 1.70 (m,
15 4H). MS: m/z 356.0 ($M+H^+$).

Step 3 – Synthesis of 2-(difluoromethyl)-5-(1-ethoxyvinyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline:

A mixture of 5-bromo-2-(difluoromethyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline (500 mg, 1.40 mmol), tributyl(1-ethoxyvinyl)stannane (1.52 g, 4.21 mmol) and
20 Pd(dppf)Cl₂ (102 mg, 140 μ mol) in dioxane (5 mL) was stirred at 90 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the crude product 3-benzyloxy-2-(difluoromethyl)-5-(1-ethoxyvinyl)-7-methyl-quinoline (487 mg, crude) was used into the next step without further purification. MS: m/z 370.1 ($M+Na^+$).

Step 4 – Synthesis of 1-(2-(difluoromethyl)-5-(1-ethoxyvinyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinolin-5-yl)ethan-1-one:

To a solution of 2-(difluoromethyl)-5-(1-ethoxyvinyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline (487 mg, crude) in dioxane (10 mL) was added HCl (2 mL, 1M in water) at room temperature. The reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with 10% KF solution (20 mL). The mixture was filtered and the filtrate was extracted
30 with EtOAc (50 mL x 2). The organic layer was washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel

chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (94 mg, 21%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.15 (s, 1H), 8.23 (s, 1H), 8.07 (s, 1H), 7.26 (t, *J* = 53.4 Hz, 1H), 4.08 - 3.91 (m, 2H), 3.60 - 3.45 (m, 2H), 3.41 - 3.35 (m, 1H), 2.76 (s, 3H), 2.59 (s, 3H), 1.80 - 1.70 (m, 4H). MS: *m/z* 320.2 (M+H⁺).

5 **Step 5 – Synthesis of (*R,E*)-*N*-(1-(2-(difluoromethyl)-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide:**

To a solution of 1-(2-(difluoromethyl)-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethan-1-one (94 mg, 294 μmol) in THF (2 mL) was added (*R*)-2-methylpropane-2-sulfinamide (214 mg, 1.77 mmol) and Ti(*i*-PrO)₄ (836 mg, 2.94 mmol) at room temperature. The mixture was stirred at 75 °C for 16 h. The reaction mixture was diluted with water (10 mL) and filtered, the filtrate was extracted with DCM (10 mL x 3), and then the organic layer was washed with brine (20 mL), dried over anhydrous Na₂SO₄ and filtered and concentrated in vacuo to give the title compound (80 mg, crude) as a yellow solid that required no further purification. MS: *m/z* 423.2 (M+H⁺).

15 **Step 6 - Synthesis of (*R,E*)-*N*-(1-(2-(difluoromethyl)-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide:**

To a solution of (*R,E*)-*N*-(1-(2-(difluoromethyl)-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide (80 mg, 189 μmol) in THF (3 mL) was added NaBH₄ (21.49 mg, 568 μmol) at 0 °C. The mixture was stirred at 0 °C for 30 min under N₂ atmosphere. Then the reaction was quenched with aq. sat. NH₄Cl (5 mL) and extracted with DCM (20 mL x 3). The organics were washed with aq. sat. NaCl (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give the title compound (70 mg, 87%, two isomers) as a white solid that required no further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.73 - 8.65 (m, 1H), 7.77 (s, 1H), 7.68 - 7.55 (m, 1H), 7.45 - 7.00 (m, 1H), 5.87 - 5.56 (m, 1H), 5.34 - 5.20 (m, 1H), 4.07 - 3.95 (m, 2H), 3.56 - 3.43 (m, 2H), 3.41 - 3.35 (m, 1H), 2.53 (s, 3H), 2.06 - 1.92 (m, 2H), 1.74 - 1.66 (m, 2H), 1.65 - 1.53 (m, 3H), 1.12 - 0.99 (m, 9H). MS: *m/z* 425.1 (M+H⁺).

25 **Step 7 - Synthesis of 1-(2-(difluoromethyl)-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethan-1-amine:**

A solution of (*R*)-*N*-((*R*)-1-(2-(difluoromethyl)-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (70 mg, 164 μmol) in MeOH (1 mL) was added 12M HCl (18 mg, 494 μmol). The reaction mixture was stirred at room temperature for 1 h.

The reaction mixture was adjusted to pH 8 with sat. NaHCO₃ solution, then diluted with water (20 mL) and extracted with DCM (30 mL x 3). The organics were dried over Na₂SO₄, filtered and concentrated in vacuo to give the title compound (50 mg, crude) as a yellow solid that required no further purification. MS: m/z 321.0 (M+H⁺).

Step 8 - Synthesis of *tert*-butyl (*R*)-2-((1-(2-(difluoromethyl)-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoate & *tert*-butyl (*S*)-2-((1-(2-(difluoromethyl)-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoate:

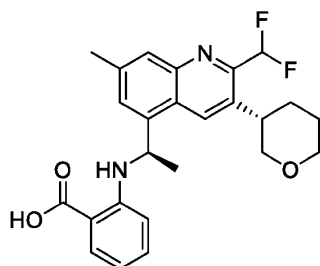
A mixture of 1-(2-(difluoromethyl)-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethan-1-amine (50 mg, crude), *tert*-butyl 2-iodobenzoate (71 mg, 234 μmol), Pd₂(dba)₃ (14 mg, 15 μmol), XantPhos (18 mg, 31 μmol) and Cs₂CO₃ (152 mg, 468 μmol) in dioxane (1 mL) was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% EtOAc in petroleum ether) to give *tert*-butyl 2-((1-(2-(difluoromethyl)-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl) amino)benzoate (60 mg, 77%, two isomers 3:2) as a white solid. The mixture was purified by using chiral SFC (DAICEL CHIRALPAK OD (250mm*30mm,10um); Supercritical CO₂ / EtOH + 0.1% NH₃•H₂O = 25/75; 80 mL/min) to afford *tert*-butyl (*S*)-2-((1-(2-(difluoromethyl)-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino) benzoate (23 mg, first peak) and *tert*-butyl (*R*)-2-((1-(2-(difluoromethyl)-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoate (30 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. MS: m/z 497.3 (M+H⁺).

Step 9 – Synthesis of (*R*)-2-((1-(2-(difluoromethyl)-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoic acid:

To a mixture of *tert*-butyl (*R*)-2-((1-(2-(difluoromethyl)-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoate (30 mg, 60 μmol) in DCM (2 mL) was added TFA (1.54 g, 13.46 mmol). The reaction mixture was stirred at room temperature for 16 h. Then the reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 63% - 93% / 0.225% formic acid in water) to give the title compound (14 mg, 52%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.79 (s, 1H), 8.75 (s, 1H), 8.52 (s, 1H), 7.85 - 7.78 (m, 1H), 7.77 - 7.73 (m, 1H), 7.52 - 7.47 (m, 1H), 7.40 - 7.09 (m, 2H), 6.57 - 6.43 (m, 2H),

5.71 - 5.51 (m, 1H), 4.12 - 3.88 (m, 2H), 3.57 - 3.45 (m, 2H), 3.42 - 3.36 (m, 1H), 2.45 (s, 3H), 2.06 - 1.88 (m, 2H), 1.77 - 1.65 (m, 2H), 1.60 (d, $J = 6.4$ Hz, 3H). MS: m/z 441.2 ($M+H^+$).

Example 23: 2-(((*R*)-1-(2-(difluoromethyl)-7-methyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (Compound 39)



5

Step 1 – Synthesis of 3-(benzyloxy)-5-bromo-7-methylquinoline-2-carbaldehyde:

A mixture of 3-(benzyloxy)-5-bromo-2,7-dimethylquinoline (14 g, 40.91 mmol) and SeO_2 (5.49 g, 49.50 mmol) in dioxane (100 mL) was stirred at 80 °C for 2 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in H_2O (30 mL) and stirred at room temperature for another 30 min. The reaction was filtered and the filter cake was concentrated in vacuo to give the title compound (17 g, crude) as a yellow solid that required no further purification. 1H NMR (400 MHz, $DMSO-d_6$) δ 10.50 - 10.19 (m, 1H), 8.01 - 7.82 (m, 3H), 7.64 - 7.54 (m, 2H), 7.48 - 7.40 (m, 2H), 7.39 - 7.32 (m, 1H), 5.47 - 5.35 (m, 2H), 2.47 (s, 3H). MS: m/z 355.9 ($M+H^+$).

15

Step 2 – Synthesis of 3-(benzyloxy)-5-bromo-2-(difluoromethyl)-7-methylquinoline:

To a solution of 3-benzyloxy-5-bromo-7-methyl-quinoline-2-carbaldehyde (10 g, 28.07 mmol) in DCM (100 mL) was added DAST (13.58 g, 84.22 mmol) at 0 °C. After the addition, the reaction mixture was stirred at 0 °C for 1 h. The mixture was quenched with saturated $NaHCO_3$ (80 mL), extracted with EtOAc (200 mL x 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (4.16 g, 39%) as a yellow solid. 1H NMR (400 MHz, $DMSO-d_6$) δ 7.95 (s, 1H), 7.92 - 7.87 (m, 2H), 7.59 - 7.53 (m, 2H), 7.46 - 7.40 (m, 2H), 7.38 - 7.34 (m, 1H), 7.33 - 7.11 (m, 1H), 5.45 (s, 2H), 2.49 - 2.43 (m, 3H). MS: m/z 378.0 ($M+H^+$).

20

Step 3 – Synthesis of 1-(3-(benzyloxy)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethan-1-one:

A mixture of 3-benzyloxy-5-bromo-2-(difluoromethyl)-7-methyl-quinoline (1 g, 2.64 mmol), tributyl(1-ethoxyvinyl)stannane (1.91 g, 5.29 mmol) and Pd(dppf)Cl₂ (193 mg, 264 μmol) in dioxane (10 mL) was stirred at 90 °C for 16 h under N₂ atmosphere. After cooling to room temperature, HCl (2 mL, 1M in water) was added to reaction mixture. The reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with 10% KF solution (30 mL). The mixture was filtered and the filtrate was extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (671 mg, 74%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.82 (s, 1H), 8.25 (s, 1H), 8.07 (s, 1H), 7.60 - 7.53 (m, 2H), 7.47 - 7.40 (m, 2H), 7.40 - 7.07 (m, 2H), 5.34 (s, 2H), 2.75 (s, 3H), 2.57 (s, 3H). MS: m/z 342.1 (M+H⁺).

Step 4 – Synthesis of 1-(3-(benzyloxy)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethan-1-amine:

A mixture of 1-(3-(benzyloxy)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethan-1-one (3.5 g, 10.25 mmol), NH₄OAc (7.90 g, 102.53 mmol) and HOAc (615 mg, 10.25 mmol) in MeOH (50 mL) was stirred at room temperature for 30 min. Then NaBH₃CN (1.93 g, 30.76 mmol) was added to the reaction mixture. After the addition, the reaction mixture was stirred at 60 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with DCM (100 mL). The mixture was washed with saturated NaHCO₃ solution (20 mL x 3), brine (20 mL), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated to give the title compound (3.51 g, crude) as a brown solid that required no further purification. MS: m/z 343.2 (M+H⁺).

Step 5 – Synthesis of *tert*-butyl (1-(3-(benzyloxy)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethyl)carbamate:

A mixture of 1-(3-(benzyloxy)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethan-1-amine (3.51 g, 10.25 mmol), TEA (5.19 g, 51.26 mmol) and Boc₂O (3.36 g, 15.38 mmol) in DCM (30 mL) was stirred at room temperature for 1 h. The mixture was diluted with H₂O (20 mL), extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated in vacuo. The crude residue

was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (1.2 g, 26%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.16 (s, 1H), 7.73 (s, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.59 - 7.53 (m, 2H), 7.50 - 7.47 (m, 1H), 7.46 - 7.47 (m, 2H), 7.39 - 7.33 (m, 1H), 7.32 - 7.08 (m, 1H), 5.48 - 5.31 (m, 3H), 2.49 (s, 3H), 1.43 - 1.37 (m, 12H). MS: *m/z* 443.2 (M+H⁺).

Step 6 – Synthesis of *tert*-butyl (1-(2-(difluoromethyl)-3-hydroxy-7-methylquinolin-5-yl)ethyl)carbamate:

To a solution of *tert*-butyl (1-(3-(benzyloxy)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethyl)carbamate (500 mg, 1.13 mmol) in MeOH (20 mL) was added wet Pd on carbon (500 mg, 10% Pd, 50% wet with water). The reaction was stirred at room temperature for 1 h under H₂ atmosphere (15 psi). The reaction was filtered through diatomaceous earth and the filtrate was concentrated to afford the title compound (410 mg, 92%) as white solid that required no further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.80 (s, 1H), 7.82 (s, 1H), 7.66 (s, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.44 (s, 1H), 7.32 - 6.97 (m, 1H), 5.25 - 5.10 (m, 1H), 2.45 (s, 3H), 1.43 - 1.36 (m, 12H). MS: *m/z* 353.2 (M+H⁺).

Step 7 – Synthesis of 5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(difluoromethyl)-7-methylquinolin-3-yl trifluoromethanesulfonate:

To a solution of *tert*-butyl (1-(2-(difluoromethyl)-3-hydroxy-7-methylquinolin-5-yl)ethyl)carbamate (410 mg, 1.16 mmol) in DCM (5 mL) was added pyridine (276.11 mg, 3.49 mmol) and Tf₂O (492 mg, 1.75 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with DCM (30 mL) and washed with 0.5M HCl (10 mL), and then the organic layer was washed with NaHCO₃ (10 mL x 2), dried over anhydrous Na₂SO₄ and filtered and concentrated in vacuo to give the title compound (260 mg, 46%) as a white solid that required no further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.81 (s, 1H), 7.92 (s, 1H), 7.69 (s, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.42 - 7.13 (m, 1H), 5.43 - 5.25 (m, 1H), 2.57 (s, 3H), 1.47 (d, *J* = 6.4 Hz, 3H), 1.36 (s, 9H). MS: *m/z* 485.2 (M+H⁺).

Step 8 – Synthesis of *tert*-butyl (1-(2-(difluoromethyl)-3-(5,6-dihydro-2H-pyran-3-yl)-7-methylquinolin-5-yl)ethyl)carbamate:

A mixture of 5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(difluoromethyl)-7-methylquinolin-3-yl trifluoromethanesulfonate (590 mg, 1.22 mmol), 2-(5,6-dihydro-2H-pyran-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (255 mg, 1.22 mmol), Pd(PPh₃)₄ (140.74 mg, 121

μmol) and K₂CO₃ (504.97 mg, 3.65 mmol) in dioxane (5 mL) and H₂O (0.5 mL). The mixture was stirred at 100 °C for 2 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (350 mg, 68%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.51 (s, 1H), 7.79 (s, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.53 (s, 1H), 7.25 - 7.00 (m, 1H), 5.96 - 5.83 (m, 1H), 5.47 - 5.32 (m, 1H), 4.37 - 4.25 (m, 2H), 3.90 - 3.75 (m, 2H), 2.52 (s, 3H), 2.31 - 2.22 (m, 2H), 1.44 (d, *J* = 6.4 Hz, 3H), 1.36 (s, 9H). MS: *m/z* 418.6 (M+H⁺).

Step 9 – Synthesis of *tert*-butyl (1-(2-(difluoromethyl)-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)carbamate:

To a solution of *tert*-butyl (1-(2-(difluoromethyl)-3-(5,6-dihydro-2H-pyran-3-yl)-7-methylquinolin-5-yl)ethyl)carbamate (100 mg, 238 μmol) in MeOH (10 mL) was added wet Pd on carbon (100 mg, 10% Pd, 50% wet with water). The reaction was stirred at room temperature for 1 h under H₂ atmosphere (15 psi). The reaction was filtered through diatomaceous earth and the filtrate was concentrated to afford the title compound (60 mg, 60%) as white solid that required no further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.65 (d, *J* = 7.6 Hz, 1H), 7.75 (s, 1H), 7.51 (s, 2H), 7.40 - 6.99 (m, 1H), 5.47 (s, 1H), 4.02 - 3.89 (m, 1H), 3.88 - 3.77 (m, 1H), 3.65 - 3.45 (m, 2H), 3.42 - 3.36 (m, 1H), 2.08 - 1.89 (m, 2H), 1.72 (s, 2H), 1.47 (d, *J* = 6.4 Hz, 3H), 1.39 (s, 9H). MS: *m/z* 421.2 (M+H⁺).

Step 10 – Synthesis of 1-(2-(difluoromethyl)-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethan-1-amine:

To a solution of *tert*-butyl (1-(2-(difluoromethyl)-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)carbamate (60 mg, 142 μmol) in HCl (3 mL, 2M in EtOAc) was stirred at room temperature for 1 h. The mixture was concentrated to give the title compound (70 mg, crude) as a white solid that required no further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.77 - 8.70 (m, 2H), 8.69 - 8.63 (m, 1H), 7.93 - 7.82 (m, 2H), 7.40 - 7.07 (m, 1H), 5.55 - 5.32 (m, 1H), 3.62 - 3.47 (m, 3H), 3.45 - 3.29 (m, 2H), 2.55 (s, 3H), 2.19 - 2.03 (m, 1H), 1.97 - 1.92 (m, 1H), 1.78 - 1.69 (m, 2H), 1.63 (d, *J* = 6.8 Hz, 3H). MS: *m/z* 321.1 (M+H⁺).

Step 11 – Synthesis of *tert*-butyl 2-((1-(2-(difluoromethyl)-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate:

A mixture of 1-(2-(difluoromethyl)-7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethan-1-amine (70 mg, crude), *tert*-butyl 2-iodobenzoate (89 mg, 294 μ mol), Pd₂(dba)₃ (17 mg, 19 μ mol), Xantphos (22 mg, 39 μ mol) and Cs₂CO₃ (191 mg, 588 μ mol) in dioxane (3 mL). The reaction mixture was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (70 mg, 71%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.70 (s, 1H), 8.23 - 8.11 (m, 1H), 7.84 - 7.74 (m, 2H), 7.57 - 7.48 (m, 1H), 7.37 - 7.01 (m, 2H), 6.64 - 6.49 (m, 2H), 5.66 - 5.48 (m, 1H), 3.97 - 3.87 (m, 1H), 3.85 - 3.76 (m, 1H), 3.58 - 3.40 (m, 2H), 2.46 (s, 3H), 1.97 - 1.86 (m, 2H), 1.73 - 1.66 (m, 2H), 1.63 (d, *J* = 6.4 Hz, 3H), 1.57 - 1.53 (m, 9H). MS: *m/z* 497.1 (M+H⁺).

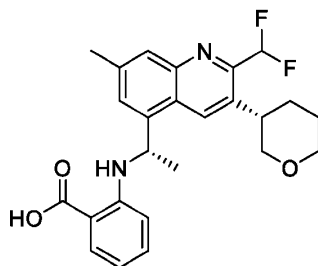
Step 12 – Synthesis of *tert*-butyl 2-(((*R*)-1-(2-(difluoromethyl)-7-methyl-3-((*R*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate & *tert*-butyl 2-(((*R*)-1-(2-(difluoromethyl)-7-methyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate & *tert*-butyl 2-(((*S*)-1-(2-(difluoromethyl)-7-methyl-3-((*R*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate & *tert*-butyl 2-(((*S*)-1-(2-(difluoromethyl)-7-methyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate:

tert-butyl 2-(((*R*)-1-(2-(difluoromethyl)-7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate (118 mg, 237 μ mol) was separated by using chiral SFC (DAICEL CHIRALPAK OJ(250mm*30mm,10 μ m); Supercritical CO₂ / EtOH + 0.1% NH₃•H₂O = 15/85; 80 mL/min) to afford *tert*-butyl 2-(((*R*)-1-(2-(difluoromethyl)-7-methyl-3-((*R*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate (35 mg, first peak), *tert*-butyl 2-(((*R*)-1-(2-(difluoromethyl)-7-methyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate (16 mg, second peak), *tert*-butyl 2-(((*S*)-1-(2-(difluoromethyl)-7-methyl-3-((*R*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate (20 mg, third peak) and *tert*-butyl 2-(((*S*)-1-(2-(difluoromethyl)-7-methyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate (19 mg, fourth peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. MS: *m/z* 497.3 (M+H⁺).

Step 13 – Synthesis of 2-(((*R*)-1-(2-(difluoromethyl)-7-methyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid:

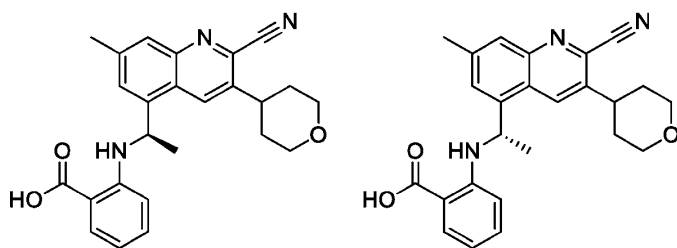
To a mixture of *tert*-butyl 2-(((*R*)-1-(2-(difluoromethyl)-7-methyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate (16 mg, 32 μ mol) in DCM (2 mL) was added TFA (1.54 g, 13.46 mmol). The reaction mixture was stirred at 40 °C for 2 h. After cooling to room temperature, the reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 55% - 85% / 0.225% formic acid in water) to give the title compound (10.47 mg, 64%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.76 (s, 1H), 8.73 (s, 1H), 8.45 (s, 1H), 7.87 - 7.78 (m, 1H), 7.75 (s, 1H), 7.56 - 7.49 (m, 1H), 7.36 - 7.04 (m, 2H), 6.63 - 6.44 (m, 2H), 5.69 - 5.43 (m, 1H), 3.97 - 3.87 (m, 1H), 3.86 - 3.78 (m, 1H), 3.57 - 3.43 (m, 3H), 2.46 (s, 3H), 1.98 - 1.87 (m, 2H), 1.72 - 1.65 (m, 2H), 1.62 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 441.2 (M+H⁺).

Example 24: 2-(((*S*)-1-(2-(difluoromethyl)-7-methyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (Compound 40)



To a mixture of *tert*-butyl 2-(((*S*)-1-(2-(difluoromethyl)-7-methyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate (19 mg, 38 μ mol) in DCM (2 mL) was added TFA (1.54 g, 13.46 mmol). The reaction mixture was stirred at 40 °C for 2 h. After cooling to room temperature, the reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 65% - 95% / 0.225% formic acid in water) to give the title compound (4.57 mg, 27%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.77 (m, 1H), 8.73 (s, 1H), 8.55 - 8.37 (m, 1H), 7.87 - 7.79 (m, 1H), 7.75 (s, 1H), 7.51 (s, 1H), 7.35 - 7.07 (m, 2H), 6.64 - 6.33 (m, 2H), 5.67 - 5.47 (m, 1H), 3.99 - 3.87 (m, 1H), 3.86 - 3.74 (m, 1H), 3.56 - 3.40 (m, 3H), 2.46 (s, 3H), 1.99 - 1.89 (m, 2H), 1.70 (s, 2H), 1.62 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 441.1 (M+H⁺).

Example 25: (*R*)-2-((1-(2-cyano-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoic acid & (*S*)-2-((1-(2-cyano-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoic acid (Compound 41 and Compound 42)



Step 1 - Synthesis of 5-bromo-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline 1-oxide:

To a solution of 5-bromo-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline (4 g, 13.06 mmol) in DCM (30 mL) was added *m*-CPBA (4.51 g, 19.60 mmol, 75% purity) at 0°C and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched by sat NaHCO₃ (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 100% EtOAc in petroleum ether) to give the title compound (3.8 g, 90%) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.60 - 8.46 (m, 2H), 7.89 (s, 1H), 7.78 (d, *J* = 1.2 Hz, 1H), 4.24 - 4.08 (m, 2H), 3.65 - 3.53 (m, 2H), 3.01 - 2.84 (m, 1H), 2.58 (s, 3H), 1.96 - 1.84 (m, 4H). MS: *m/z* 323.9 (M+H⁺).

Step 2 - Synthesis of 5-bromo-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline-2-carbonitrile:

A mixture of 5-bromo-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline 1-oxide (3.8 g, 11.79 mmol), 1-ethoxyphosphonyloxyethane (3.04 mL, 23.59 mmol), TEA (3.28 mL, 23.59 mmol), CCl₄ (2.27 mL, 23.59 mmol) and trimethylsilylformonitrile (2.15 mL, 17.22 mmol) in DCM (40 mL) was degassed and purged with N₂ atmosphere for 3 times, and then the mixture was stirred at room temperature for 16 h under N₂ atmosphere. The reaction mixture was diluted with DCM (50 mL) and washed with NaHCO₃ (50 mL x 2), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 1% MeOH in DCM) to give the title compound (3.54 g, 90%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.45 (s, 1H), 7.89 (s, 1H), 7.83 (s, 1H), 4.24 - 4.15 (m, 2H), 3.76 - 3.65 (m, 2H), 3.53 - 3.38 (m, 1H), 2.60 (s, 3H), 2.04 - 1.94 (m, 4H). MS: *m/z* 331.0 (M+H⁺).

Step 3 - Synthesis of 5-acetyl-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline-2-carbonitrile:

A mixture of 5-bromo-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinoline-2-carbonitrile (3.54 g, 10.69 mmol), tributyl(1-ethoxyvinyl)stannane (8.58 g, 23.76 mmol) and Pd(dppf)Cl₂ (782 mg, 1.07 mmol) in dioxane (60 mL) was degassed and purged with N₂ atmosphere for 3 times. The reaction mixture was stirred at 90 °C for 16 h under N₂ atmosphere. After cooling to room temperature, HCl (3 mL, 1 M) was added. The mixture was stirred at room temperature for 0.5 h. The reaction mixture was added 50 mL 10% KF aqueous solution, stirred at room temperature for 2 h. The mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to give the title compound (2.8 g, 60%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 9.20 (s, 1H), 8.05 - 7.90 (m, 2H), 4.13 - 3.99 (m, 3H), 3.63 - 3.55 (m, 2H), 3.34 - 3.28 (m, 1H), 2.71 (s, 3H), 2.57 (s, 3H), 1.92 - 1.83 (m, 4H). MS: m/z 295.1 (M+H⁺).

Step 4 - Synthesis of (*R,E*)-*N*-(1-(2-cyano-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide:

To a solution of 5-acetyl-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinoline-2-carbonitrile (2.8 g, 9.51 mmol) in THF (60 mL) was added tetraisopropoxytitanium (16.84 mL, 57.08 mmol) and (*R*)-2-methylpropane-2-sulfinamide (11.53 g, 95.13 mmol). The mixture was stirred at 75 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was quenched by addition water (200 mL) at room temperature, and then extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (3.5 g, 81%) as yellow oil. MS: m/z 398.1 (M+H⁺).

Step 5 - Synthesis of (*R*)-*N*-(1-(2-cyano-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide:

To a solution of (*R,E*)-*N*-(1-(2-cyano-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide (3.5 g, 8.80 mmol) in THF (30 mL) was added NaBH₄ (1.03 g, 27.34 mmol) at room temperature under N₂ atmosphere. The mixture was stirred at room temperature for 1 h under N₂ atmosphere. The reaction was quenched with sat.NH₄Cl (20 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (40 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified

by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (2.5 g, 71%) as a yellow solid. MS: m/z 400.1 (M+H⁺).

Step 6 - Synthesis of 5-(1-aminoethyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline-2-carbonitrile:

5 To a solution of (*R*)-*N*-(1-(2-cyano-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinolin-5-yl)ethyl)-2-methylpropane-2-sulfonamide (2.50 g, 6.26 mmol) in MeCN (38 mL) was added HCl (1.56 mL, 12 M) at room temperature. The mixture was stirred at room temperature for 1 h. The reaction was quenched with sat.NaHCO₃ (20 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with brine(40 mL), dried over Na₂SO₄, filtered and
10 concentrated in vacuo to give the title compound (1.2 g, 65%) as yellow solid that required no further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.71 (s, 1H), 7.80 (s, 1H), 7.74 (s, 1H), 4.88 - 4.83 (m, 1H), 4.11 - 4.00 (m, 2H), 3.60 - 3.50 (m, 2H), 3.31 - 3.20 (m, 1H), 2.51 (s, 3H), 2.02 - 1.79 (m, 4H), 1.43 - 1.32 (m, 3H). MS: m/z 296.2 (M+H⁺).

Step 7 - Synthesis of *tert*-butyl 2-((1-(2-cyano-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoate:

A mixture of (*R*)-5-(1-aminoethyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline-2-carbonitrile (150 mg, 508 μmol), *tert*-butyl 2-iodobenzoate (231 mg, 762 μmol), Cs₂CO₃ (496 mg, 1.52 mmol), Pd₂(dba)₃ (46.50 mg, 50.78 μmol) and Xantphos (29.38 mg, 50.78 μmol) in dioxane (8 mL), the reaction mixture was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to
20 room temperature, the reaction was filtered and the filtrate was concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% EtOAc in petroleum ether) to give the title compound (200 mg, 84%) as white solid. MS: m/z 472.1 (M+H⁺).

Step 8 – Synthesis of 2-((1-(2-cyano-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoic acid:

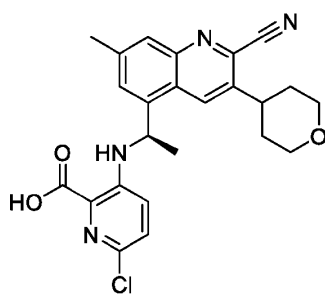
25 To a mixture of *tert*-butyl 2-((1-(2-cyano-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoate (200 mg, 424 μmol) in DCM (12 mL) was added TFA (1mL). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated and the crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% Ethyl acetate in Petroleum ether) to give the title compound (150 mg, 85%) as yellow solid. ¹H NMR
30 (400 MHz, DMSO-*d*₆) δ 12.80 (s, 1H), 8.76 (s, 1H), 8.45 (m, 1H), 7.85 - 7.75 (m, 2H), 7.58 (d, *J* = 1.2 Hz, 1H), 7.26 - 7.12 (m, 1H), 6.58 - 6.43 (m, 2H), 5.67 - 5.58 (m, 1H), 4.09 - 3.99 (m, 3H),

3.60 - 3.49 (m, 2H), 3.30 - 3.24 (m, 1H), 2.48 - 2.46 (m, 3H), 2.05 - 1.90 (m, 3H), 1.87 - 1.79 (m, 2H), 1.61 (d, $J = 6.4$ Hz, 3H). MS: m/z 416.2 ($M+H^+$).

Step 9 - Synthesis of (*R*)-2-((1-(2-cyano-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoic acid & (*S*)-2-((1-(2-cyano-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoic acid:

2-((1-(2-cyano-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoic acid (88 mg, 212 μ mol) was separated by using chiral SFC (DAICEL CHIRALCEL OD (250mm*30mm,10 μ m); Supercritical CO₂ / EtOH+0.1% NH₃•H₂O = 45/55; 80 mL/min) to afford (*R*)-2-((1-(2-cyano-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoic acid (27.3 mg, first peak) and (*S*)-2-((1-(2-cyano-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoic acid (25.11 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. First peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.82 (s, 1H), 8.76 (s, 1H), 8.45 (d, $J = 5.2$ Hz, 1H), 7.87 - 7.77 (m, 2H), 7.58 (d, $J = 1.2$ Hz, 1H), 7.25 - 7.14 (m, 1H), 6.56 - 6.52 (m, 1H), 6.50 (d, $J = 8.4$ Hz, 1H), 5.68 - 5.58 (m, 1H), 4.09 - 4.00 (m, 2H), 3.60 - 3.50 (m, 2H), 3.30 - 3.23 (m, 1H), 2.48 (s, 3H), 2.07 - 1.90 (m, 2H), 1.87 - 1.79 (m, 2H), 1.61 (d, $J = 6.4$ Hz, 3H). MS: m/z 416.2 ($M+H^+$). Second peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.79 (s, 1H), 8.76 (s, 1H), 8.46 (d, $J = 5.2$ Hz, 1H), 7.86 - 7.76 (m, 2H), 7.58 (d, $J = 1.2$ Hz, 1H), 7.24 - 7.13 (m, 1H), 6.58 - 6.51 (m, 1H), 6.50 (d, $J = 8.4$ Hz, 1H), 5.67 - 5.60 (m, 1H), 4.09 - 3.99 (m, 2H), 3.59 - 3.50 (m, 2H), 3.29 - 3.24 (m, 1H), 2.48 (s, 3H), 2.07 - 1.90 (m, 2H), 1.87 - 1.79 (m, 2H), 1.61 (d, $J = 6.4$ Hz, 3H). MS: m/z 416.2 ($M+H^+$).

Example 26: (*R*)-6-chloro-3-((1-(2-cyano-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)picolinic acid (Compound 43)



Step 1 - Synthesis of *tert*-butyl 6-chloro-3-((1-(2-cyano-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)picolinate:

A mixture of 5-(1-aminoethyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline-2-carbonitrile (200 mg, 677 μmol), *tert*-butyl 3-bromo-6-chloro-pyridine-2-carboxylate (297 mg, 1.02 mmol), Cs_2CO_3 (662 mg, 2.03 mmol), $\text{Pd}_2(\text{dba})_3$ (39.18 mg, 67.71 μmol) and Xantphos (39.18 mg, 67.71 μmol) in dioxane (8 mL), the reaction mixture was stirred at 100 °C for 16 h under N_2 atmosphere. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% EtOAc in petroleum ether) to give the title compound (180 mg, 31%) as yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.72 (s, 1H), 8.19 (d, $J = 6.4$ Hz, 1H), 7.81 (s, 1H), 7.56 (s, 1H), 7.32 (d, $J = 8.8$ Hz, 1H), 7.02 (d, $J = 8.8$ Hz, 1H), 5.75 - 5.63 (m, 1H), 4.09 - 3.99 (m, 2H), 3.60 - 3.50 (m, 2H), 3.30 - 3.23 (m, 1H), 2.50 (s, 3H), 2.06 - 1.90 (m, 2H), 1.88 - 1.80 (m, 2H), 1.66 - 1.58 (m, 12H). MS: m/z 529.3 ($\text{M}+\text{H}^+$).

Step 2 - Synthesis of *tert*-butyl (*R*)-6-chloro-3-((1-(2-cyano-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinolin-5-yl)ethyl)amino)picolinate & *tert*-butyl (*S*)-6-chloro-3-((1-(2-cyano-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinolin-5-yl)ethyl)amino)picolinate:

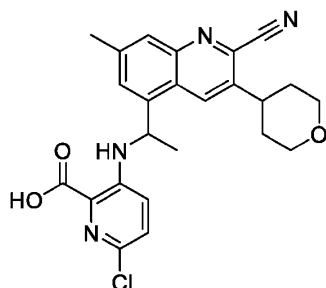
tert-butyl 6-chloro-3-((1-(2-cyano-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinolin-5-yl)ethyl)amino)picolinate (130 mg, 256 μmol) was separated by using chiral SFC (DAICEL CHIRALCEL OD (250mm*30mm,10 μm); Supercritical CO_2 / EtOH+0.1% $\text{NH}_3\cdot\text{H}_2\text{O} = 70/30$; 150 mL/min) to afford *tert*-butyl (*R*)-6-chloro-3-((1-(2-cyano-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinolin-5-yl)ethyl)amino)picolinate (45 mg, first peak) and *tert*-butyl (*S*)-6-chloro-3-((1-(2-cyano-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinolin-5-yl)ethyl)amino) picolinate (38 mg, second batch) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. MS: m/z 529.1 ($\text{M}+\text{H}^+$).

Step 3 – Synthesis of (*R*)-6-chloro-3-((1-(2-cyano-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinolin-5-yl)ethyl)amino)picolinic acid:

To a mixture of *tert*-butyl (*R*)-6-chloro-3-((1-(2-cyano-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinolin-5-yl)ethyl)amino)picolinate (45 mg, 88.75 μmol) in DCM (12 mL) was added TFA (945 μL , 12.72 mmol). The reaction mixture was stirred at room temperature for 16 h. The residue was purified by reverse phase chromatography (acetonitrile 57% - 87% / 0.225% formic acid in water) to give the title compound (13.72 mg, 34%) as white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.17 (s, 1H), 8.72 (s, 1H), 8.43 (d, $J = 6.4$ Hz, 1H), 7.81 (s, 1H), 7.55 (s, 1H), 7.34 (d, $J = 8.8$ Hz, 1H), 7.01 (d, $J = 8.8$ Hz, 1H), 5.73 - 5.68 (m, 1H), 4.10 - 3.98 (m, 2H), 3.57 - 3.53 (m,

2H), 3.30 - 3.24 (m, 1H), 2.49 (s, 3H), 2.11 - 1.91 (m, 2H), 1.87 - 1.80 (m, 2H), 1.62 (d, $J = 6.8$ Hz, 3H). MS: m/z 451.1 ($M+H^+$).

Example 27: 6-chloro-3-((1-(2-cyano-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinolin-5-yl)ethyl)amino)picolinic acid (Compound 44)

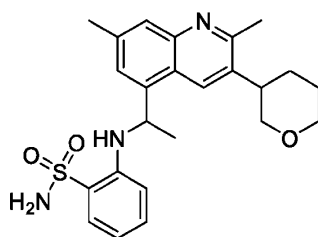


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To a mixture of tert-butyl 6-chloro-3-((1-(2-cyano-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinolin-5-yl)ethyl)amino)picolinate (130 mg, 256 μ mol) in DCM (12 mL) was added TFA (945 μ L, 12.72 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated and the crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% MeOH in DCM) to give the title compound (60 mg, 51%) as yellow solid. 1H NMR (400 MHz, $DMSO-d_6$) δ 13.16 (s, 1H), 8.72 (s, 1H), 8.44 (d, $J = 6.4$ Hz 1H), 7.81 (s, 1H), 7.55 (s, 1H), 7.33 (d, $J = 8.8$ Hz, 1H), 7.01 (d, $J = 8.8$ Hz, 1H), 5.78 - 5.63 (m, 1H), 4.13 - 3.98 (m, 2H), 3.62 - 3.50 (m, 2H), 3.28 - 3.22 (m, 1H), 2.47 (s, 3H), 2.10 - 1.91 (m, 2H), 1.88 - 1.79 (m, 2H), 1.62 (d, $J = 6.4$ Hz, 3H). MS: m/z 451.2 ($M+H^+$).

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Example 28: 2-((1-(2,7-dimethyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide (Compound 45)



Step 1 – Synthesis of 5-bromo-2,7-dimethylquinolin-3-ol:

To a solution of 2-amino-6-bromo-4-methylbenzaldehyde (6.0 g, 28.0 mmol) in *n*-BuOH (60 mL) and H_2O (6 mL) was added NaOH (2.2 g, 56.1 mmol) and 1-hydroxypropan-2-one (2.5

20

g, 33.6 mmol). The mixture was stirred at 110 °C for 1 h. After cooling to room temperature. The mixture was separated between EtOAc (100 mL) and H₂O (30 mL). The organic layer was washed with brine (30 mL), dried over anhydrous Na₂SO₄. The filtrate was concentrated to give the title compound (7.0 g, crude) as a yellow solid that required no further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.58 (s, 1H), 7.64 (s, 2H), 7.59 (s, 1H), 2.53 (s, 3H), 2.43 (s, 3H). MS: m/z 251.8 (M+H⁺).

Step 2 – Synthesis of 5-(1-ethoxyvinyl)-2,7-dimethylquinolin-3-ol:

A mixture of 5-bromo-2,7-dimethylquinolin-3-ol (5.5 g, 22.7 mmol), tributyl(1-ethoxyvinyl)stannane (9.8 g, 27.1 mmol) and Pd(dppf)Cl₂ (1.6 g, 2.2 mmol) in dioxane (50 mL) was degassed with N₂ for 3 times. The reaction mixture was stirred at 90 °C for 16 h. After cooling to room temperature, the reaction was quenched with 10% KF solution (30 mL). The mixture was filtered and the filtrate was separated between EtOAc (50 mL) and H₂O (30 mL). The organic layer was washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% EtOAc in petroleum ether) to give the title compound (4.50 g, 85%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.15 (s, 1H), 7.69 - 7.55 (m, 2H), 7.26 (d, *J* = 1.2 Hz, 1H), 4.51 (d, *J* = 1.6 Hz, 1H), 4.32 (d, *J* = 1.6 Hz, 1H), 3.96 (q, *J* = 7.2 Hz, 2H), 2.43 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H). MS: m/z 244.1 (M+H⁺).

Step 3 – Synthesis of 5-(1-ethoxyvinyl)-2,7-dimethylquinolin-3-yl trifluoromethanesulfonate:

A mixture of 5-(1-ethoxyvinyl)-2,7-dimethylquinolin-3-ol (5.9 g, 24.1 mmol), pyridine (5.8 g, 72.8 mmol) and trifluoromethanesulfonic anhydride (10.3 g, 36.4 mmol) in DCM (60 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 0 °C for 1 h under N₂ atmosphere. The reaction mixture was filtered and the filtrate concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (8.0 g, 88%) as a yellow solid. MS: m/z 376.0 (M+H⁺).

Step 4 – Synthesis of 5-acetyl-2,7-dimethylquinolin-3-yl trifluoromethanesulfonate:

To a mixture of 5-(1-ethoxyvinyl)-2,7-dimethylquinolin-3-yl trifluoromethanesulfonate (8.0 g, 21.3 mmol) in DCM (80 mL) was added HCl (1 M, 10 mL). The reaction was stirred at room temperature for 1 h. The reaction mixture was quenched with sat. aq. NaHCO₃ and adjusted to pH 7. The mixture was extracted with DCM (100 mL × 3). The combined organics were dried

over Na₂SO₄, filtrated and concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 40% EtOAc in petroleum ether) to give the title compound (5.9 g, 79%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.15 (s, 1H), 8.30 (d, *J* = 1.2 Hz, 1H), 8.07 (s, 1H), 2.76 (s, 3H), 2.70 (s, 3H), 2.61 (s, 3H). MS: *m/z* 348.0. (M+H⁺).

Step 5 – Synthesis of 1-(3-(5,6-dihydro-2*H*-pyran-3-yl)-2,7-dimethylquinolin-5-yl)ethan-1-one:

To a mixture of 5-acetyl-2,7-dimethylquinolin-3-yl trifluoromethanesulfonate (4.1 g, 11.8 mmol), K₂CO₃ (4.9 g, 35.4 mmol) and 2-(5,6-dihydro-2*H*-pyran-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.5 g, 11.8 mmol) in dioxane (50 mL) and water (5 mL) was added Pd(PPh₃)₄ (682 mg, 590 μmol). The reaction mixture was heated to 100 °C and stirred for 2 h under N₂ atmosphere. After cooling to room temperature. The reaction was diluted with water (30 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (20 mL x 2), dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 15% EtOAc in petroleum ether) to give the title compound (3.1 g, 93%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.65 (s, 1H), 8.05 (s, 1H), 7.91 (s, 1H), 5.87 (s, 1H), 4.21 (s, 2H), 3.83 (t, *J* = 5.6 Hz, 2H), 2.71 (s, 3H), 2.62 (s, 3H), 2.55 (s, 3H), 2.31 - 2.26 (m, 2H). MS: *m/z* 282.1. (M+H⁺).

Step 6 – Synthesis of 1-(3-(5,6-dihydro-2*H*-pyran-3-yl)-2,7-dimethylquinolin-5-yl)ethan-1-ol:

To a solution of 1-(3-(5,6-dihydro-2*H*-pyran-3-yl)-2,7-dimethylquinolin-5-yl)ethan-1-one (1.9 g, 6.75 mol) in THF (20 mL) was added NaBH₄ (570 mg, 15.07 mmol) at room temperature for 1 h. The mixture was quenched with aq. sat. NH₄Cl (20 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to give the title compound (1.9, 99%) as colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.15 (s, 1H), 7.73 (s, 1H), 7.48 (s, 1H), 5.89 - 5.86 (m, 1H), 5.59 - 5.53 (m, 1H), 4.32 - 4.28 (m, 2H), 3.96 - 3.93 (m, 2H), 2.71 (s, 3H), 2.54 (s, 3H), 2.42 - 2.32 (m, 2H), 1.67 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 284.0 (M+H⁺).

Step 7 – Synthesis of 1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethan-1-ol:

To a solution of 1-(3-(5,6-dihydro-2*H*-pyran-3-yl)-2,7-dimethylquinolin-5-yl)ethan-1-ol (1.9 g, 6.71 mmol) in MeOH (30 mL) was added Pd(OH)₂ on carbon (2.35 g, 20% Pd, 50% wet with water). The reaction was stirred at room temperature for 1 h under H₂ atmosphere (15 psi). The reaction was filtered through diatomaceous earth and the filtrate was concentrated in vacuo to give the title compound (1 g, crude) as yellow solid that required no further purification. MS: m/z 286.0 (M+H⁺).

Step 8 – Synthesis of 5-(1-bromoethyl)-2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinoline:

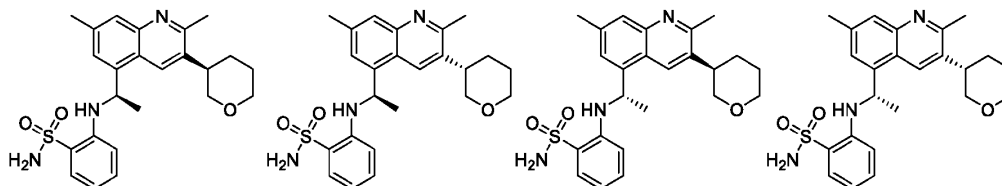
To a solution of 1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethan-1-ol (900 mg, 3.15 mmol) in DCM (30 mL) was added PBr₃ (1.02 g, 3.78 mmol). The mixture was stirred at 0 °C for 2 h. The mixture was quenched with saturated NaHCO₃ (30 mL) and extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (20 mL x 2), dried over Na₂SO₄, filtered and concentrated in vacuo to remove EtOAc and give the title compound (1.0 g, 91% yield) as yellow oil that required no further purification. ¹H NMR (400 MHz, CDCl₃) δ 8.35 - 8.32 (m, 1H), 7.79 (s, 1H), 7.52 (s, 1H), 5.92 - 5.85 (m, 1H), 4.12 - 4.03 (m, 2H), 3.69 - 3.46 (m, 2H), 3.29 - 3.18 (m, 1H), 2.80 (s, 3H), 2.56 (s, 3H), 2.29 - 2.27 (m, 3H), 1.93 - 1.86 (m, 4H). MS: m/z 349.9 (M+H⁺).

Step 9 – Synthesis of 2-(((1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide:

To a solution of 5-(1-bromoethyl)-2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinoline (1.0 g, 2.87 mmol) in dioxane (30 mL) was added 2-aminobenzenesulfonamide (989 mg, 5.74 mmol). The mixture was stirred at 90 °C for 16 h. After cooling to room temperature, the solvent was removed in vacuo to get crude residue. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 100% EtOAc in petroleum ether) to give the title compound (700 mg, 55%) as yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.92 (s, 1H), 7.81 - 7.64 (m, 3H), 7.62 - 7.55 (m, 2H), 7.22 - 7.13 (m, 1H), 6.66 (m, 1H), 6.54 - 6.39 (m, 2H), 5.73 - 5.60 (m, 1H), 3.98 - 3.88 (m, 2H), 3.64 - 3.45 (m, 2H), 3.25 - 3.12 (m, 1H), 2.91 (s, 3H), 2.50 (s, 3H), 2.07 - 1.95 (m, 2H), 1.81 - 1.67 (m, 2H), 1.66 - 1.57 (m, 3H). MS: m/z 440.1 (M+H⁺).

Example 29: 2-(((*R*)-1-(2,7-dimethyl-3-((*R*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide & 2-(((*R*)-1-(2,7-dimethyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide & 2-(((*S*)-1-(2,7-dimethyl-3-((*R*)-

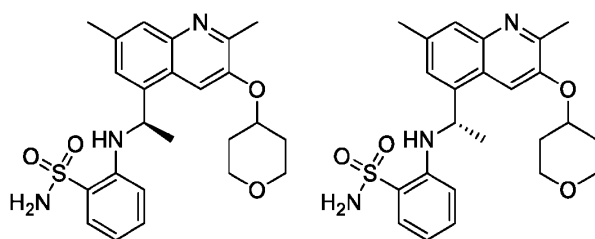
tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide & 2-(((*S*)-1-(2,7-dimethyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide (Compound 46, Compound 47, Compound 48, and Compound 49)



2-(((1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide (150 mg, 341.24 μmol) was separated by using chiral SFC (DAICEL CHIRALCEL OD (250mm*30mm,10 μm); Supercritical CO_2 / EtOH+0.1% $\text{NH}_3\cdot\text{H}_2\text{O}$ = 60/40; 150 mL/min) to afford 2-(((*R*)-1-(2,7-dimethyl-3-((*R*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide (18.69 mg, first peak), 2-(((*R*)-1-(2,7-dimethyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide (21.34 mg, second peak), 2-(((*S*)-1-(2,7-dimethyl-3-((*R*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide (11.82 mg, third peak) and 2-(((*S*)-1-(2,7-dimethyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide (8.7 mg, fourth peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. First peak: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.55 (s, 1H), 7.70 - 7.60 (m, 2H), 7.59 - 7.51 (m, 3H), 7.24 - 6.97 (m, 1H), 6.67 - 6.60 (m, 1H), 6.50 - 6.40 (m, 2H), 5.59 - 5.47 (m, 1H), 3.94 - 3.90 (m, 2H), 3.58 - 3.42 (m, 2H), 3.19 - 3.08 (m, 1H), 2.77 (s, 3H), 2.43 (s, 3H), 2.05 - 1.88 (m, 2H), 1.80 - 1.66 (m, 2H), 1.62 (d, J = 6.4 Hz, 3H). MS: m/z 440.3 ($\text{M}+\text{H}^+$). Second peak: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.37 (s, 1H), 7.69 - 7.64 (m, 1H), 7.60 - 7.40 (m, 4H), 7.18 - 7.14 (m, 1H), 6.64 - 6.60 (m, 1H), 6.45 - 6.40 (m, 2H), 5.53 - 5.48 (m, 1H), 3.92 (m, 2H), 3.48 (m, 2H), 3.17 - 3.04 (m, 1H), 2.70 (s, 3H), 2.39 (s, 3H), 2.02 - 1.90 (m, 2H), 1.78 - 1.67 (m, 2H), 1.60 (d, J = 6.4 Hz, 3H). MS: m/z 440.3 ($\text{M}+\text{H}^+$). Third peak: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.38 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.60 - 7.53 (m, 3H), 7.45 (s, 1H), 7.18 - 7.14 (m, 1H), 6.65 - 6.61 (m, 1H), 6.48 - 6.39 (m, 2H), 5.53 - 5.48 (m, 1H), 3.94 - 3.90 (m, 2H), 3.51 - 3.46 (m, 2H), 3.16 - 3.06 (m, 1H), 2.71 (s, 3H), 2.39 (s, 3H), 2.02 - 1.89 (m, 2H), 1.79 - 1.67 (m, 2H), 1.60 (d, J = 6.4 Hz, 3H). MS: m/z 440.3 ($\text{M}+\text{H}^+$). Fourth peak: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.38 (s, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.60 - 7.51 (m, 3H), 7.49 - 7.43 (m, 1H), 7.22 - 7.12 (m, 1H), 6.64 - 6.60 (m, 1H), 6.49 - 6.40

(m, 2H), 5.49 - 5.43 (m, 1H), 3.97 - 3.86 (m, 2H), 3.54 - 3.43 (m, 2H), 3.16 - 3.04 (m, 1H), 2.70 (s, 3H), 2.40 (s, 3H), 2.04 - 1.87 (m, 2H), 1.80 - 1.66 (m, 2H), 1.60 (d, $J = 6.4$ Hz, 3H). MS: m/z 440.3 ($M+H^+$).

Example 30: (*R*)-2-((1-(2,7-dimethyl-3-((tetrahydro-2*H*-pyran-4-yl)oxy)quinolin-5-yl)ethyl)amino)benzenesulfonamide & (*S*)-2-((1-(2,7-dimethyl-3-((tetrahydro-2*H*-pyran-4-yl)oxy)quinolin-5-yl)ethyl)amino)benzenesulfonamide (Compound 50 and Compound 51)



Step 1 – Synthesis of 5-bromo-2,7-dimethylquinolin-3-ol:

To a solution of 2-amino-6-bromo-4-methyl-benzaldehyde (2 g, 9.34 mmol) and 1-hydroxypropan-2-one (830 mg, 11.21 mmol) in *n*-BuOH (20 mL) and H₂O (2 mL) was added NaOH (747 mg, 18.69 mmol). After the addition, the reaction mixture was stirred at 110 °C for 1 h. After cooling to room temperature, the reaction mixture was quenched with water (20 mL) and adjusted to pH 6 with 3 N HCl. Then filtered and the solid was washed with water (20 mL x 2) to give the title compound (1.8 g, 76%) as a white solid that required no further purification. MS: m/z 251.8 ($M+H^+$).

Step 2 – Synthesis of 5-bromo-2,7-dimethyl-3-((tetrahydro-2*H*-pyran-4-yl)oxy)quinoline:

To a solution of 5-bromo-2,7-dimethyl-quinolin-3-ol (1 g, 3.97 mmol) and 4-bromotetrahydropyran (1.96 g, 11.90 mmol) in DMF (15 mL) was added Cs₂CO₃ (3.88 g, 11.90 mmol) and the reaction vessel was sealed and stirred at 120 °C under microwave for 4h. After cooling to room temperature, the reaction mixture was filtered and the solvent was removed in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (740 mg, 55%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.65 (s, 1H), 7.56 - 7.44 (m, 2H), 4.71 - 4.68 (m, 1H), 3.96 - 3.92 (m, 2H), 3.65 - 3.61 (m, 2H), 2.60 (s, 3H), 2.42 (s, 3H), 2.13 - 2.02 (m, 2H), 1.87 - 1.80 (m, 2H). MS: m/z 335.7 ($M+H^+$).

Step 3 – Synthesis of 1-(2,7-dimethyl-3-((tetrahydro-2H-pyran-4-yl)oxy)quinolin-5-yl)ethan-1-one:

A mixture of 5-bromo-2,7-dimethyl-3-((tetrahydro-2H-pyran-4-yl)oxy)quinoline (740 mg, 2.20 mmol), tributyl(1-ethoxyvinyl)stannane (2.74 g, 7.59 mmol) and Pd(dppf)Cl₂ (80.52 mg, 110 μmol) in dioxane (6 mL) was degassed and purged with N₂ atmosphere for 3 times. The reaction mixture was stirred at 90 °C for 16 h under N₂ atmosphere. After cooling to room temperature, HCl (3 mL, 1 M) was added. The mixture was stirred at room temperature for 0.5 h. The reaction mixture was added 50 mL 10% KF aqueous solution, stirred at room temperature for 2 h. The mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to give the title compound (550 mg, 50%) as yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.66 (s, 1H), 7.97 (s, 1H), 7.90 (s, 1H), 4.81 - 4.73 (m, 1H), 4.04 - 3.98 (m, 2H), 3.73 - 3.68 (m, 2H), 2.77 (s, 3H), 2.67 (s, 3H), 2.58 (s, 3H), 2.19 - 2.12 (m, 2H), 1.98 - 1.86 (m, 2H). MS: m/z 300.1 (M+H⁺).

Step 4 – Synthesis of 1-(2,7-dimethyl-3-((tetrahydro-2H-pyran-4-yl)oxy)quinolin-5-yl)ethan-1-ol:

To a solution of 1-(2,7-dimethyl-3-((tetrahydro-2H-pyran-4-yl)oxy)quinolin-5-yl)ethan-1-one (870 mg, 2.91 mmol) in THF (20 mL) was added NaBH₄ (270 mg, 7.14 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h under N₂ atmosphere. The mixture was quenched with sat. aq. NH₄Cl (20 mL), diluted with water (20 mL), extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to give the title compound (740 mg, 82%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.71 (s, 1H), 7.68 (s, 1H), 7.39 (s, 1H), 5.46 - 5.40 (m, 1H), 4.73 - 4.67 (m, 1H), 4.04 - 3.98 (m, 2H), 3.72 - 3.66 (m, 2H), 2.66 (s, 3H), 2.50 (s, 3H), 2.17 - 2.07 (m, 2H), 1.96 - 1.86 (m, 2H), 1.68 (d, *J* = 6.4 Hz, 3H). MS: m/z 302.0 (M+H⁺).

Step 5 – Synthesis of 5-(1-bromoethyl)-2,7-dimethyl-3-((tetrahydro-2H-pyran-4-yl)oxy)quinoline:

To a solution of 1-(2,7-dimethyl-3-((tetrahydro-2H-pyran-4-yl)oxy)quinolin-5-yl)ethan-1-ol (650 mg, 2.16 mmol) in DCM (20 mL) was added PBr₃ (700 mg, 2.59 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h under N₂ atmosphere. The mixture was

quenched with sat. aq. NaHCO₃ (30 mL), extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give the title compound (700 mg, 89%) as yellow oil that required no further purification. MS: m/z 364.0 (M+H⁺).

5 **Step 6 – Synthesis of 2-((1-(2,7-dimethyl-3-((tetrahydro-2H-pyran-4-yl)oxy)quinolin-5-yl)ethyl)amino)benzenesulfonamide:**

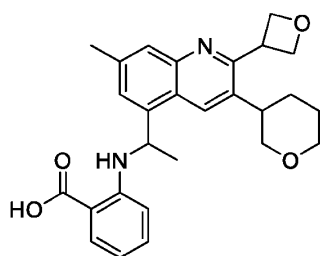
To a solution of 5-(1-bromoethyl)-2,7-dimethyl-3-((tetrahydro-2H-pyran-4-yl)oxy)quinoline (671 mg, 1.84 mmol) in dioxane (30 mL) was added 2-aminobenzenesulfonamide (635 mg, 3.69 mmol). The mixture was stirred at 90 °C for 16 hr. After
10 cooling to room temperature, the solvent was removed in vacuo to get crude residue. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 100% EtOAc in petroleum ether) to give the title compound (220 mg, 26%) as yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.47 (s, 1H), 7.77 - 7.64 (m, 3H), 7.62 - 7.53 (m, 2H), 7.23 - 7.09 (m, 1H), 6.67 (m, 1H), 6.49 (d, *J* = 8.4 Hz, 1H), 6.40 (m, 1H), 5.69 - 5.58 (m, 1H), 5.17 - 5.05 (m, 1H), 3.93 - 3.83 (m, 3H),
15 3.56 - 3.48 (m, 4H), 2.77 (s, 3H), 2.50 - 2.44 (m, 3H), 2.11 - 1.98 (m, 2H), 1.80 - 1.67 (m, 2H), 1.64 - 1.56 (m, 3H). m/z 456.1 (M+H⁺).

Step 7 – Synthesis of (*R*)-2-((1-(2,7-dimethyl-3-((tetrahydro-2H-pyran-4-yl)oxy)quinolin-5-yl)ethyl)amino)benzenesulfonamide and (*S*)-2-((1-(2,7-dimethyl-3-((tetrahydro-2H-pyran-4-yl)oxy)quinolin-5-yl)ethyl)amino)benzenesulfonamide:

20 2-((1-(2,7-dimethyl-3-((tetrahydro-2H-pyran-4-yl)oxy)quinolin-5-yl)ethyl)amino)benzenesulfonamide (100 mg, 219 μmol) was separated by using chiral SFC (DAICEL CHIRALCEL OD (250mm*30mm,10um); Supercritical CO₂ / EtOH+0.1% NH₃•H₂O = 63/35; 120 mL/min) to afford (*R*)-2-((1-(2,7-dimethyl-3-((tetrahydro-2H-pyran-4-yl)oxy)quinolin-5-yl)ethyl)amino)benzenesulfonamide (20.01 mg, first peak) and (*S*)-2-((1-(2,7-dimethyl-3-
25 ((tetrahydro-2H-pyran-4-yl)oxy)quinolin-5-yl)ethyl)amino) benzenesulfonamide (19.50 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. First Peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.86 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.54 (s, 3H), 7.44 (s, 1H), 7.19 - 7.15 (m, 1H), 6.65 - 6.60 (m, 1H), 6.48 (d, *J* = 8.4 Hz, 1H), 6.38 (d, *J* = 5.6 Hz, 1H), 5.50 - 5.40 (m, 1H), 4.95 - 4.86 (m, 1H), 3.91 - 3.80 (m, 2H), 3.58 - 3.45 (m,
30 2H), 2.55 (s, 3H), 2.38 (s, 3H), 2.07 - 1.96 (m, 2H), 1.75 - 1.63 (m, 2H), 1.58 (d, *J* = 6.4 Hz, 3H). MS: m/z 456.1 (M+H⁺). Second Peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.85 (s, 1H), 7.64 (d, *J*

= 7.8 Hz, 1H), 7.54 (s, 3H), 7.44 (s, 1H), 7.19 - 7.14 (m, 1H), 6.66 - 6.61 (m, 1H), 6.48 (d, J = 8.4 Hz, 1H), 6.38 (d, J = 5.6 Hz, 1H), 5.50 - 5.39 (m, 1H), 4.93 - 4.88 (m, 1H), 3.87 - 3.81 (m, 2H), 3.57 - 3.46 (m, 2H), 2.55 (s, 3H), 2.38 (s, 3H), 2.07 - 1.97 (m, 2H), 1.75 - 1.63 (m, 2H), 1.58 (d, J = 6.4 Hz, 3H). MS: m/z 456.1 ($M+H^+$).

5 **Example 31: 2-((1-(7-methyl-2-(oxetan-3-yl)-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (Compound 52)**



Step 1 – Synthesis of 5-chloro-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinoline:

To a solution of 2-amino-6-chloro-4-methylbenzaldehyde (2.8 g, 16.5 mmol) and 2-
 10 (tetrahydro-2H-pyran-3-yl)acetaldehyde (2.15 g, 16.5 mmol) in *n*-BuOH (30 mL) and H₂O (3 mL) was added NaOH (1.32 g, 33 mmol). After the addition, the reaction mixture was stirred at 110 °C for 1 h. After cooling to room temperature, the mixture was quenched with H₂O (40 mL), extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (30 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by
 15 silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (2.5 g, 58%) as yellow oil. MS: m/z 261.9 ($M+H^+$).

Step 2 – Synthesis of 5-chloro-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinoline 1-oxide:

A mixture of 5-chloro-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinoline (2.5 g, 9.55 mmol)
 20 and *m*-CPBA (3.88 g, 19.1 mmol, 85% purity) in DCM (30 mL) was stirred at room temperature for 16 h. The reaction mixture was quenched with sat. aq. Na₂S₂O₃ (20 mL) at room temperature, and then extracted with DCM (30 mL). The organic layer was washed with NaHCO₃ (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 100% EtOAc in petroleum ether) to give the
 25 title compound (2.3 g, 87%) as a yellow solid. MS: m/z 277.9 ($M+H^+$).

Step 3 – Synthesis of 2-bromo-5-chloro-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinoline:

To a solution of 5-chloro-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinoline 1-oxide in DCM (20 mL) was added POBr₃ (2.85 g, 9.94 mmol) and DMF (302 mg, 4.14 mmol) at 0 °C. After the addition, the mixture was stirred at room temperature for 1 h. The mixture was poured into saturated NaHCO₃ (30 mL), extracted with DCM (30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 5% EtOAc in petroleum ether) to give the title compound (1.1 g, 39%) as a gray solid. MS: m/z 341.9 (M+H⁺).

Step 4 – Synthesis of 5-chloro-7-methyl-2-(oxetan-3-yl)-3-(tetrahydro-2H-pyran-3-yl)quinoline:

A mixture of oxetan-3-ol (190 mg, 2.57 mmol) in *t*-BuOMe (10 mL) was added NHC-1 (928 mg, 2.35 mmol), then a solution of pyridine (186 mg, 2.35 mmol) in *t*-BuOMe (2 mL) was added slowly, the mixture was stirred at room temperature for 30 min under N₂ atmosphere, then filtered and the filtrate added to the mixture of 2-bromo-5-chloro-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinoline (500 mg, 1.47 mmol), Ir(ppy)₂(dtbbpy)PF₆ (20 mg, 22 μmol), NiBr₂•dtbbpy (107 mg, 220 μmol), Quinuclidine (286 mg, 2.57 mmol) in DMA (12 mL). The reaction mixture was stirred at room temperature for 16 h under blue LEDs (hν = 455nm). The reaction was diluted with water (30 mL), extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (30 mL x 2), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% EtOAc in petroleum ether) to give the title compound (130 mg, 28%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.27 (s, 1H), 7.82 (s, 1H), 7.63 (s, 1H), 5.07 - 4.93 (m, 4H), 4.93 - 4.85 (m, 1H), 3.92 - 3.86 (m, 1H), 3.84 - 3.78 (m, 1H), 3.56 - 3.48 (m, 1H), 3.47 - 3.41 (m, 1H), 2.82 - 2.70 (m, 1H), 1.97 - 1.89 (m, 1H), 1.87 - 1.75 (m, 1H), 1.74 - 1.66 (m, 2H). MS: m/z 318.0 (M+H⁺).

Step 5 – Synthesis of 7-methyl-5-(1-nitroethyl)-2-(oxetan-3-yl)-3-(tetrahydro-2H-pyran-3-yl)quinoline:

A mixture of 5-chloro-7-methyl-2-(oxetan-3-yl)-3-(tetrahydro-2H-pyran-3-yl)quinoline (220 mg, 692 μmol), nitroethane (156 mg, 2.08 mmol), Pd₂(dba)₃ (63 mg, 69 μmol), di-*tert*-butyl(2'-methyl-[1,1'-biphenyl]-2-yl)phosphane (22 mg, 69 μmol) and Cs₂CO₃ (677 mg, 2.08 mmol) in dioxane (3 mL) was degassed with N₂ for 3 times and stirred at 80 °C for 3 h under N₂

atmosphere. After cooling to room temperature, the mixture was quenched with H₂O (10 mL) and adjusted to pH 7 with 1 N HCl. The mixture was extracted with DCM (20 mL x 2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 4% MeOH in DCM) to give the title compound (150 mg, 61%) as yellow oil.
5 MS: m/z 357.1 (M+H⁺).

Step 6 - Synthesis of 1-(7-methyl-2-(oxetan-3-yl)-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethan-1-amine:

A mixture of 7-methyl-5-(1-nitroethyl)-2-(oxetan-3-yl)-3-(tetrahydro-2H-pyran-3-yl)quinoline (150 mg, 421 μmol), Fe (235 mg, 4.21 mmol) and NH₄Cl (450 mg, 8.42 mmol) in EtOH (3 mL) and H₂O (3 mL) was stirred at 80 °C for 1 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (30 mL) and filtered. The filtrate was washed with saturated NaHCO₃ solution (10 mL x 3), brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give the title compound (137 mg, crude) as a yellow solid that required
15 no further purification. MS: m/z 327.1 (M+H⁺).

Step 7 – Synthesis of methyl 2-((1-(7-methyl-2-(oxetan-3-yl)-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate:

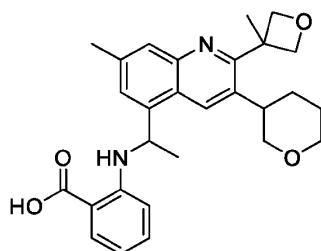
A mixture of 1-(7-methyl-2-(oxetan-3-yl)-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethan-1-amine (170 mg, 521 μmol), methyl 2-iodobenzoate (273 mg, 1.04 mmol), Cs₂CO₃ (509 mg, 1.56 mmol), Pd₂(dba)₃ (48 mg, 52 μmol) and Xantphos (30 mg, 52 μmol) in dioxane (3 mL) was degassed with N₂ for 3 times and stirred at 100 °C for 2 h under N₂ atmosphere. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (119 mg, 50%) as a yellow solid. MS: m/z 461.2 (M+H⁺).
20

Step 8 – Synthesis of 2-((1-(7-methyl-2-(oxetan-3-yl)-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid:

To a solution of methyl 2-((1-(7-methyl-2-(oxetan-3-yl)-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate (20 mg, 43 μmol) in EtOH (1 mL) and H₂O (1 mL) was added KOH (24 mg, 434 μmol). The reaction mixture was stirred at 100 °C for 1 h. After cooling to room temperature, the reaction mixture was adjusted to pH 4 with 1 N HCl. The mixture was extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (10 mL),
30

dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the residue was purified by prep_TLC (10% MeOH in DCM) to give the title compound (4.3 mg, 22%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.47 (s, 1H), 8.43 (d, $J = 2.4$ Hz, 1H), 7.84 - 7.78 (m, 1H), 7.69 (s, 1H), 7.41 - 7.35 (m, 1H), 7.23 - 7.15 (m, 1H), 6.57 - 6.46 (m, 2H), 5.53 - 5.42 (m, 1H), 5.08 - 4.91 (m, 4H), 4.88 - 4.80 (m, 1H), 3.92 - 3.85 (m, 1H), 3.78 - 3.71 (m, 1H), 3.55 - 3.48 (m, 2H), 2.74 - 7.68 (m, 1H), 2.46 - 2.42 (m, 3H), 1.87 - 1.63 (m, 4H), 1.61 (d, $J = 6.4$ Hz, 3H). MS: m/z 447.2 ($\text{M}+\text{H}^+$).

Example 32: 2-((1-(7-methyl-2-(3-methyloxetan-3-yl)-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (Compound 53)



Step 1 – Synthesis of 5-chloro-7-methyl-2-(3-methyloxetan-3-yl)-3-(tetrahydro-2H-pyran-3-yl)quinoline:

A mixture of 5-chloro-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinoline (0.8 g, 3.06 mmol), 3-methyloxetan-3-carboxylic acid (1.06 g, 9.17 mmol), $\text{PhI}(\text{TFA})_2$ (2.63 g, 6.11 mmol), 9-Mes-10-Me-Acr (13 mg, 31 μmol) and acetonitrile (10 mL) was degassed with nitrogen for 5 min. The reaction mixture was stirred at room temperature for 3 days under blue LEDs ($h\nu = 455\text{nm}$). The solvent was evaporated and the residue was diluted with ethyl acetate (100 mL). The mixture washed with sat. aq. NaHCO_3 (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 10% - 50% EtOAc in petroleum ether) to give the title compound (390 mg, 38%) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.31 (s, 1H), 7.73 (s, 1H), 7.62 (d, $J = 1.2$ Hz, 1H), 5.18 - 5.12 (m, 2H), 4.64 - 4.60 (m, 2H), 3.96 - 3.79 (m, 2H), 3.61 - 3.47 (m, 2H), 2.54 (s, 3H), 2.31 - 2.25 (m, 1H), 1.97 - 1.95 (m, 1H), 1.91 - 1.79 (m, 1H), 1.74 (s, 3H), 1.72 - 1.64 (m, 2H). MS: m/z 332.0 ($\text{M}+\text{H}^+$).

Step 2 – Synthesis of 7-methyl-2-(3-methyloxetan-3-yl)-5-(1-nitroethyl)-3-(tetrahydro-2H-pyran-3-yl)quinoline:

A mixture of 5-chloro-7-methyl-2-(3-methyloxetan-3-yl)-3-(tetrahydro-2H-pyran-3-yl)quinoline (480 mg, 1.45 mmol), nitroethane (221 mg, 2.94 mmol), Pd₂(dba)₃ (132 mg, 0.14 mmol), di-*tert*-butyl(2'-methyl-[1,1'-biphenyl]-2-yl)phosphane (132 mg, 0.14 mmol) and Cs₂CO₃ (1.41 g, 4.34 mmol) in dioxane (8 mL) was degassed with N₂ for 3 times and stirred at 60 °C for 3 h under N₂ atmosphere. After cooling to room temperature, the mixture was quenched with H₂O (10 mL) and adjusted to pH 7 with 1 N HCl. The mixture was extracted with DCM (40 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 5% MeOH in DCM) to give the title compound (400 mg, 65%) as a yellow solid. MS: m/z 371.1 (M+H⁺).

Step 3 - Synthesis of 1-(7-methyl-2-(3-methyloxetan-3-yl)-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethan-1-amine:

A mixture of 7-methyl-2-(3-methyloxetan-3-yl)-5-(1-nitroethyl)-3-(tetrahydro-2H-pyran-3-yl)quinoline (390 mg, 1.05 mmol), Fe (589 mg, 10.53 mmol) and NH₄Cl (1.13 g, 21.06 mmol) in EtOH (15 mL) and H₂O (5 mL) was stirred at 80 °C for 1 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (50 mL) and filtered. The filtrate was washed with saturated NaHCO₃ solution (20 mL x 3), brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give the title compound (350 mg, crude) as a brown solid that required no further purification. MS: m/z 341.2 (M+H⁺).

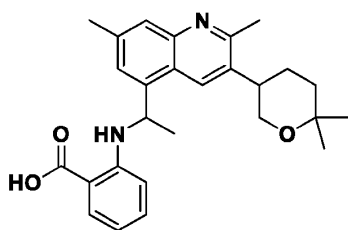
Step 4 - Synthesis of methyl 2-((1-(7-methyl-2-(3-methyloxetan-3-yl)-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate:

A solution of 1-(7-methyl-2-(3-methyloxetan-3-yl)-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethan-1-amine (300 mg, 0.88 mmol) in dioxane (10 mL) was added methyl 2-iodobenzoate (346 mg, 1.32 mmol), Pd₂(dba)₃ (81 mg, 88 μmol), Xantphos (51 mg, 88 μmol) and Cs₂CO₃ (861 mg, 2.64 mmol). The mixture was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to give the title compound (300 mg, 71%) as a yellow solid. MS: m/z 475.2 (M+H⁺).

Step 5 - Synthesis of 2-((1-(7-methyl-2-(3-methyloxetan-3-yl)-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid:

To a solution of methyl 2-((1-(7-methyl-2-(3-methyloxetan-3-yl)-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate (20 mg, 42 μ mol) in THF (1 mL), MeOH (1 mL) and H₂O (0.5 mL) was added LiOH·H₂O (18 mg, 0.42 mmol). The mixture was stirred at 60 °C for 2 h. After cooling to room temperature, the reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 45% - 75% / 0.225% formic acid in water) to give the title compound (4.66 mg, 24%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.75 - 8.39 (m, 2H), 7.83 - 7.80 (m, 1H), 7.59 (s, 1H), 7.36 (s, 1H), 7.24 - 7.14 (m, 1H), 6.57 - 6.44 (m, 2H), 5.53 - 5.50 (m, 1H), 5.17 - 5.10 (m, 2H), 4.65 - 4.55 (m, 2H), 3.91 - 3.88 (m, 1H), 3.78 - 3.75 (m, 1H), 3.51 - 3.45 (m, 2H), 2.41 (s, 3H), 2.29 - 2.19 (m, 1H), 1.97 - 1.78 (m, 2H), 1.73 (s, 3H), 1.70 - 1.62 (m, 2H), 1.58 (d, *J* = 6.8 Hz, 3H). MS: *m/z* 461.2 (M+H⁺).

Example 33: 2-((1-(3-(6,6-dimethyltetrahydro-2H-pyran-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid (Compound 12)



Step 1 – Synthesis of (6,6-dimethyltetrahydro-2H-pyran-3-yl)methanol:

To a solution of methyl 6,6-dimethyltetrahydro-2H-pyran-3-carboxylate (7.9 g, 45.87 mmol) (prepared according to the procedure in WO201629454) in THF (90 mL) was added LiAlH₄ (22.02 mL, 2.5 M in THF) at 0 °C under N₂ atmosphere. Then the mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with Na₂SO₄·10H₂O (4 g) and stirred for 20 min. Then the mixture was dried with anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% ethyl acetate in petroleum ether) to give the title compound (4.5 g, 68%) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 3.87 - 3.77 (m, 1H), 3.58 - 3.55 (m, 2H), 3.49 - 3.45 (m, 1H), 1.80 - 1.68 (m, 2H), 1.58 - 1.53 (m, 1H), 1.53 - 1.42 (m, 2H), 1.23 (s, 3H), 1.20 (s, 3H).

Step 2 – Synthesis of 2-(6,6-dimethyltetrahydro-2H-pyran-3-yl)acetonitrile:

A mixture of (6,6-dimethyltetrahydro-2H-pyran-3-yl)methanol (4.3 g, 29.82 mmol) in THF (85 mL) was added PPh₃ (17.21 g, 65.60 mmol) at 0 °C under N₂ atmosphere. The mixture

was stirred at 0 °C for 15 min before DEAD (11.42 g, 65.60 mmol) was added dropwise. Then the mixture was stirred at 0 °C for 20 min. To the mixture was added 2-hydroxy-2-methylpropanenitrile (3.11 g, 36.54 mmol) dropwise at 0 °C. The mixture was stirred at room temperature for 16 h under N₂ atmosphere. The mixture was quenched with saturated NaHCO₃ (80 mL). The mixture was extracted with ethyl acetate (90 mL x 2). The combined organic layers were washed with brine (90 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% ethyl acetate in petroleum ether) to give the title compound (3.5 g, 77%) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 3.79 - 3.74 (m, 1H), 3.46 - 3.42 (m, 1H), 2.40 - 2.27 (m, 2H), 1.99 - 1.85 (m, 2H), 1.63 - 1.58 (m, 1H), 1.36 - 1.26 (m, 2H), 1.24 (s, 3H), 1.22 (s, 3H).

Step 3 – Synthesis of methyl 2-(6,6-dimethyltetrahydro-2H-pyran-3-yl)acetate:

A solution of acetyl chloride (7.87 g, 100.25 mmol) in MeOH (20 mL) was stirred at 0 °C for 10 min. The reaction mixture was added 2-(6,6-dimethyltetrahydro-2H-pyran-3-yl)acetonitrile (1.28 g, 8.35 mmol). The mixture was stirred at 60 °C for 16 h under N₂ atmosphere. The reaction mixture was concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% ethyl acetate in petroleum ether) to give the title compound (630 mg, 40%) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 3.73 - 3.68 (m, 1H), 3.67 (s, 3H), 3.37 - 3.34 (m, 1H), 2.31 - 2.16 (m, 2H), 2.09 - 1.96 (m, 1H), 1.77 - 1.74 (m, 1H), 1.58 - 1.45 (m, 2H), 1.42 - 1.32 (m, 1H), 1.22 (s, 3H), 1.19 (s, 3H).

Step 4 – Synthesis of 5-chloro-3-(6,6-dimethyltetrahydro-2H-pyran-3-yl)-7-methylquinolin-2(1H)-one:

A mixture of methyl 2-(6,6-dimethyltetrahydro-2H-pyran-3-yl)acetate (630 mg, 3.38 mmol) and 2-amino-6-chloro-4-methylbenzaldehyde (200 mg, 1.18 mmol) in THF (7 mL) was added LiHMDS (3.89 mL, 1 M) dropwise at -78 °C under N₂ atmosphere. The mixture was warmed to room temperature for 3 h under N₂ atmosphere. The mixture was quenched with saturated NH₄Cl solution (20 mL). The mixture was extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% ethyl acetate in petroleum ether) to give the title compound (340 mg, 89%) as yellow oil. MS: m/z 306.1 (M+H⁺).

Step 5 - Synthesis of 5-chloro-3-(6,6-dimethyltetrahydro-2H-pyran-3-yl)-7-methylquinolin-2-yl trifluoromethanesulfonate:

A mixture of 5-chloro-3-(6,6-dimethyltetrahydro-2H-pyran-3-yl)-7-methylquinolin-2(1H)-one (320 mg, 1.05 mmol) in DCM (5 mL) was added pyridine (248.32 mg, 3.14 mmol) at 0 °C for 10 min, and then the mixture was added Tf₂O (442.86 mg, 1.57 mmol) at 0 °C. The mixture was stirred at 0 °C for 0.5 h under N₂ atmosphere. The reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (30 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give the title compound (450 mg, crude) as yellow oil that required no further purification. MS: m/z 438.0 (M+H⁺).

Step 6 - Synthesis of 5-chloro-3-(6,6-dimethyltetrahydro-2H-pyran-3-yl)-2,7-dimethylquinoline:

A mixture of 5-chloro-3-(6,6-dimethyltetrahydro-2H-pyran-3-yl)-7-methylquinolin-2-yl trifluoromethanesulfonate (400 mg, 914 μmol) in dioxane (5 mL) was added methylboronic acid (60 mg, 1.00 mmol), CsF (416 mg, 2.74 mmol), Pd(dppf)Cl₂ (67 mg, 91 μmol). The reaction mixture was stirred at 100 °C for 2 h under N₂ atmosphere. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% ethyl acetate in petroleum ether) to give the title compound (150 mg, 54%) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.30 (s, 1H), 7.69 (s, 1H), 7.57 (d, *J* = 1.2 Hz, 1H), 3.80 - 3.76 (m, 1H), 3.68 - 3.55 (m, 1H), 3.11 - 3.00 (m, 1H), 2.72 (s, 3H), 2.49 (s, 3H), 1.98 - 1.87 (m, 2H), 1.72 - 1.57 (m, 2H), 1.29 (s, 3H), 1.23 (s, 3H). MS: m/z 304.4 (M+H⁺).

Step 7 - Synthesis of 3-(6,6-dimethyltetrahydro-2H-pyran-3-yl)-5-(1-ethoxyvinyl)-2,7-dimethylquinoline:

A mixture of 5-chloro-3-(6,6-dimethyltetrahydro-2H-pyran-3-yl)-2,7-dimethylquinoline (110 mg, 362.05 μmol) in toluene (3 mL) was added CsF (109.99 mg, 724.10 μmol), tributyl(1-ethoxyvinyl)stannane (523 mg, 1.45 mmol) and SPhos Pd G3 (28 mg, 36 μmol) under N₂ atmosphere. The reaction mixture was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the mixture was quenched with 10 mL of 10% KF aqueous solution and stirred for 30 min. The mixture was extracted with EtOAc (15 mL x 2). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered and concentrated

in vacuo to give the title compound (100 mg, crude) as a yellow solid that required no further purification. MS: m/z 340.5 ($M+H^+$).

Step 8 – Synthesis of 1-(3-(6,6-dimethyltetrahydro-2H-pyran-3-yl)-2,7-dimethylquinolin-5-yl)ethan-1-one:

5 A mixture of 3-(6,6-dimethyltetrahydro-2H-pyran-3-yl)-5-(1-ethoxyvinyl)-2,7-dimethylquinoline (100 mg, 294.58 μ mol) in THF (2 mL) was added HCl (2 mL, 1 M). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was extracted with ethyl acetate (10 mL x 2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered. The crude residue was purified by silica gel chromatography
10 (solvent gradient: 0 - 50% ethyl acetate in petroleum ether) to give the title compound (55 mg, 60%) as a yellow solid. 1H NMR (400 MHz, $DMSO-d_6$) δ 8.91 (s, 1H), 8.05 (s, 1H), 7.90 (d, J = 0.8 Hz, 1H), 3.78 - 3.70 (m, 1H), 3.55 - 3.41 (m, 2H), 2.73 (s, 3H), 2.69 (s, 3H), 2.55 (s, 3H), 1.93 - 1.83 (m, 2H), 1.72 - 1.55 (m, 2H), 1.29 (s, 3H), 1.23 (s, 3H). MS: m/z 312.3 ($M+H^+$).

Step 9 – Synthesis of 1-(3-(6,6-dimethyltetrahydro-2H-pyran-3-yl)-2,7-dimethylquinolin-5-yl)ethan-1-amine:

15 A mixture of 1-(3-(6,6-dimethyltetrahydro-2H-pyran-3-yl)-2,7-dimethylquinolin-5-yl)ethan-1-one (55 mg, 176.61 μ mol) in MeOH (5 mL) was added NH_4OAc (204.21 mg, 2.65 mmol) and AcOH (1.06 mg, 17.66 μ mol). The reaction mixture was stirred at room temperature for 1 h. Then $NaBH_3CN$ (33.30 mg, 529.84 μ mol) was added to the reaction mixture. After the
20 addition, the reaction mixture was stirred at 60 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with DCM (30 mL). The mixture was washed with saturated $NaHCO_3$ solution (10 mL x 3), brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give the title compound (60 mg, crude) as a yellow solid that required no further purification. MS: m/z 313.1 ($M+H^+$).

Step 10 – Synthesis of *tert*-butyl 2-((1-(3-(6,6-dimethyltetrahydro-2H-pyran-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate:

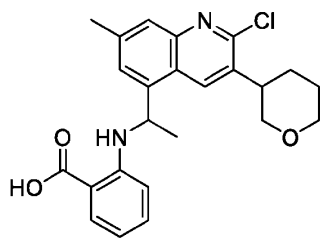
25 A mixture of 1-(3-(6,6-dimethyltetrahydro-2H-pyran-3-yl)-2,7-dimethylquinolin-5-yl)ethan-1-amine (60 mg, 192 μ mol) and *tert*-butyl 2-iodobenzoate (117 mg, 384 μ mol) in dioxane (1 mL) was added Xantphos (22 mg, 38 μ mol), Cs_2CO_3 (188 mg, 576 μ mol) and $Pd_2(dba)_3$ (18
30 mg, 19 μ mol) under N_2 atmosphere. The reaction mixture was stirred at 100 °C for 2 h under N_2 atmosphere. After cooling to room temperature, the reaction was filtered and the filtrate was

concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% ethyl acetate in petroleum ether) to give the title compound (20 mg, 21%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.33 - 8.20 (m, 1H), 7.94 - 7.84 (m, 1H), 7.80 - 7.59 (m, 1H), 7.43 (s, 1H), 7.23 - 6.99 (m, 2H), 6.57 - 6.53 (m, 1H), 6.36 (d, *J* = 8.4 Hz, 1H), 5.31 - 5.13 (m, 1H), 3.89 - 3.86 (m, 1H), 3.76 - 3.57 (m, 1H), 3.17 - 3.04 (m, 1H), 2.80 (s, 3H), 2.47 (s, 3H), 2.01 - 1.88 (m, 2H), 1.78 - 1.73 (m, 2H), 1.63 - 1.58 (m, 9H), 1.33 - 1.27 (m, 6H). MS: *m/z* 489.3 (M+H⁺).

Step 11 – Synthesis of 2-((1-(3-(6,6-dimethyltetrahydro-2H-pyran-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid:

A mixture of *tert*-butyl 2-((1-(3-(6,6-dimethyltetrahydro-2H-pyran-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (20 mg, 41 μmol) in DCM (3 mL) was added TFA (1.54 g, 13.46 mmol, 1 mL). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 25% - 55% / 0.225% formic acid in water) to give the title compound (11.4 mg, 64%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.70 (s, 1H), 8.36 (s, 2H), 7.82 - 7.79 (m, 1H), 7.58 (s, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.23 - 7.20 (m, 1H), 6.60 - 6.49 (m, 2H), 5.58 - 5.43 (m, 1H), 3.70 - 3.67 (m, 1H), 3.62 - 3.47 (m, 1H), 3.03 - 2.94 (m, 1H), 2.68 (s, 3H), 2.44 - 2.40 (m, 3H), 2.06 - 1.85 (m, 1H), 1.80 - 1.77 (m, 1H), 1.67 - 1.55 (m, 5H), 1.25 - 1.20 (m, 6H). MS: *m/z* 433.2 (M+H⁺).

Example 34: 2-((1-(2-chloro-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (Compound 55)



Step 1 - Synthesis of 5-bromo-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinolone:

To a solution of 2-(tetrahydro-2H-pyran-3-yl)acetaldehyde (1.58 g, 12.33 mmol) (prepared according to the procedure in WO2008101867) and 2-amino-6-bromo-4-methylbenzaldehyde (2.2 g, 10.28 mmol) in *n*-BuOH (22 mL) and H₂O (2.2 mL) was added NaOH (822 mg, 20.56 mmol). The reaction mixture was stirred at 110 °C for 1 h. The reaction was adjusted to pH 5 with 1 N

HCl, then was added water (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (20 mL x 2), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 16% EtOAc in petroleum ether) to give the title compound (2.40 g, 75%) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 8.79 (s, 1H), 8.26 (d, *J* = 1.6 Hz, 1H), 7.84 (s, 1H), 7.69 (d, *J* = 1.2 Hz, 1H), 4.12 - 4.04 (m, 2H), 3.59 - 3.51 (m, 2H), 3.17 - 3.07 (m, 1H), 2.55 (s, 3H), 2.21 - 2.14 (m, 1H), 1.98 - 1.83 (m, 3H). MS: *m/z* 305.9 (M+H⁺).

Step 2 - Synthesis of 1-(7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethan-1-one:

A mixture of 5-bromo-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinoline (2.40 g, 7.84 mmol), tributyl(1-ethoxyvinyl)stannane (4.25 g, 11.76 mmol) and Pd(dppf)Cl₂ (574 mg, 784 μmol) in dioxane (30 mL) was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, HCl (10 mL, 1 M) was added. The mixture was stirred at room temperature for 2 h. The reaction mixture was added 15 mL 10% KF aqueous solution, stirred at room temperature for 2 h. The mixture was extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine (30 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 33% EtOAc in dichloromethane) to give the title compound (1.7 g, 80%) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 9.02 (d, *J* = 1.6 Hz, 1H), 8.81 (d, *J* = 2.0 Hz, 1H), 8.05 (s, 1H), 7.91 (s, 1H), 4.09 - 4.03 (m, 2H), 3.57 - 3.49 (m, 2H), 3.13 - 3.05 (m, 1H), 2.77 (s, 3H), 2.62 (s, 3H), 2.18 - 2.12 (m, 1H), 1.96 - 1.75 (m, 3H). MS: *m/z* 270.0 (M+H⁺).

Step 3 - Synthesis of 1-(7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethan-1-amine:

To a solution of 1-(7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethan-1-one (1.70 g, 6.31 mmol), NH₄OAc (7.30 g, 94.68 mmol) and AcOH (361 μL, 6.31 mmol) in MeOH (70 mL) was stirred at room temperature for 1 h. Then the mixture was added NaBH₃CN (1.19 g, 18.94 mmol). The reaction was heated to 60 °C for 16 h. After cooling to room temperature, the reaction mixture was concentrated then diluted with DCM (20 mL). The mixture was washed with saturated NaHCO₃ solution (30 mL x 4), brine (20 mL), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated to give the title compound (1.70 g, crude) as a brown solid that required no further purification. MS: *m/z* 271.0 (M+H⁺).

Step 4 - Synthesis of *tert*-butyl 2-((1-(7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate:

To a solution of 1-(7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethan-1-amine (1.50 g, 5.55 mmol), *tert*-butyl 2-iodobenzoate (3.37 g, 11.11 mmol), Cs₂CO₃ (5.42 g, 16.64 mmol), Pd₂(dba)₃ (508 mg, 555 μmol) and Xantphos (642 mg, 1.11 mmol) in dioxane (30 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 16 h under N₂ atmosphere. The mixture was cooled to room temperature, quenched with water (20 mL). The mixture was extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (20 mL x 2), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 25% EtOAc in petroleum ether) to give the title compound (600 mg, 24%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.81 - 8.78 (m, 1H), 8.34 - 8.29 (m, 1H), 8.28 - 8.24 (m, 1H), 7.92 - 7.87 (m, 1H), 7.75 (s, 1H), 7.48 (s, 1H), 7.13 - 7.08 (m, 1H), 6.57 - 6.52 (m, 1H), 6.31 - 6.26 (m, 1H), 5.25 - 5.18 (m, 1H), 4.10 - 4.01 (m, 2H), 3.57 - 3.49 (m, 2H), 3.13 - 3.04 (m, 1H), 2.48 (s, 3H), 2.21 - 2.11 (m, 1H), 1.90 - 1.77 (m, 3H), 1.73 (d, *J* = 6.4 Hz, 3H), 1.63 (s, 9H). MS: *m/z* 447.2 (M+H⁺).

Step 5 - Synthesis of 5-(1-((2-(*tert*-butoxycarbonyl)phenyl)amino)ethyl)-7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinoline 1-oxide:

To a solution of *tert*-butyl 2-((1-(7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate (300 mg, 671 μmol) in DCM (5 mL) was added *m*-CPBA (348 mg, 2.02 mmol) at 0 °C. The reaction was stirred at room temperature for 16 h. The reaction mixture was quenched with sat. aq. Na₂SO₃ (10 mL), the mixture was extracted with EtOAc (40 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 80% EtOAc in petroleum ether) to give the title compound (140 mg, 38%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.63 (s, 1H), 8.25 (s, 1H), 8.21 - 8.16 (m, 1H), 8.10 (s, 1H), 7.79 - 7.76 (m, 1H), 7.51 - 7.47 (m, 1H), 7.21 - 7.17 (m, 1H), 6.59 - 6.52 (m, 1H), 6.44 - 6.38 (m, 1H), 5.51 - 5.40 (m, 1H), 3.94 - 3.86 (m, 2H), 3.54 - 3.39 (m, 2H), 3.02 - 2.94 (m, 1H), 2.45 (s, 3H), 2.06 - 2.00 (m, 1H), 1.90 - 1.80 (m, 1H), 1.69 - 1.64 (m, 2H), 1.62 - 1.60 (m, 3H), 1.57 (s, 9H). MS: *m/z* 463.1 (M+H⁺).

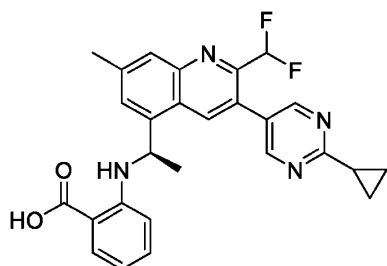
Step 6 - Synthesis of *tert*-butyl 2-((1-(2-chloro-7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate:

To a solution of 5-(1-((2-(*tert*-butoxycarbonyl)phenyl)amino)ethyl)-7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinoline 1-oxide (140 mg, 303 μ mol) in DCM (1 mL) was added POCl₃ (34 μ L, 363 μ mol) slowly at 0 °C under N₂ atmosphere, then DMF (12 μ L, 151 μ mol) in DCM (0.2 mL) was added slowly at 0 °C under N₂ atmosphere, the reaction mixture was stirred at room temperature for 3h. The reaction was adjusted to pH 9 with saturation NaHCO₃, and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (10 mL x 2), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (15 mg, 10%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.58 - 8.53 (m, 1H), 8.18 - 8.12 (m, 1H), 7.82 - 7.74 (m, 1H), 7.62 (s, 1H), 7.48 - 7.42 (m, 1H), 7.24 - 7.19 (m, 1H), 6.60 - 6.48 (m, 2H), 5.54 - 5.43 (m, 1H), 3.99 - 3.84 (m, 2H), 3.48 - 3.38 (m, 2H), 3.28 - 3.24 (m, 1H), 2.45 - 2.43 (m, 3H), 2.02 - 1.85 (m, 2H), 1.73 - 1.66 (m, 2H), 1.64 - 1.61 (m, 3H), 1.56 - 1.53 (m, 9H). MS: *m/z* 481.1 (M+H⁺).

Step 7 - Synthesis of 2-((1-(2-chloro-7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid:

To a mixture of *tert*-butyl 2-((1-(2-chloro-7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate (15 mg, 31 μ mol) in DCM (3 mL) was added TFA (1 mL, 13.46 mmol). The reaction mixture was stirred at room temperature for 16 h. The mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 60% - 90% / 0.225% formic acid in water) to give the title compound (9 mg, 67%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.77 (s, 1H), 8.56 (s, 1H), 8.48 - 8.38 (m, 1H), 7.83 - 7.78 (m, 1H), 7.61 (s, 1H), 7.48 - 7.43 (m, 1H), 7.23 - 7.17 (m, 1H), 6.56 - 6.46 (m, 2H), 5.53 - 5.44 (m, 1H), 3.95 - 3.86 (m, 2H), 3.47 - 3.40 (m, 2H), 3.26 - 3.23 (m, 1H), 2.45 - 2.42 (m, 3H), 2.00 - 1.83 (m, 2H), 1.73 - 1.66 (m, 2H), 1.63 - 1.58 (m, 3H). MS: *m/z* 425.2 (M+H⁺).

Example 35: (R)-2-((1-(3-(2-cyclopropylpyrimidin-5-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid (Compound 56)



Step 1 - Synthesis of 1-(2-(difluoromethyl)-3-hydroxy-7-methylquinolin-5-yl)ethanone:

A mixture of 1-(3-(benzyloxy)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethan-1-one (4.2 g, 12.30 mmol) in TFA (30 mL). The mixture was stirred at 75 °C for 16 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The crude product was triturated with EtOAc (10 mL) at room temperature, then the suspension was filtrated and the filter cake was dry in vacuo to give the title compound (3 g, 97%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.03 (s, 1H), 8.69 (s, 1H), 8.19 (s, 1H), 8.00 (s, 1H), 7.15 (t, *J* = 54.0 Hz, 1H), 2.73 (s, 3H), 2.54 (s, 3H). MS: *m/z* 252.1 (M+H⁺).

Step 2 - Synthesis of 5-acetyl-2-(difluoromethyl)-7-methylquinolin-3-yl trifluoromethanesulfonate:

To a solution of 1-(2-(difluoromethyl)-3-hydroxy-7-methylquinolin-5-yl)ethanone (3.0 g, 11.94 mmol) in DCM (35 mL) was added pyridine (2.8 g, 35.82 mmol) and Tf₂O (4 g, 14.33 mmol). The mixture was stirred at 0 °C for 2 h. After the reaction was completed, the reaction was quenched with water (30 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated in vacuo to give the title compound (4.4 g, crude) as a yellow solid that required no further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.41 (s, 1H), 8.48 (s, 1H), 8.24 (s, 1H), 7.30 (t, *J* = 52.8 Hz, 1H), 2.79 (s, 3H), 2.65 (s, 3H). MS: *m/z* 383.9 (M+H⁺).

Step 3 - Synthesis of 1-(3-(2-cyclopropylpyrimidin-5-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethan-1-one:

A mixture of 5-acetyl-2-(difluoromethyl)-7-methylquinolin-3-yl trifluoromethanesulfonate (400 mg, 1.04 mmol), 2-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (385 mg, 1.57 mmol), Pd(PPh₃)₄ (120 mg, 104 μmol) and K₂CO₃ (432 mg, 3.13 mmol) in dioxane (8 mL) and H₂O (1 mL). The mixture was stirred at 100 °C for 2

h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to give the title compound (220 mg, 59%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 9.21 (s, 1H), 8.68 (s, 2H), 8.17 (s, 1H), 8.05 (s, 1H), 6.91 - 6.60 (m, 1H), 2.78 (s, 3H), 2.68 (s, 3H), 2.39 - 2.32 (m, 1H), 1.35 - 1.10 (m, 4H). MS: m/z 354.3 (M+H⁺).

Step 4 – Synthesis of (*R,E*)-*N*-(1-(3-(2-cyclopropylpyrimidin-5-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide:

To a solution of 1-(3-(2-cyclopropylpyrimidin-5-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethan-1-one (220 mg, 622 μmol) in THF (6 mL) was added (*R*)-2-methylpropane-2-sulfinamide (754 mg, 26.23 mmol) and Ti(*i*-PrO)₄ (1.06 g, 3.74 mmol) at room temperature. The mixture was stirred at 75 °C for 16 h. The reaction mixture was diluted with water (50 mL) and extracted with DCM (50 mL x 3), and then the organic layer was washed with brine (100 mL), dried over anhydrous Na₂SO₄ and filtered and concentrated in vacuo to give the title compound (120 mg, 42%) as a yellow solid that required no further purification. ¹H NMR (400 MHz, CDCl₃) δ 8.74 (s, 1H), 8.63 (s, 2H), 8.07 (s, 1H), 7.67 (s, 1H), 6.90 - 6.62 (m, 1H), 2.91 (s, 3H), 2.66 (s, 3H), 2.38 - 2.33 (m, 1H), 1.26 (s, 9H), 1.26 - 1.22 (m, 2H), 1.19 - 1.16 (m, 2H). MS: m/z 457.1 (M+H⁺).

Step 5 - Synthesis of (*R*)-*N*-((*R*)-1-(3-(2-cyclopropylpyrimidin-5-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide & (*R*)-*N*-((*S*)-1-(3-(2-cyclopropylpyrimidin-5-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide:

A mixture of (*R,E*)-*N*-(1-(3-(2-cyclopropylpyrimidin-5-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide (120 mg, 262 μmol) in THF (6 mL) was added NaBH₄ (100 mg, 2.64 mmol) at 0 °C, and then the mixture was stirred at 0 °C for 2h under N₂ atmosphere. The reaction was quenched with aq. sat. NH₄Cl (5 mL) and extracted with DCM (20 mL x 3). The organics were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to give mixture (120 mg, two isomers 1:1). The mixture was separated by using chiral SFC (DAICEL CHIRALCEL OJ-H (250mm*30mm,5μm); Supercritical CO₂ / EtOH + 0.1% NH₃•H₂O = 70/30; 60 ml/min) to afford the (*R*)-*N*-((*R*)-1-(3-(2-cyclopropylpyrimidin-5-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethyl)-2-methylpropane-

2-sulfonamide (40 mg, first peak) and (*R*)-*N*-((*S*)-1-(3-(2-cyclopropylpyrimidin-5-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethyl)-2-methylpropane-2-sulfonamide (40 mg, second peak) both as yellow solid. MS: *m/z* 481.1 (*M*+Na⁺).

Step 6 - Synthesis of (*R*)-1-(3-(2-cyclopropylpyrimidin-5-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethan-1-amine:

A solution of (*R*)-*N*-((*S*)-1-(3-(2-cyclopropylpyrimidin-5-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethyl)-2-methylpropane-2-sulfonamide (40 mg, 87 μmol) in MeOH (1 mL) was added 12M HCl (9 mg, 261 μmol). The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was adjusted to pH 8 with NaHCO₃ saturated solution, then diluted with water (20 mL) and extracted with DCM (30 mL x 3). The organics were dried over Na₂SO₄, filtered and concentrated in vacuo to give the title compound (20 mg, crude) as a yellow solid that required no further purification. MS: *m/z* 355.0 (*M*+H⁺).

Step 7 - Synthesis of *tert*-butyl (*R*)-2-((1-(3-(2-cyclopropylpyrimidin-5-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethyl)amino)benzoate:

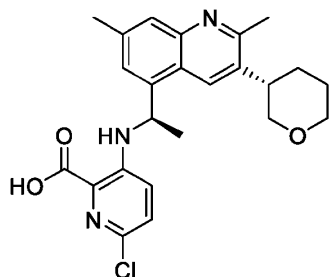
A mixture of (*R*)-1-(3-(2-cyclopropylpyrimidin-5-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethan-1-amine (20 mg, 56 μmol), *tert*-butyl 2-iodobenzoate (34 mg, 112 μmol), Pd₂(dba)₃ (5 mg, 5 μmol), XantPhos (6 mg, 11 μmol) and Cs₂CO₃ (55 mg, 169 μmol) in dioxane (1 mL) was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the mixture was quenched with water (10 mL), extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% EtOAc in petroleum ether) to give the title compound (15 mg, 50%) as a yellow solid. MS: *m/z* 531.2 (*M*+H⁺).

Step 8 - Synthesis of (*R*)-2-((1-(3-(2-cyclopropylpyrimidin-5-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid:

To a solution of *tert*-butyl (*R*)-2-((1-(3-(2-cyclopropylpyrimidin-5-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethyl)amino)benzoate (15 mg, 28 μmol) in DCM (3 mL) was added TFA (1.54 g, 476.22 mmol). The reaction mixture was stirred at 40 °C for 16 h. After cooling to room temperature, the reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 60% - 90% / 0.225% formic acid in water) to give the title compound (4 mg, 31%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.89 (s, 1H), 8.81 (s, 2H), 8.21

(s, 1H), 7.86 (s, 1H), 7.84 - 7.80 (m, 1H), 7.55 (s, 1H), 7.30 - 6.93 (m, 2H), 6.51 - 6.46 (m, 1H), 6.36 - 6.32 (m, 1H), 5.58 - 5.47 (m, 1H), 2.48 (s, 3H), 2.33 - 2.29 (m, 1H), 1.57 (d, $J = 6.4$ Hz, 3H), 1.15 - 1.08 (m, 4H). MS: m/z 475.1 ($M+H^+$).

Example 36: 6-chloro-3-(((*R*)-1-(2,7-dimethyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)picolinic acid (Compound 57)



Step 1 – Synthesis of *tert*-butyl (1-(3-(benzyloxy)-2,7-dimethylquinolin-5-yl)ethyl)carbamate:

A mixture of 1-(3-benzyloxy-2,7-dimethyl-5-quinolyl)ethanamine (2 g, 4.57 mmol), TEA (694 mg, 6.85 mmol) and Boc_2O (997 mg, 4.57 mmol) in DCM (20 mL) was degassed and purged with N_2 for 3 times, the final mixture was stirred at room temperature for 16 h under N_2 atmosphere. The reaction was diluted with water (20 mL) and EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL x 2), dried over anhydrous Na_2SO_4 , filtered and concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (660 mg, 35%) as a white solid. MS: m/z 406.9 ($M+H^+$).

Step 2 – Synthesis of *tert*-butyl (1-(3-hydroxy-2,7-dimethylquinolin-5-yl)ethyl)carbamate:

To a solution of *tert*-butyl (1-(3-(benzyloxy)-2,7-dimethylquinolin-5-yl)ethyl)carbamate (460 mg, 1.13 mmol) in MeOH (15 mL) was added wet Pd/C (451.69 mg, 10% Pd, 50% wet with water). The reaction was stirred at room temperature for 0.5 h under H_2 atmosphere (15 psi). The reaction was filtered through diatomaceous earth and the filtrate was concentrated to afford the title compound (355 mg, crude) as white solid that required no further purification. MS: m/z 317.0 ($M+H^+$).

Step 3 – Synthesis of 5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2,7-dimethylquinolin-3-yl trifluoromethanesulfonate:

To a solution of *tert*-butyl (1-(3-hydroxy-2,7-dimethylquinolin-5-yl)ethyl)carbamate (355 mg, 1.12 mmol) in DCM (5 mL) was added pyridine (266 mg, 3.37 mmol) and Tf₂O (475 mg, 1.68 mmol). The mixture was stirred at 0 °C for 2 h. After the reaction was completed, the reaction was quenched with water (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The reaction mixture was filtrate to give the title compound (500 mg, crude) as a yellow solid that required no further purification. MS: m/z 449.1 (M+H⁺).

Step 4 – Synthesis of *tert*-butyl (1-(3-(5,6-dihydro-2*H*-pyran-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)carbamate:

To a mixture of 5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2,7-dimethylquinolin-3-yl trifluoromethanesulfonate (500 mg, 1.11 mmol), K₂CO₃ (462.27 mg, 3.34 mmol) and 2-(3,6-dihydro-2*H*-pyran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (281 mg, 1.34 mmol) in dioxane (5 mL) and water (0.5 mL) was added Pd(PPh₃)₄ (129 mg, 111 μmol). The reaction mixture was heated to 100 °C and stirred for 2 h under N₂ atmosphere. The reaction was diluted with water (20 mL) and EtOAc (20 mL x 3). The combined organic phase was washed with brine (20 mL x 2), dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel eluting with (solvent gradient: 0 - 30% EtOAc in petroleum ether) to afford the title compound (380 mg, 89%) as a yellow solid. MS: m/z 383.1 (M+H⁺).

Step 5 – Synthesis of *tert*-butyl (1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)carbamate:

A mixture of *tert*-butyl (1-(3-(5,6-dihydro-2*H*-pyran-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)carbamate (350 mg, 915 μmol) in MeOH (15 mL) was added wet Pd/C (390 mg, 10% Pd, 50% wet with water). The mixture was stirred at room temperature for 1 h under H₂ atmosphere (15 psi). The reaction was filtered through diatomaceous earth and the filtrate was concentrated to afford the title compound (350 mg, crude) as a colorless oil that required no further purification. MS: m/z 385.2 (M+H⁺).

Step 6 – Synthesis of 1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethan-1-amine:

To a solution of *tert*-butyl (1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)carbamate (350 mg, 915 μ mol) in DCM (5 mL) was added HCl (5 mL, 4M in dioxane). After the addition, the reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated to give the title compound (260 mg, crude) as a white solid that required no further purification. MS: m/z 285.1 ($M+H^+$).

Step 7 – Synthesis of *tert*-butyl 6-chloro-3-((1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)picolinate:

A mixture of 1-(2,7-dimethyl-3-tetrahydropyran-3-yl-5-quinolyl)ethanamine (130 mg, 405 μ mol), *tert*-butyl 3-bromo-6-chloro-pyridine-2-carboxylate (177.8 mg, 608 μ mol), Cs₂CO₃ (660 mg, 2 mmol), Pd₂(dba)₃ (37 mg, 45 μ mol) and Xantphos (47 mg, 81 μ mol) in dioxane (5 mL), the reaction mixture was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (140 mg, 70%) as a yellow solid. MS: m/z 496.0 ($M+H^+$).

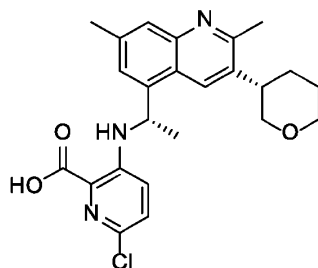
Step 8 – Synthesis of *tert*-butyl 6-chloro-3-(((*R*)-1-(2,7-dimethyl-3-((*R*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)picolinate & *tert*-butyl 6-chloro-3-(((*R*)-1-(2,7-dimethyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino) picolinate & *tert*-butyl 6-chloro-3-(((*S*)-1-(2,7-dimethyl-3-((*R*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)picolinate & *tert*-butyl 6-chloro-3-(((*S*)-1-(2,7-dimethyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino) picolinate:

tert-butyl 6-chloro-3-((1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)picolinate (140 mg, 231 μ mol) was separated by using chiral SFC (DAICEL CHIRALCEL OD-H (250mm*30mm,10 μ m); Supercritical CO₂ / EtOH + 0.1% NH₃•H₂O = 75/25; 70 ml/min) to afford *tert*-butyl 6-chloro-3-(((*R*)-1-(2,7-dimethyl-3-((*R*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)picolinate (35 mg, first peak), *tert*-butyl 6-chloro-3-(((*R*)-1-(2,7-dimethyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)picolinate (10 mg, second peak), *tert*-butyl 6-chloro-3-(((*S*)-1-(2,7-dimethyl-3-((*R*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)picolinate (20 mg, third peak) and *tert*-butyl 6-chloro-3-(((*S*)-1-(2,7-dimethyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)picolinate (35 mg, fourth peak) as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. MS: m/z 496.0 ($M+H^+$).

Step 9 – Synthesis of 6-chloro-3-(((*R*)-1-(2,7-dimethyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)picolinic acid:

To a mixture of *tert*-butyl 6-chloro-3-(((*R*)-1-(2,7-dimethyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino) picolinate (10 mg, 20 μ mol) in DCM (3 mL) was added TFA (1 mL). The reaction was stirred at room temperature for 16 h. This mixture was concentrated in vacuo and then diluted with MeOH (2 mL). The solution was adjusted pH to 10 with aq. LiOH (2 M), then adjusted pH to 6 with formic acid. The solution was purified by reverse phase chromatography (acetonitrile 20%-50% / 0.225% formic acid in water) to give the title compound (3 mg, 33%) as a white solid. ^1H NMR (400 MHz, DMSO-*d*₆): δ 8.55 (s, 1H), 8.29 (s, 1H), 7.58 (s, 1H), 7.33 - 7.28 (m, 2H), 7.03 (d, *J* = 9.2 Hz, 1H), 5.53 - 5.45 (m, 1H), 3.93 - 3.87 (m, 2H), 3.55 - 3.53 (m, 2H), 3.10 - 3.05 (m, 1H), 2.68 (s, 3H), 2.41 (s, 3H), 1.96 - 1.93 (m, 1H), 1.84 - 1.79 (m, 1H), 1.69 - 1.67 (m, 2H), 1.61 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 440.1 (*M*+*H*⁺).

Example 37: 6-chloro-3-(((*S*)-1-(2,7-dimethyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)picolinic acid (Compound 58)

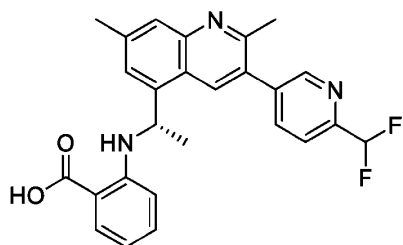


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To a mixture of *tert*-butyl 6-chloro-3-(((*S*)-1-(2,7-dimethyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)picolinate (35 mg, 71 μ mol) in DCM (3 mL) was added TFA (1 mL). The reaction was stirred at room temperature for 16 h. This mixture was concentrated in vacuo and then diluted with MeOH (2 mL). The solution was adjusted pH to 10 with aq. LiOH (2 M), then adjusted pH to 6 with formic acid. The solution was purified by reverse phase chromatography (acetonitrile 17% - 47% / 0.225% formic acid in water) to give the title compound (23 mg, 74%) as a white solid. ^1H NMR (400 MHz, DMSO-*d*₆) δ 8.41 (d, *J* = 6.4 Hz, 1H), 8.30 (s, 1H), 7.58 (s, 1H), 7.33 (d, *J* = 9.2 Hz, 1H), 7.28 (s, 1H), 7.01 (d, *J* = 9.2 Hz, 1H), 5.58 - 5.48 (m, 1H), 3.95 - 3.88 (m, 2H), 3.52 - 3.44 (m, 2H), 3.12 - 3.05 (m, 1H), 2.69 (s, 3H), 2.40 (s, 3H), 1.99 - 1.91 (m, 1H), 1.90 - 1.80 (m, 1H), 1.76 - 1.67 (m, 2H), 1.61 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 440.5 (*M*+*H*⁺).

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Example 38: (*S*)-2-((1-(3-(6-(difluoromethyl)pyridin-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid (Compound 59)



Step 1 – Synthesis of 1-(3-(6-(difluoromethyl)pyridin-3-yl)-2,7-dimethylquinolin-5-yl)ethan-1-one:

To a mixture of (5-acetyl-2,7-dimethyl-3-quinolyl) trifluoromethanesulfonate (500 mg, 1.44 mmol), K₂CO₃ (597 mg, 4.32 mmol) and 2-(difluoromethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (367 mg, 1.44 mmol) in dioxane (5 mL) and water (1 mL) was added Pd(PPh₃)₄ (166 mg, 144 μmol). The reaction mixture was heated to 100 °C and stirred for 2 h under N₂ atmosphere. The reaction was diluted with water (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (20 mL x 2), dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% EtOAc in petroleum ether) to give the title compound (450 mg, 96%) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.83 - 8.82 (m, 2H), 8.20 - 8.13 (m, 2H), 8.02 (s, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.21 - 6.90 (m, 1H), 2.73 (s, 3H), 2.61 (s, 3H), 2.59 (s, 3H). MS: *m/z* 327.1 (M+H⁺).

Step 2 – Synthesis of (*R,E*)-*N*-(1-(3-(6-(difluoromethyl)pyridin-3-yl)-2,7-dimethylquinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide:

A mixture of 1-(3-(6-(difluoromethyl)pyridin-3-yl)-2,7-dimethylquinolin-5-yl)ethan-1-one (450 mg, 1.38 mmol), (*R*)-2-methylpropane-2-sulfinamide (1.67 g, 13.79 mmol) and Ti(*i*-PrO)₄ (3.92 g, 13.79 mmol) in THF (10 mL) was degassed and purged with N₂ for 3 times. The mixture was stirred at 75 °C for 16 h under N₂ atmosphere. The reaction mixture was added water (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to give the title compound (590 mg, crude) as a yellow oil that required no further purification. MS: *m/z* 430.0 (M+H⁺).

Step 3 – Synthesis of (*R*)-*N*-((*S*)-1-(3-(6-(difluoromethyl)pyridin-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide and (*R*)-*N*-((*R*)-1-(3-(6-(difluoromethyl)pyridin-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide:

5 To a solution of (*R,E*)-*N*-(1-(3-(6-(difluoromethyl)pyridin-3-yl)-2,7-dimethylquinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide (590 mg, 1.37 mmol) in THF (20 mL) was added NaBH₄ (0.16 g, 4.23 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h under N₂ atmosphere. The mixture was quenched with saturated NH₄Cl (10 mL) at 0 °C, diluted with water (20 mL), extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine
10 (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by reverse phase chromatography (acetonitrile 45% - 75% / 0.05% NH₃•H₂O + 10 mM NH₄HCO₃ in water) to afford (*R*)-*N*-((*S*)-1-(3-(6-(difluoromethyl)pyridin-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (120 mg, first peak) and (*R*)-*N*-((*R*)-1-(3-(6-(difluoromethyl)pyridin-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)-2-methylpropane-2-
15 sulfinamide (120 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. MS: m/z 432.1 (M+H⁺).

Step 4 – Synthesis of (*S*)-1-(3-(6-(difluoromethyl)pyridin-3-yl)-2,7-dimethylquinolin-5-yl)ethan-1-amine:

A mixture of (*R*)-*N*-((*R*)-1-(3-(6-(difluoromethyl)pyridin-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (120 mg, 278 μmol) in MeOH (2 mL) was added HCl
20 (12 M, 70 μL). The mixture was stirred at room temperature for 0.5 h. The reaction mixture was quenched with sat. aq. NaHCO₃ (30 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to give the title compound (90 mg, crude) as yellow oil that required no further
25 purification. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.85 (s, 1H), 8.46 (s, 1H), 8.22 - 8.19 (m 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.65 (s, 1H), 7.61 (s, 1H), 7.22 - 6.90 (m, 1H), 4.91 - 4.78 (m, 1H), 2.58 (s, 3H), 2.52 (s, 3H), 1.37 (d, J = 6.4 Hz, 3H). MS: m/z 328.1 (M+H⁺).

Step 5 – Synthesis of *tert*-butyl (*S*)-2-((1-(3-(6-(difluoromethyl)pyridin-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate:

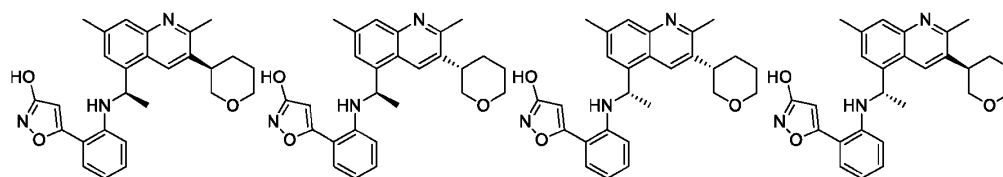
30 A mixture of (*S*)-1-(3-(6-(difluoromethyl)pyridin-3-yl)-2,7-dimethylquinolin-5-yl)ethan-1-amine (48 mg, 147 μmol), *tert*-butyl 2-bromobenzoate (45 mg, 147 μmol), Cs₂CO₃ (143 mg, 440

μmol), Pd₂(dba)₃ (13 mg, 15 μmol) and Xantphos (17 mg, 29 μmol) in dioxane (2 mL), the reaction mixture was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% EtOAc in petroleum ether) to give the title compound (50 mg, 68%) as a yellow solid. MS: m/z 504.1 (M+H⁺).

Step 6 – Synthesis of (S)-2-((1-(3-(6-(difluoromethyl)pyridin-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid:

To a mixture of *tert*-butyl (S)-2-((1-(3-(6-(difluoromethyl)pyridin-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoate (60 mg, 119 μmol) in DCM (6 mL) was added TFA (2 mL, 626.9 mmol). The reaction mixture was stirred at room temperature for 16 h. The mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 35% - 65% / 0.225% formic acid in water) to give the title compound (6 mg, 11%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.91 (s, 1H), 8.61 (s, 1H), 8.55 - 8.44 (m, 1H), 8.26 - 8.23 (m, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.82 - 7.79 (m, 1H), 7.68 (s, 1H), 7.37 (s, 1H), 7.21 - 6.94 (m, 2H), 6.53 - 6.49 (m, 1H), 6.41 - 6.38 (m, 1H), 5.53 - 5.50 (m, 1H), 2.61 (s, 3H), 2.44 (s, 3H), 1.57 (d, J = 6.0 Hz, 3H). MS: m/z 448.1 (M+H⁺).

Example 39: 5-(2-(((R)-1-(2,7-dimethyl-3-((R)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)phenyl)isoxazol-3-ol & 5-(2-(((R)-1-(2,7-dimethyl-3-((S)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)phenyl)isoxazol-3-ol & 5-(2-(((S)-1-(2,7-dimethyl-3-((S)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)phenyl)isoxazol-3-ol & 5-(2-(((S)-1-(2,7-dimethyl-3-((R)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)phenyl)isoxazol-3-ol (Compound 60, Compound 61, Compound 62, and Compound 63)



Step 1 – Synthesis of 1-(3-(5,6-dihydro-2H-pyran-3-yl)-2,7-dimethylquinolin-5-yl)ethan-1-amine:

A mixture of 1-(3-(5,6-dihydro-2*H*-pyran-3-yl)-2,7-dimethylquinolin-5-yl)ethan-1-one (3.1 g, 11.0 mmol), NH₄OAc (12.7 g, 165.1 mmol) and AcOH (66 mg, 1.10 mmol) in MeOH (50 mL) was stirred at room temperature for 1 h. Then to the mixture was added NaBH₃CN (2.1 g, 33.1 mmol). After the addition, the reaction mixture was stirred at 60 °C for 4 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (60 mL). The mixture was washed with saturated NaHCO₃ solution (30 mL x 3), brine (20 mL), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated to give the title compound (3.5 g, crude) as a yellow solid that required no further purification. MS: m/z 283.1 (M+H⁺).

Step 2 – Synthesis of *tert*-butyl (1-(3-(5,6-dihydro-2*H*-pyran-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)carbamate:

To a solution of 1-(3-(5,6-dihydro-2*H*-pyran-3-yl)-2,7-dimethylquinolin-5-yl)ethan-1-amine (3.5 g, 12.4 mmol) in DCM (50 mL) was added TEA (3.8 g, 37.2 mmol) and Boc₂O (5.4 g, 24.8 mmol). The mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (2.5 g, 53%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.17 (s, 1H), 7.59 (s, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.35 (s, 1H), 5.90 - 5.86 (m, 1H), 5.36 - 5.29 (m, 1H), 4.28 - 4.24 (m, 2H), 3.85 - 3.80 (m, 2H), 2.62 (s, 3H), 2.48 (s, 3H), 2.30 - 2.24 (m, 2H), 1.41 - 1.33 (m, 12H). MS: m/z 383.2 (M+H⁺).

Step 3 – Synthesis of *tert*-butyl (1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)carbamate:

To a solution of *tert*-butyl (1-(3-(5,6-dihydro-2*H*-pyran-3-yl)-2,7-dimethylquinolin-5-yl)ethyl)carbamate (2.5 g, 6.5 mmol) in MeOH (25 mL) was added Pd(OH)₂ on carbon (1.3 g, 20% Pd, 50% wet with water). The reaction was stirred at room temperature for 1 h under H₂ atmosphere (15 psi). The reaction was filtered through diatomaceous earth and the filtrate was concentrated to afford the title compound (2.3 g, 90%) as a white solid that required no further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.27 - 8.23 (m, 1H), 7.57 (s, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.32 (s, 1H), 5.45 - 5.32 (m, 1H), 3.98 - 3.87 (m, 2H), 3.50 - 3.35 (m, 2H), 3.13 - 3.01 (m, 1H), 2.68 (s, 3H), 2.46 (s, 3H), 2.04 - 1.85 (m, 2H), 1.81 - 1.63 (m, 2H), 1.44 (d, *J* = 6.8 Hz, 3H), 1.39 (s, 9H). MS: m/z 385.2 (M+H⁺).

Step 4 – Synthesis of 1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethan-1-amine:

To a mixture of *tert*-butyl (1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)carbamate (2.3 g, 5.9 mmol) in THF (25 mL) was added HCl (10 mL, 1M in water) at room temperature. The reaction mixture was stirred at room temperature for 1 h. The mixture was quenched with saturated NaHCO₃ (10 mL), extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na₂SO₄. The filtrate was concentrated to give the title compound (1.8 g, crude) as a white solid that required no further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.30 (s, 1H), 7.53 (s, 2H), 4.85 - 4.74 (m, 1H), 3.95 - 3.85 (m, 2H), 3.54 - 3.39 (m, 2H), 3.13 - 3.03 (m, 1H), 2.67 (s, 3H), 2.47 (s, 3H), 2.01 - 1.95 (m, 2H), 1.93 - 1.83 (m, 1H), 1.78 - 1.67 (m, 2H), 1.35 (d, *J* = 6.8 Hz, 3H). MS: *m/z* 285.2 (M+H⁺).

Step 5 – Synthesis of *N*-(1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)-2-iodoaniline:

To a solution of 1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethan-1-amine (520 mg, 1.8 mmol) in dioxane (8 mL) was added 1,2-diiodobenzene (1.2 g, 3.7 mmol), XantPhos (212 mg, 366 μmol), Cs₂CO₃ (1.8 g, 5.5 mmol) and Pd₂(dba)₃ (167 mg, 183 μmol). The mixture was stirred at 100 °C for 2 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% EtOAc in petroleum ether) to give the title compound (657 mg, 74%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.36 - 8.29 (m, 1H), 7.68 - 7.61 (m, 1H), 7.56 (s, 1H), 7.38 - 7.32 (m, 1H), 7.28 - 7.15 (m, 1H), 7.08 - 7.01 (m, 1H), 6.44 - 6.32 (m, 2H), 5.47 - 5.35 (m, 1H), 4.90 - 4.86 (m, 1H), 3.94 - 3.84 (m, 2H), 3.50 - 3.39 (m, 2H), 3.14 - 3.05 (m, 1H), 2.68 (s, 3H), 2.41 (s, 3H), 1.97 - 1.76 (m, 2H), 1.75 - 1.66 (m, 2H), 1.63 (d, *J* = 6.8 Hz, 3H). MS: *m/z* 487.1 (M+H⁺).

Step 6 – Synthesis of methyl 3-(2-((1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)phenyl)propionate:

A mixture of *N*-(1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)-2-iodoaniline (540 mg, 1.1 mmol), methyl prop-2-ynoate (187 mg, 2.2 mmol), CuI (63 mg, 333 μmol), K₂CO₃ (460 mg, 3.3 mmol) and Pd(PPh₃)₂Cl₂ (78 mg, 111 μmol) in DMF (10 mL) was stirred at 100 °C for 2 h under N₂ atmosphere. After cooling to room temperature, the reaction was quenched with water (20 mL), extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 16% EtOAc in

petroleum ether) to give the title compound (420 mg, 85%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.35 (s, 1H), 7.57 (s, 1H), 7.48 - 7.36 (m, 2H), 7.31 - 7.12 (m, 3H), 6.62 - 6.55 (m, 1H), 6.50 - 6.41 (m, 1H), 5.79 - 5.73 (m, 1H), 5.51 - 5.42 (m, 1H), 3.95 - 3.85 (m, 2H), 3.78 (s, 3H), 3.48 - 3.37 (m, 2H), 3.15 - 3.04 (m, 1H), 2.68 (s, 3H), 2.42 (s, 3H), 2.01 - 1.87 (m, 2H), 1.71 - 1.63 (m, 2H), 1.62 (d, *J* = 6.8 Hz, 3H). MS: *m/z* 443.0 (M+H⁺).

Step 7 – Synthesis of 5-(2-((1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)phenyl)isoxazol-3-ol:

To a mixture of methyl 3-(2-((1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)phenyl)propionate (500 mg, 1.1 mmol) in EtOH (4 mL) was added NH₂OH (4.5 mL, 2.3 mmol, 50% in water). The reaction mixture was stirred at room temperature for 16 h. The mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 20% - 50% / 0.225% formic acid in water) to give the title compound (150 mg, 30%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.41 - 8.31 (m, 1H), 7.56 (s, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.44 - 7.40 (m, 1H), 7.13 - 7.05 (m, 1H), 6.68 - 6.62 (m, 1H), 6.53 - 6.46 (m, 1H), 6.41 (s, 1H), 5.89 (d, *J* = 5.6 Hz, 1H), 5.48 - 5.34 (m, 1H), 3.95 - 3.83 (m, 2H), 3.48 - 3.35 (m, 2H), 3.14 - 3.02 (m, 1H), 2.68 (s, 3H), 2.41 (s, 3H), 1.97 - 1.77 (m, 2H), 1.76 - 1.66 (m, 2H), 1.62 (d, *J* = 6.8 Hz, 3H). MS: *m/z* 444.2 (M+H⁺).

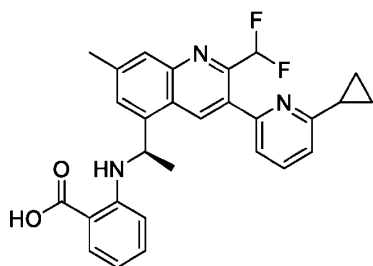
Step 8 – Synthesis of 5-(2-(((*R*)-1-(2,7-dimethyl-3-((*R*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)phenyl)isoxazol-3-ol & 5-(2-(((*R*)-1-(2,7-dimethyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)phenyl)isoxazol-3-ol & 5-(2-(((*S*)-1-(2,7-dimethyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)phenyl)isoxazol-3-ol & 5-(2-(((*S*)-1-(2,7-dimethyl-3-((*R*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)phenyl)isoxazol-3-ol:

5-(2-((1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)phenyl)isoxazol-3-ol (130 mg, 293 μmol) was separated by using chiral SFC (DAICEL CHIRALPAK AD (250mm*30mm,10μm); Supercritical CO₂ / MeOH + 0.1% NH₃•H₂O = 60/40; 80 mL/min) to afford 5-(2-(((1*R*)-1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)phenyl)isoxazol-3-ol (70 mg, first peak, mixture), 5-(2-(((*S*)-1-(2,7-dimethyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)phenyl)isoxazol-3-ol (28.9 mg, second peak) and 5-(2-(((*S*)-1-(2,7-dimethyl-3-((*R*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)phenyl)isoxazol-3-ol (36.7 mg, third peak) both as white solid. Absolute

configuration was arbitrarily assigned to each enantiomer. Second peak: ^1H NMR (400 MHz, DMSO- d_6) δ 8.37 (s, 1H), 7.56 (s, 1H), 7.51 - 7.47 (m, 1H), 7.42 (s, 1H), 7.12 - 7.05 (m, 1H), 6.68 - 6.62 (m, 1H), 6.49 (d, J = 8.4 Hz, 1H), 6.40 (s, 1H), 5.89 (d, J = 5.6 Hz, 1H), 5.42 - 5.37 (m, 1H), 3.94 - 3.82 (m, 2H), 3.47 - 3.39 (m, 2H), 3.12 - 3.02 (m, 1H), 2.68 (s, 3H), 2.41 (s, 3H), 1.99 - 1.77 (m, 2H), 1.76 - 1.65 (m, 2H), 1.62 (d, J = 6.8 Hz, 3H). MS: m/z 444.1 ($\text{M}+\text{H}^+$). Third peak: ^1H NMR (400 MHz, DMSO- d_6) δ 8.35 (s, 1H), 7.56 (s, 1H), 7.51 - 7.46 (m, 1H), 7.41 (d, J = 1.2 Hz, 1H), 7.12 - 7.04 (m, 1H), 6.68 - 6.61 (m, 1H), 6.48 (d, J = 8.4 Hz, 1H), 6.41 (s, 1H), 5.89 (d, J = 5.6 Hz, 1H), 5.44 - 5.36 (m, 1H), 3.94 - 3.83 (m, 2H), 3.49 - 3.40 (m, 2H), 3.13 - 2.99 (m, 1H), 2.68 (s, 3H), 2.40 (s, 3H), 1.95 - 1.78 (m, 2H), 1.75 - 1.66 (m, 2H), 1.62 (d, J = 6.8 Hz, 3H). MS: m/z 444.1 ($\text{M}+\text{H}^+$).

5-(2-(((1*R*)-1-(2,7-dimethyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)phenyl)isoxazol-3-ol (70 mg, first peak, mixture) was separated by using chiral SFC (DAICEL CHIRALPAK AD (250mm*30mm,10um); Supercritical CO_2 / MeOH + 0.1% $\text{NH}_3\cdot\text{H}_2\text{O}$ = 75/15; 80 mL/min) to afford 5-(2-(((*R*)-1-(2,7-dimethyl-3-((*R*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)phenyl)isoxazol-3-ol (25.4 mg, first peak) and 5-(2-(((*R*)-1-(2,7-dimethyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)phenyl)isoxazol-3-ol (28.5 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. First peak: ^1H NMR (400 MHz, DMSO- d_6) δ 11.39 (s, 1H), 8.37 (s, 1H), 7.56 (s, 1H), 7.50 - 7.46 (m, 1H), 7.42 (s, 1H), 7.11 - 7.05 (m, 1H), 6.67 - 6.62 (m, 1H), 6.49 (d, J = 8.4 Hz, 1H), 6.41 (s, 1H), 5.89 (d, J = 6.0 Hz, 1H), 5.43 - 5.35 (m, 1H), 3.94 - 3.84 (m, 2H), 3.45 - 3.36 (m, 2H), 3.12 - 3.02 (m, 1H), 2.68 (s, 3H), 2.41 (s, 3H), 2.00 - 1.75 (m, 2H), 1.75 - 1.64 (m, 2H), 1.62 (d, J = 6.4 Hz, 3H). MS: m/z 444.2 ($\text{M}+\text{H}^+$). Second peak: ^1H NMR (400 MHz, DMSO- d_6) δ 11.37 (s, 1H), 8.36 (s, 1H), 7.56 (s, 1H), 7.51 - 7.46 (m, 1H), 7.41 (d, J = 1.2 Hz, 1H), 7.12 - 7.04 (m, 1H), 6.68 - 6.62 (m, 1H), 6.48 (d, J = 8.4 Hz, 1H), 6.42 (s, 1H), 5.90 (d, J = 5.6 Hz, 1H), 5.45 - 5.36 (m, 1H), 3.98 - 3.81 (m, 2H), 3.47 - 3.36 (m, 2H), 3.12 - 3.02 (m, 1H), 2.68 (s, 3H), 2.40 (s, 3H), 1.95 - 1.77 (m, 2H), 1.75 - 1.66 (m, 2H), 1.62 (d, J = 6.8 Hz, 3H). MS: m/z 444.1 ($\text{M}+\text{H}^+$).

Example 40: (*R*)-2-((1-(3-(6-cyclopropylpyridin-2-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid (Compound 64)



Step 1 - Synthesis of 2-bromo-6-cyclopropylpyridine:

A mixture of methyl 2,6-dibromopyridine (2 g, 8.4 mmol), cyclopropylboronic acid (1.5 g, 16.9 mmol), Pd(PPh₃)₄ (488 mg, 422 μmol) and Cs₂CO₃ (8.3 g, 25 mmol) in dioxane (35 mL). The mixture was stirred at 100 °C for 1 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 5% EtOAc in petroleum ether) to give the title compound (800 mg, 34%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.62 - 7.55 (m, 1H), 7.38 - 7.30 (m, 2H), 2.14 - 2.05 (m, 1H), 1.02 - 0.95 (m, 2H), 0.89 - 0.85 (m, 2H). MS: m/z 198.0 (M+H⁺).

Step 2 – Synthesis of 2-cyclopropyl-6-(trimethylstannyl)pyridine:

A mixture of methyl 2-bromo-6-cyclopropylpyridine (200 mg, 1.0 mmol), trimethyl(trimethylstannyl)stannane (364 mg, 1.1 mmol) and Pd(PPh₃)₄ (117 mg, 101 μmol) in dioxane (4mL). The mixture was stirred at 110 °C for 3 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo to give the title compound (180 mg, crude) as a yellow solid that required no further purification. MS: m/z 284.1 (M+H⁺).

Step 3 – Synthesis of 1-(3-(6-cyclopropylpyridin-2-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethan-1-one:

A mixture of methyl 2-cyclopropyl-6-(trimethylstannyl)pyridine (180 mg, 638 μmol), 5-acetyl-2-(difluoromethyl)-7-methylquinolin-3-yl trifluoromethanesulfonate (204 mg, 532 μmol), CuI (30 mg, 160 μmol) and Pd(PPh₃)₂Cl₂ (37 mg, 53 μmol) in DMF (3 mL) was stirred at 100 °C for 16 h. After cooling to room temperature, the reaction mixture was quenched with water (10 mL), extracted with EtOAc (15 mL x 2). The combined organic layers were washed with brine (15 mL x 2) and brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (167 mg, 89%) as a yellow solid. ¹H NMR (400 MHz,

DMSO-*d*₆) δ 9.21 (s, 1H), 8.31 (s, 1H), 8.19 (s, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.48 - 7.38 (m, 2H), 2.77 (s, 3H), 2.64 (s, 3H), 1.02 - 0.98 (m, 4H). MS: *m/z* 353.1 (M+H⁺).

Step 4 – Synthesis of (*R,E*)-*N*-(1-(3-(6-cyclopropylpyridin-2-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide:

5 A mixture of 1-(3-(6-cyclopropylpyridin-2-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethan-1-one (167 mg, 474 μ mol), (*R*)-2-methylpropane-2-sulfinamide (574 mg, 4.7 mmol), tetrakisopropoxytitanium (808 mg, 2.8 mmol) in THF (5 mL) was stirred at 75 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was quenched with water (10 mL), extracted with EtOAc (15 mL x 2). The combined organic layers were washed with brine
10 (10 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 15% EtOAc in petroleum ether) to give the title compound (134 mg, 62%) as a white solid. MS: *m/z* 456.1 (M+H⁺).

Step 5 – Synthesis of (*R*)-*N*-((*R*)-1-(3-(6-cyclopropylpyridin-2-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide:

15 A mixture of (*R,E*)-*N*-(1-(3-(6-cyclopropylpyridin-2-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide (125 mg, 274 μ mol) in THF (3 mL) was added NaBH₄ (12 mg, 329 μ mol) at 0 °C. The mixture was stirred at room temperature for 4 h under N₂ atmosphere. The reaction was quenched with sat. aq. NH₄Cl (2 mL), diluted with water (10 mL), extracted with EtOAc (10 mL x 2). The combined organic layers were washed with
20 brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 15% EtOAc in petroleum ether) to give the title compound (60 mg, 48%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.81 (s, 1H), 7.90 - 7.83 (m, 2H), 7.74 - 7.65 (m, 2H), 7.49 - 7.18 (m, 2H), 5.86 (d, *J* = 6.0 Hz, 1H), 5.30 - 5.23 (m, 1H), 2.58 (s, 3H), 2.24 - 2.17 (m, 1H), 1.59 (d, *J* = 6.8 Hz, 3H), 1.06 (s, 9H), 1.02
25 - 0.96 (m, 4H). MS: *m/z* 458.2 (M+H⁺).

Step 6 – Synthesis of (*R*)-1-(3-(6-cyclopropylpyridin-2-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethan-1-amine:

A mixture of (*R*)-*N*-((*R*)-1-(3-(6-cyclopropylpyridin-2-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (60 mg, 131 μ mol), HCl (1 mL, 12M)
30 in MeOH (2 mL) was stirred at room temperature for 4 h. The mixture was basified with sat. aq. NaHCO₃ to pH 7. Then the mixture was extracted with EtOAc (20 mL x 2). The combined organic

layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give the title compound (40 mg, crude) as a yellow solid that required no further purification. MS: m/z 354.1 (M+H⁺).

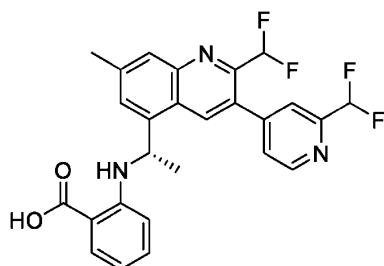
Step 7 – Synthesis of *tert*-butyl (*R*)-2-((1-(3-(6-cyclopropylpyridin-2-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethyl)amino)benzoate:

A mixture of (*R*)-1-(3-(6-cyclopropylpyridin-2-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethan-1-amine (40 mg, 113 μmol), *tert*-butyl 2-iodobenzoate (52 mg, 170 μmol), Pd2(dba)₃ (10 mg, 11 μmol), XantPhos (13 mg, 23 μmol) and Cs₂CO₃ (111 mg, 340 μmol) in dioxane (2 mL). The mixture was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (30 mg, 50%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.90 (s, 1H), 8.21 (d, *J* = 6.4 Hz, 1H), 7.88 - 7.82 (m, 2H), 7.71 - 7.64 (m, 1H), 7.69 (d, *J* = 7.2 Hz, 1H), 7.54 (d, *J* = 1.2 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.39 - 7.20 (m, 1H), 7.19 - 7.12 (m, 1H), 6.61 - 6.52 (m, 1H), 6.47 (d, *J* = 8.4 Hz, 1H), 5.66 - 5.55 (m, 1H), 2.55 - 2.51 (m, 3H), 2.25 - 2.16 (m, 1H), 1.64 (d, *J* = 6.8 Hz, 3H), 1.56 (s, 9H), 1.03 - 0.96 (m, 4H). MS: m/z 530.3 (M+H⁺).

Step 8 - Synthesis of (*R*)-2-((1-(3-(6-cyclopropylpyridin-2-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid:

A mixture of *tert*-butyl (*R*)-2-((1-(3-(6-cyclopropylpyridin-2-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethyl)amino)benzoate (30 mg, 57 μmol) in DCM (2 mL) was added TFA (1.3 g, 11.3 mmol). The reaction mixture was stirred at room temperature for 16 h. After cooling to room temperature, the reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 55%-85% / 0.225% formic acid in water) to give the title compound (15.7 mg, 58%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.78 (s, 1H), 8.91 (s, 1H), 8.45 (d, *J* = 5.6 Hz, 1H), 7.88 - 7.85 (m, 2H), 7.85 - 7.80 (m, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.53 (s, 1H), 7.50 - 7.21 (m, 2H), 7.19 - 7.12 (m, 1H), 6.56 - 6.48 (m, 1H), 6.45 (d, *J* = 8.4 Hz, 1H), 5.71 - 5.52 (m, 1H), 2.48 (s, 3H), 2.26 - 2.17 (m, 1H), 1.62 (d, *J* = 6.8 Hz, 3H), 1.04 - 0.96 (m, 4H). MS: m/z 474.1 (M+H⁺).

Example 41: (*S*)-2-((1-(2-(difluoromethyl)-3-(2-(difluoromethyl)pyridin-4-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid (Compound 65)



Step 1 – Synthesis of 1-(2-(difluoromethyl)-3-(2-(difluoromethyl)pyridin-4-yl)-7-methylquinolin-5-yl)ethan-1-one:

A mixture of 2-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (350 mg, 686 μ mol), 5-acetyl-2-(difluoromethyl)-7-methylquinolin-3-yl trifluoromethanesulfonate (263 mg, 686 μ mol), Pd(PPh₃)₄ (79 mg, 69 μ mol) and K₂CO₃ (189.64 mg, 1.37 mmol) in dioxane (4 mL) and H₂O (0.8 mL). The mixture was stirred at 100 °C for 2 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (240 mg, 97%) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.05 (s, 1H), 8.84 (d, *J* = 4.8 Hz, 1H), 8.34 (s, 1H), 8.22 (s, 1H), 7.82 (s, 1H), 7.73 (d, *J* = 4.8 Hz, 1H), 7.24 - 6.93 (m, 2H), 2.76 (s, 3H), 2.66 (s, 3H). MS: *m/z* 363.0 (M+H⁺).

Step 2 – Synthesis of (*R,E*)-N-(1-(2-(difluoromethyl)-3-(2-(difluoromethyl)pyridin-4-yl)-7-methylquinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide:

To a solution of 1-(2-(difluoromethyl)-3-(2-(difluoromethyl)pyridin-4-yl)-7-methylquinolin-5-yl)ethan-1-one (240 mg, 662 μ mol) in THF (3 mL) was added tetrakispropoxytitanium (1.13 g, 3.97 mmol) and (*R*)-2-methylpropane-2-sulfinamide (803 mg, 6.62 mmol). The mixture was stirred at 75 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the mixture was quenched with saturated NaHCO₃ (20 mL), extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄ and filtered. The crude was purified by flash silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (270 mg, 88%) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.90 - 8.80 (m, 2H), 8.12 (s, 1H), 8.01 (s, 1H), 7.79 - 7.67 (m, 2H), 7.12 - 6.93 (m, 2H), 2.86 (s, 3H), 2.63 (s, 3H), 1.12 (s, 9H). MS: *m/z* 466.1 (M+H⁺).

Step 3 – Synthesis of (*R*)-*N*-((*R*)-1-(2-(difluoromethyl)-3-(2-(difluoromethyl)pyridin-4-yl)-7-methylquinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide & (*R*)-*N*-((*S*)-1-(2-(difluoromethyl)-3-(2-(difluoromethyl)pyridin-4-yl)-7-methylquinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide:

5 A mixture of (*R,E*)-*N*-(1-(2-(difluoromethyl)-3-(2-(difluoromethyl)pyridin-4-yl)-7-methylquinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide (270 mg, 580 μ mol), NaBH₄ (66 mg, 1.74 mmol) in THF (3 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 0 °C for 1 h under N₂ atmosphere. The reaction was quenched with sat. NH₄Cl (20 mL) and extracted with DCM (40 mL x 3). The combined organic layers were washed with brine
10 (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (solvent gradient: 0 - 80% EtOAc in petroleum ether) to give (*R*)-*N*-((*R*)-1-(2-(difluoromethyl)-3-(2-(difluoromethyl)pyridin-4-yl)-7-methylquinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (70 mg, 26%, first peak) and (*R*)-*N*-
15 ((*S*)-1-(2-(difluoromethyl)-3-(2-(difluoromethyl)pyridin-4-yl)-7-methylquinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (100 mg, 37%, second peak) both as yellow oil. First peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.85 - 8.82 (m, 1H), 8.73 (s, 1H), 7.94 - 7.70 (m, 4H), 7.26 - 6.91 (m, 2H), 5.89 - 5.83 (m, 1H), 5.30 - 5.21 (m, 1H), 2.59 (s, 3H), 1.63 (d, *J* = 6.8 Hz, 3H), 1.05 (s, 9H). MS: *m/z* 468.2 (M+H⁺). Second peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.85 - 8.80 (m, 1H), 8.75 (s, 1H), 7.93 - 7.69 (m, 4H), 7.22 - 6.93 (m, 2H), 5.59 - 5.53 (m, 1H), 5.26 - 5.21 (m, 1H), 2.58 (s, 3H), 1.63 (d, *J* = 6.8 Hz, 3H), 1.02 (s, 9H). MS: *m/z* 468.2 (M+H⁺).
20

Step 4 – Synthesis of (*S*)-1-(2-(difluoromethyl)-3-(2-(difluoromethyl)pyridin-4-yl)-7-methylquinolin-5-yl)ethanamine:

To a solution of (*R*)-*N*-((*S*)-1-(2-(difluoromethyl)-3-(2-(difluoromethyl)pyridin-4-yl)-7-methylquinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (70 mg, 150 μ mol) in acetonitrile (1
25 mL) was added dropwise HCl (12 M, 38 μ L). The mixture was stirred at room temperature for 0.5 h. The reaction mixture was concentrated under reduced pressure to remove acetonitrile. The mixture was poured into water (10 mL) and the mixture was adjusted to pH 8 with 4N NaHCO₃ solution. The aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10 mL x 3), dried with anhydrous Na₂SO₄, and filtered. The filtrate was
30 concentrated to give the title compound (50 mg, 92%) as a yellow solid that required no further purification. MS: *m/z* 364.0 (M+H⁺).

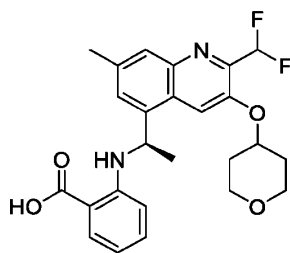
Step 5 – Synthesis of *tert*-butyl (*S*)-2-((1-(2-(difluoromethyl)-3-(2-(difluoromethyl)pyridin-4-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoate:

A mixture of (*S*)-1-(2-(difluoromethyl)-3-(2-(difluoromethyl)pyridin-4-yl)-7-methylquinolin-5-yl)ethanamine (50 mg, 125 μ mol), *tert*-butyl 2-iodobenzoate (46 mg, 150 μ mol), Xantphos (7 mg, 13 μ mol), Cs₂CO₃ (122 mg, 375 μ mol) and Pd₂(dba)₃ (11 mg, 12 μ mol) in dioxane (1 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 16 hr under N₂ atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure to remove dioxane. The residue was diluted with EtOAc (20 mL), and washed with H₂O (20 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether). to give the title compound (50 mg, 74%) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.90 - 8.81 (m, 2H), 8.25 - 8.17 (m, 1H), 7.92 - 7.88 (m, 2H), 7.82 - 7.75 (m, 2H), 7.57 (s, 1H), 7.22 - 6.94 (m, 3H), 6.58 - 6.49 (m, 1H), 6.42 (d, *J* = 8.8 Hz, 1H), 5.64 - 5.49 (m, 1H), 2.54 (s, 3H), 1.61 ((d, *J* = 6.4 Hz, 3H), 1.57 (s, 9H). MS: *m/z* 540.2 (M+H⁺).

Step 6 – Synthesis of (*S*)-2-((1-(2-(difluoromethyl)-3-(2-(difluoromethyl)pyridin-4-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid:

To a solution of *tert*-butyl (*S*)-2-((1-(2-(difluoromethyl)-3-(2-(difluoromethyl)pyridin-4-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoate (50 mg, 93 μ mol) in DCM (1 mL) was added TFA (768 mg, 6.73 mmol). The reaction mixture was stirred at room temperature for 16 h. The mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 60%-90% / 0.225% formic acid in water) to give the title compound (15 mg, 33%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.87 - 8.81 (m, 2H), 7.87 (s, 2H), 7.83 - 7.73 (m, 2H), 7.54 (s, 1H), 7.27 - 6.89 (m, 3H), 6.57 - 6.49 (m, 1H), 6.40 (d, *J* = 8.8 Hz, 1H), 5.59 - 5.52 (m, 1H), 2.48 (s, 3H), 1.58 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 484.2 (M+H⁺).

Example 42: (*R*)-2-((1-(2-(difluoromethyl)-7-methyl-3-((tetrahydro-2*H*-pyran-4-yl)oxy)quinolin-5-yl)ethyl)amino)benzoic acid (Compound 66)



Step 1 – Synthesis of 5-bromo-2,7-dimethyl-3-((tetrahydro-2H-pyran-4-yl)oxy)quinoline:

To a solution of 5-bromo-2,7-dimethyl-quinolin-3-ol (1 g, 3.97 mmol) and 4-bromotetrahydropyran (1.96 g, 11.90 mmol) in DMF (10 mL) was added Cs₂CO₃ (3.88 g, 11.90 mmol) and KI (659 mg, 3.97 mmol). The mixture was stirred at 120 °C for 5 h. After cooling to room temperature, the mixture was filtered, and the filtrate was quenched with water (30 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (20 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (1 g, 50%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.75 - 7.68 (m, 2H), 7.61 (s, 1H), 4.93 - 4.85 (m, 1H), 3.92 - 3.81 (m, 2H), 3.63 - 3.55 (m, 2H), 2.58 (s, 3H), 2.46 (s, 3H), 2.14 - 2.01 (m, 2H), 1.80 - 1.68 (m, 2H). MS: m/z 335.9 (M+H⁺).

Step 2 – Synthesis of 5-bromo-7-methyl-3-((tetrahydro-2H-pyran-4-yl)oxy)quinoline-2-carbaldehyde:

To a solution of 5-bromo-2,7-dimethyl-3-((tetrahydro-2H-pyran-4-yl)oxy) quinoline (1.2 g, 3.57 mmol) and in dioxane (12 mL) was added SeO₂ (479 mg, 4.32 mmol). The mixture was stirred at 80 °C for 1.5 h. After cooling to room temperature, the mixture was filtered, and the filtrate was quenched with water (30 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (20 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (1 g, 80%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 10.54 (s, 1H), 8.02 - 7.90 (m, 2H), 7.82 - 7.72 (m, 1H), 4.89 - 4.82 (m, 1H), 4.12 - 4.02 (m, 2H), 3.77 - 3.65 (m, 2H), 2.54 (s, 3H), 2.26 - 2.13 (m, 2H), 2.07 - 1.94 (m, 2H). MS: m/z 349.9 (M+H⁺).

Step 3 – Synthesis of 5-bromo-2-(difluoromethyl)-7-methyl-3-((tetrahydro-2H-pyran-4-yl)oxy)quinoline:

A mixture of 5-bromo-7-methyl-3-((tetrahydro-2H-pyran-4-yl)oxy)quinoline-2-carbaldehyde (1 g, 2.86 mmol) in DCM (10 mL) was added DAST (1.38 g, 8.57 mmol, 1.13 mL) at 0 °C, and then the mixture was stirred at room temperature for 1 h under N₂ atmosphere. The reaction mixture was quenched with aq. sat. NaHCO₃ (20 mL), extracted with DCM (20 mL x 3), the mixture solution was concentrated under reduced pressure to give a residue. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% EtOAc in petroleum ether) to give the title compound (570 mg, 54%) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.95 - 7.84 (m, 3H), 7.41 - 7.04 (m, 1H), 5.07 - 4.99 (m, 1H), 3.92 - 3.81 (m, 2H), 3.64 - 3.52 (m, 2H), 2.49 (s, 3H), 2.11 - 2.01 (m, 2H), 1.81 - 1.69 (m, 2H). MS: m/z 371.9 (M+H⁺).

Step 4 – Synthesis of 2-(difluoromethyl)-5-(1-ethoxyvinyl)-7-methyl-3-((tetrahydro-2H-pyran-4-yl)oxy)quinoline:

A mixture of 5-bromo-2-(difluoromethyl)-7-methyl-3-((tetrahydro-2H-pyran-4-yl)oxy)quinoline (570 mg, 1.53 mmol), tributyl(1-ethoxyvinyl)stannane (1.11 g, 3.06 mmol, 1.03 mL), Pd(dppf)Cl₂ (56 mg, 77 μmol) in dioxane (6 mL) was stirred at 90 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction was quenched with 10% KF solution (30 mL). The mixture was quenched with water (30 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated to give the title compound (500 mg, crude) as a yellow solid that required no further purification. MS: m/z 364.3 (M+H⁺).

Step 5 - Synthesis of 1-(2-(difluoromethyl)-7-methyl-3-((tetrahydro-2H-pyran-4-yl)oxy)quinolin-5-yl)ethan-1-one:

To a solution of 2-(difluoromethyl)-5-(1-ethoxyvinyl)-7-methyl-3-((tetrahydro-2H-pyran-4-yl)oxy)quinoline (500 mg, 1.38 mmol) was added HCl (2 mL, 2M). The reaction mixture was stirred at room temperature for 1 h. The mixture was quenched with sat. aq. NaHCO₃ (20 mL), extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (400 mg, 87%) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.72 (s, 1H), 8.23 (s,

1H), 8.05 (s, 1H), 7.40 - 7.06 (m, 1H), 4.88 - 4.77 (m, 1H), 3.95 - 3.80 (m, 2H), 3.65 - 3.50 (m, 2H), 2.74 (s, 3H), 2.56 (s, 3H), 2.13 - 2.01 (m, 2H), 1.82 - 1.67 (m, 2H). MS: m/z 336.0 (M+H⁺).

Step 6 – Synthesis of (*R,E*)-*N*-(1-(2-(difluoromethyl)-7-methyl-3-((tetrahydro-2*H*-pyran-4-yl)oxy)quinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide:

5 To a solution of 1-(2-(difluoromethyl)-7-methyl-3-((tetrahydro-2*H*-pyran-4-yl)oxy)quinolin-5-yl) ethan-1-one (400 mg, 1.19 mmol) in THF (4 mL) was added tetrakisopropoxytitanium (2.03 g, 7.16 mmol, 2.11 mL) and (*R*)-2-methylpropane-2-sulfinamide (1.45 g, 11.93 mmol). The mixture was stirred at 75 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the mixture was quenched with saturated NaHCO₃ (20 mL), extracted with
10 EtOAc (30 mL x 2). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (400 mg, 76%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.43 (s, 1H), 7.98 - 7.82 (m, 2H), 7.34 - 7.07 (m, 1H), 4.82 - 4.66 (m, 1H), 3.91 - 3.84 (m, 2H), 3.59 - 3.48 (m, 2H), 2.83 (s, 3H), 2.54 (s, 3H), 2.11 - 2.01 (m, 2H), 1.75 - 1.65 (m, 2H), 1.19 - 1.17 (m, 9H). MS: m/z 439.3 (M+H⁺).

Step 7 – Synthesis of (*R*)-*N*-((*R*)-1-(2-(difluoromethyl)-7-methyl-3-((tetrahydro-2*H*-pyran-4-yl)oxy)quinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide & (*R*)-*N*-((*S*)-1-(2-(difluoromethyl)-7-methyl-3-((tetrahydro-2*H*-pyran-4-yl)oxy)quinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide:

20 A mixture of (*R*)-*N*-((*R*)-1-(2-(difluoromethyl)-7-methyl-3-((tetrahydro-2*H*-pyran-4-yl)oxy)quinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (400 mg, 912 μmol), NaBH₄ (104 mg, 2.74 mmol) in THF (4 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at room temperature for 0.5 h under N₂ atmosphere. The reaction was quenched with
25 sat. aq. NH₄Cl (20 mL) and extracted with DCM (30 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 100% EtOAc in petroleum ether) to give (*R*)-*N*-((*R*)-1-(2-(difluoromethyl)-7-methyl-3-((tetrahydro-2*H*-pyran-4-yl)oxy)quinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (150 mg, 37%, first peak) and (*R*)-*N*-
30 ((*S*)-1-(2-(difluoromethyl)-7-methyl-3-((tetrahydro-2*H*-pyran-4-yl)oxy)quinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (98 mg, 24%, second peak) both as yellow oil. First peak: ¹H NMR

(400 MHz, DMSO-*d*₆) δ 8.18 (s, 1H), 7.75 (s, 1H), 7.61 (s, 1H), 7.37 - 7.05 (m, 1H), 5.79 - 5.73 (m, 1H), 5.20 - 5.09 (m, 1H), 5.08 - 5.00 (m, 1H), 3.92 - 3.82 (m, 2H), 3.62 - 3.53 (m, 2H), 2.51 - 2.51 (m, 3H), 2.10 - 2.00 (m, 2H), 1.80 - 1.67 (m, 2H), 1.59 (d, *J* = 6.8 Hz, 3H), 1.08 (s, 9H). MS: *m/z* 441.2(M+H⁺). Second peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.14 (s, 1H), 7.73 (s, 1H), 7.59 - 7.56 (m, 1H), 7.20 (s, 1H), 5.61 - 5.56 (m, 1H), 5.25 - 5.19 (m, 1H), 5.13 - 4.99 (m, 1H), 3.93 - 3.82 (m, 2H), 3.64 - 3.51 (m, 2H), 2.54 (s, 3H), 2.08 - 2.00 (m, 2H), 1.76 - 1.67 (m, 2H), 1.60 (d, *J* = 6.8 Hz, 3H), 1.09 (s, 9H). MS: *m/z* 441.2(M+H⁺).

Step 8 – Synthesis of (*R*)-1-(2-(difluoromethyl)-7-methyl-3-((tetrahydro-2*H*-pyran-4-yl)oxy)quinolin-5-yl)ethan-1-amine:

To a solution of (*R*)-*N*-((*R*)-1-(2-(difluoromethyl)-7-methyl-3-((tetrahydro-2*H*-pyran-4-yl)oxy)quinolin-5-yl)ethyl)-2-methylpropane-2-sulfonamide (150 mg, 341 μ mol) in acetonitrile (1.5 mL) was added dropwise HCl (12 M, 85 μ L). The mixture was stirred at room temperature for 0.5 h. The reaction mixture was concentrated under reduced pressure to remove acetonitrile. The mixture was added water (10 mL) and adjusted to pH 8 with sat. aq. NaHCO₃ solution. The aqueous phase was extracted with EtOAc (30 mL x 3). The combined organic phase was washed with brine (20 mL x 2), dried with anhydrous Na₂SO₄ and filtered. The filtrate was concentrated to give the title compound (106 mg, 93%) as a yellow solid that required no further purification. MS: *m/z* 337.2 (M+H⁺).

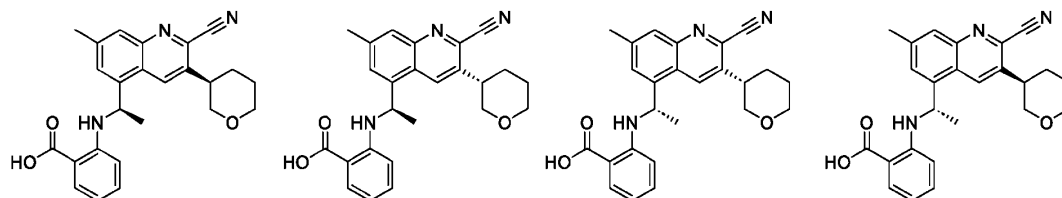
Step 9 – Synthesis of *tert*-butyl (*R*)-2-((1-(2-(difluoromethyl)-7-methyl-3-((tetrahydro-2*H*-pyran-4-yl)oxy)quinolin-5-yl)ethyl)amino)benzoate:

A mixture of (*R*)-1-(2-(difluoromethyl)-7-methyl-3-((tetrahydro-2*H*-pyran-4-yl)oxy)quinolin-5-yl)ethan-1-amine (106 mg, 315 μ mol), *tert*-butyl 2-iodobenzoate (115 mg, 378 μ mol), Xantphos (18 mg, 32 μ mol), Pd₂(dba)₃ (29 mg, 32 μ mol), and Cs₂CO₃ (308 mg, 945 μ mol) in dioxane (1 mL). The reaction mixture was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% EtOAc in petroleum ether) to give the title compound (120 mg, 74%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.15 - 8.11 (m, 2H), 7.79 - 7.71 (m, 2H), 7.47 (s, 1H), 7.37 - 7.06 (m, 2H), 6.62 - 6.48 (m, 2H), 5.59 - 5.45 (m, 1H), 5.00 - 4.91 (m, 1H), 3.89 - 3.80 (m, 2H), 3.56 - 3.41 (m, 2H), 2.43 (s, 3H), 2.01 - 1.91 (m, 2H), 1.75 - 1.67 (m, 2H), 1.60 (d, *J* = 6.4 Hz, 3H), 1.55 (s, 9H). MS: *m/z* 513.2 (M+H⁺).

Step 10 – Synthesis of (*R*)-2-((1-(2-(difluoromethyl)-7-methyl-3-((tetrahydro-2*H*-pyran-4-yl)oxy)quinolin-5-yl)ethyl)amino)benzoic acid:

To a mixture of *tert*-butyl (*R*)-2-((1-(2-(difluoromethyl)-7-methyl-3-((tetrahydro-2*H*-pyran-4-yl)oxy)quinolin-5-yl)ethyl)amino)benzoate (120 mg, 234 μ mol) in DCM (1 mL) was added TFA (789 mg, 6.92 mmol, 514 μ L). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 60% - 90% / 0.225% formic acid in water) to give the title compound (58.85 mg, 55%) as a white solid. ^1H NMR (400 MHz, DMSO-*d*₆) δ 12.99 - 12.54 (m, 1H), 8.43 (s, 1H), 8.16 (s, 1H), 7.83 - 7.79 (m, 1H), 7.72 (s, 1H), 7.48 (s, 1H), 7.36 - 7.06 (m, 2H), 6.56 - 6.46 (m, 2H), 5.53 - 5.46 (m, 1H), 5.01 - 4.94 (m, 1H), 3.88 - 3.81 (m, 2H), 3.56 - 3.46 (m, 2H), 2.42 (s, 3H), 2.04 - 1.94 (m, 2H), 1.74 - 1.63 (m, 2H), 1.63 - 1.57 (m, 3H) MS: *m/z* 457.4 (*M*+*H*⁺).

Example 43: 2-(((*R*)-1-(2-cyano-7-methyl-3-((*R*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid & 2-(((*R*)-1-(2-cyano-7-methyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid & 2-(((*S*)-1-(2-cyano-7-methyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid & 2-(((*S*)-1-(2-cyano-7-methyl-3-((*R*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (Compound 67, Compound 68, Compound 69, and Compound 70)

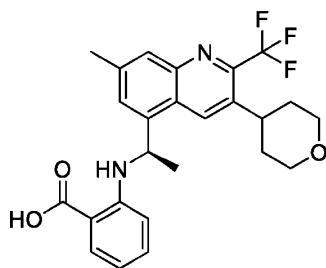


2-((1-(2-cyano-7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (92 mg, 221 μ mol) was separated by using chiral SFC (DAICEL CHIRALCEL OD (250mm*30mm,10 μ m); Supercritical CO₂ / EtOH+0.1% NH₃•H₂O = 60/40; 70 mL/min) to afford 2-(((*S*)-1-(2-cyano-7-methyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino) benzoic acid (10 mg, first peak), 2-(((1*R*)-1-(2-cyano-7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (30 mg, mixture, second peak and third peak, inseparable) and 2-(((*S*)-1-(2-cyano-7-methyl-3-((*R*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (10 mg, fourth peak) both as white solid. The mixture of 2-(((1*R*)-1-(2-cyano-7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (20 mg, 70 μ mol) was

separated by using chiral SFC (DAICEL CHIRALPAK AD (250mm*30mm,10um); Supercritical CO₂ / *i*-PrOH+0.1% NH₃•H₂O = 70/30; 70 mL/min) to afford 2-(((*R*)-1-(2-cyano-7-methyl-3-((*R*)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (7 mg, third peak) and 2-(((*R*)-1-(2-cyano-7-methyl-3-((*S*)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (9 mg, second peak). Absolute configuration was arbitrarily assigned to each enantiomer. Third peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.76 (s, 1H), 8.76 (s, 1H), 8.45 (d, *J* = 4.0 Hz, 1H), 7.85 - 7.76 (m, 2H), 7.60 (d, *J* = 1.2 Hz, 1H), 7.24 - 7.14 (m, 1H), 6.56 - 6.51 (m, 1H), 6.47 (d, *J* = 8.4 Hz, 1H), 5.62 - 5.47 (m, 1H), 3.99 - 3.88 (m, 2H), 3.57 - 3.46 (m, 2H), 3.27 - 3.22 (m, 1H), 2.47 (s, 3H), 2.10 - 1.89 (m, 2H), 1.76 - 1.67 (m, 2H), 1.61 (d, *J* = 6.8 Hz, 3H). MS: *m/z* 416.2 (M+H⁺).

Second peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.77 (s, 1H), 8.56 - 8.41 (m, 1H), 7.92 - 7.75 (m, 2H), 7.58 (d, *J* = 1.2 Hz, 1H), 7.28 - 7.11 (m, 1H), 6.58 - 6.51 (m, 1H), 6.44 (d, *J* = 8.4 Hz, 1H), 5.64 - 5.52 (m, 1H), 4.04 - 3.87 (m, 2H), 3.57 - 3.47 (m, 2H), 3.28 - 3.22 (m, 1H), 2.47 (s, 3H), 2.08 - 1.94 (m, 2H), 1.79 - 1.68 (m, 2H), 1.61 (d, *J* = 6.8 Hz, 3H). MS: *m/z* 416.2 (M+H⁺). First peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.20 - 12.28 (m, 1H), 8.76 (s, 1H), 8.44 (d, *J* = 5.2 Hz, 1H), 7.85 - 7.76 (m, 2H), 7.60 (d, *J* = 1.2 Hz, 1H), 7.24 - 7.16 (m, 1H), 6.57 - 6.51 (m, 1H), 6.50 - 6.45 (m, 1H), 5.61 - 5.51 (m, 1H), 4.00 - 3.87 (m, 2H), 3.57 - 3.50 (m, 1H), 3.50 - 3.42 (m, 1H), 3.26 - 3.21 (m, 1H), 2.48 - 2.46 (m, 3H), 2.08 - 1.89 (m, 2H), 1.75 - 1.67 (m, 2H), 1.61 (d, *J* = 6.8 Hz, 3H). MS: *m/z* 416.2 (M+H⁺). Fourth peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.76 (s, 1H), 8.76 (s, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 7.85 - 7.76 (m, 2H), 7.57 (d, *J* = 1.2 Hz, 1H), 7.22 - 7.15 (m, 1H), 6.58 - 6.50 (m, 1H), 6.44 (d, *J* = 8.4 Hz, 1H), 5.68 - 5.48 (m, 1H), 4.04 - 3.86 (m, 2H), 3.55 - 3.46 (m, 2H), 3.28 - 3.22 (m, 1H), 2.46 (s, 3H), 2.08 - 1.92 (m, 2H), 1.77 - 1.68 (m, 2H), 1.61 (d, *J* = 6.8 Hz, 3H). MS: *m/z* 416.2 (M+H⁺).

Example 44: (*R*)-2-((1-(7-methyl-3-(tetrahydro-2H-pyran-4-yl)-2-(trifluoromethyl)quinolin-5-yl)ethyl)amino)benzoic acid (Compound 71)



25

Step 1 – Synthesis of 5-bromo-2-chloro-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline:

A mixture of 5-bromo-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline 1-oxide (3.1 g, 9.62 mmol) in DCM (50 mL) at 0 °C, then POCl₃ (1.8 g, 12 mmol) was added dropwise to the rapidly stirring solution, followed by DMF (352 mg, 4.81 mmol). The mixture was stirred at room temperature for 16 h. The mixture was quenched with sat. aq. NaHCO₃ (30 mL). The resulting mixture was separated and the aqueous layers were extracted with DCM (30 mL x 2). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford the crude. The crude was purified by flash silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (2.4 g, 73%) as a white solid. ¹H NMR (400MHz, CDCl₃) δ 8.30 (s, 1H), 7.74 (s, 1H), 7.68 (s, 1H), 4.18 - 4.15 (m, 2H), 3.68 - 3.61 (m, 2H), 3.41 - 3.32 (m, 1H), 2.54 (s, 3H), 2.01 - 1.95 (m, 2H), 1.94 - 1.84 (m, 2H). MS: m/z 340.0 (M+H⁺).

Step 2 – Synthesis of 5-bromo-2-iodo-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline:

A mixture of 5-bromo-2-chloro-7-methyl-3-(tetrahydro-2H-pyran-4-yl) quinoline (2.4 g, 7.1 mmol), KI (17.6 g, 105.7 mmol) in MeCN (30 mL), then acetyl chloride (830 mg, 10.6 mmol) was dropwise at 0 °C, the mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the mixture was quenched with water (30 mL), extracted with EtOAc (60 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (2.46 g, 81%) as a white solid. ¹H NMR (400MHz, CDCl₃) δ 8.08 (s, 1H), 7.77 (s, 1H), 7.69 (s, 1H), 4.24 - 4.12 (m, 2H), 3.68 - 3.62 (m, 2H), 3.24 - 3.14 (m, 1H), 2.53 (s, 3H), 2.01 - 1.94 (m, 2H), 1.90-1.83 (m, 2H). MS: m/z 431.9 (M+H⁺).

Step 3 – Synthesis of 5-bromo-7-methyl-3-(tetrahydro-2H-pyran-4-yl)-2-(trifluoromethyl)quinoline:

A mixture of 5-bromo-2-iodo-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline (200 mg, 463 μmol), triethyl(trifluoromethyl)silane (171 mg, 926 μmol), KF (54 mg, 926 μmol), CuI (9 mg, 46 μmol) and 1,10-phenanthroline (8 mg, 46 μmol) in DMF (2 mL) was stirred at 60 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was quenched with

(30 mL), extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The crude residue was purified by flash silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (150 mg, 86%) as a white solid. ¹H NMR (400MHz, DMSO-*d*₆) δ 8.55 (s, 1H), 8.04 (s, 1H), 7.98 (s, 1H), 4.04 - 4.00 (m, 2H), 3.54 - 3.47 (m, 2H), 3.28 - 3.20 (m, 1H), 2.55 (s, 3H), 1.94 - 1.83 (m, 2H), 1.81 - 1.74 (m, 2H). MS: m/z 374.0 (M+H⁺).

Step 4 – Synthesis of 5-(1-ethoxyvinyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)-2-(trifluoromethyl)quinoline:

A mixture of 5-bromo-7-methyl-3-tetrahydropyran-4-yl-2-(trifluoromethyl)quinoline (150 mg, 401 μ mol), tributyl(1-ethoxyvinyl)stannane (290 mg, 802 μ mol) and Pd(dppf)Cl₂ (29 mg, 40 μ mol) in dioxane (3 mL), the mixture was stirred at 90 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the 10% KF aqueous solution (30 mL) was added to reaction mixture and stirred for 2 h. The aqueous layers were extracted with DCM (50 mL x 2). The combined organic layers were washed with brine (30 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to give the title compound (146 mg, crude) as yellow oil that required no further purification. MS: m/z 366.2 (M+H⁺).

Step 5 – Synthesis of 1-(7-methyl-3-(tetrahydro-2H-pyran-4-yl)-2-(trifluoromethyl)quinolin-5-yl)ethan-1-one:

A mixture of 5-(1-ethoxyvinyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)-2-(trifluoromethyl)quinoline (146 mg, 400 μ mol) in dioxane (5 mL) was added HCl (2 M, 2 mL), then the mixture was stirred at room temperature for 2 h. The reaction mixture was extracted with DCM (30 mL x 2). The combined organic layers were washed with brine (30 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude was purified by flash silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (110 mg, 82%) as a white solid. ¹H NMR (400MHz, DMSO-*d*₆) δ 9.28 (s, 1H), 8.32 - 8.30 (m, 1H), 8.14 (s, 1H), 4.03 - 3.99 (m, 2H), 3.53 - 3.46 (m, 2H), 3.23 - 3.18 (m, 1H), 2.78 (s, 3H), 2.61 (s, 3H), 1.83 - 1.72 (m, 4H). MS: m/z 338.1 (M+H⁺).

Step 6 – Synthesis of (R,E)-2-methyl-N-(1-(7-methyl-3-(tetrahydro-2H-pyran-4-yl)-2-(trifluoromethyl)quinolin-5-yl)ethylidene)propane-2-sulfinamide:

A mixture of 1-(7-methyl-3-(tetrahydro-2H-pyran-4-yl)-2-(trifluoromethyl)quinolin-5-yl)ethan-1-one (110 mg, 326 μ mol), (R)-2-methylpropane-2-sulfinamide (198 mg, 1.63 mmol,

5 SnCl_4), $\text{Ti}(i\text{-PrO})_4$ (278 mg, 978 μmol) in THF (3 mL), the mixture was stirred at 75 °C for 16 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was quenched with water (20 mL), filtrated and the filtrate was extracted with DCM (40 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to give the title compound (106 mg, 74%) as yellow oil. MS: m/z 441.1 ($\text{M}+\text{H}^+$).

Step 7 – Synthesis of (*R*)-2-methyl-*N*-((*R*)-1-(7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)-2-(trifluoromethyl)quinolin-5-yl)ethyl)propane-2-sulfonamide:

10 A solution of (*R,E*)-2-methyl-*N*-(1-(7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)-2-(trifluoromethyl)quinolin-5-yl)ethylidene)propane-2-sulfonamide (106 mg, 241 μmol) in THF (3 mL) was added NaBH_4 (27 mg, 722 μmol). The mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with sat. aq. NH_4Cl (20 mL) at 0°C, extracted with DCM (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give crude. The crude was purified by prep_TLC (petroleum ether / EtOA = 1:1) to give the title compound (60 mg, 56%) as yellow oil. ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ 8.83 (s, 1H), 7.83 (s, 1H), 7.72 (s, 1H), 5.87 (d, J = 5.6 Hz, 1H), 5.33 - 5.28 (m, 1H), 4.03 - 4.00 (m, 2H), 3.49 - 3.46 (m, 2H), 3.23 - 3.14 (m, 1H), 2.55 (s, 3H), 2.10 - 1.99 (m, 2H), 1.71 - 1.64 (m, 2H), 1.60 (d, J = 6.8 Hz, 3H), 1.05 (s, 9H). MS: m/z 443.1 ($\text{M}+\text{H}^+$).

Step 8 – Synthesis of (*R*)-1-(7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)-2-(trifluoromethyl)quinolin-5-yl)ethan-1-amine:

25 A solution of (*R*)-2-methyl-*N*-((*R*)-1-(7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)-2-(trifluoromethyl)quinolin-5-yl)ethyl)propane-2-sulfonamide (60 mg, 136 μmol) in MeOH (2 mL) was added HCl (12 M, 34 μL). The mixture was stirred at room temperature for 0.5 h. The mixture was quenched with sat. aq. NaHCO_3 (30 mL), then extracted with DCM (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give the title compound (45 mg, crude) as yellow oil. MS: m/z 339.1 ($\text{M}+\text{H}^+$).

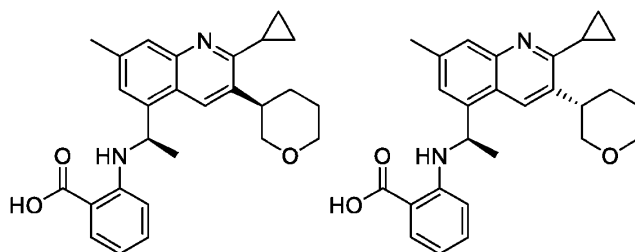
Step 9 – Synthesis of *tert*-butyl (*R*)-2-((1-(7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)-2-(trifluoromethyl)quinolin-5-yl)ethyl)amino)benzoate:

A mixture of (*R*)-1-(7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)-2-(trifluoromethyl)quinolin-5-yl)ethan-1-amine (45 mg, 133 μ mol), *tert*-butyl 2-iodobenzoate (81 mg, 266 μ mol), Pd₂(dba)₃ (12 mg, 13 μ mol), Xantphos (15 mg, 27 μ mol), Cs₂CO₃ (130 mg, 399 μ mol) in dioxane (2 mL), the mixture was stirred at 110 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was quenched with water (10 mL), extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by flash silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (53 mg, 77%) as yellow oil. MS: *m/z* 515.3 (M+H⁺).

Step 10 – Synthesis of (*R*)-2-((1-(7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)-2-(trifluoromethyl)quinolin-5-yl)ethyl)amino)benzoic acid:

A solution of *tert*-butyl (*R*)-2-((1-(7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)-2-(trifluoromethyl)quinolin-5-yl)ethyl)amino)benzoate (53 mg, 103 μ mol) in DCM (3 mL) was added TFA (1 mL), the mixture was stirred at 40 °C for 16 h. After cooling to room temperature, the mixture was concentrated in vacuo. The residue was purified by reverse phase chromatography (acetonitrile 27% - 57% / 0.05% NH₃•H₂O + 10 mM NH₄HCO₃ in water) to give the title compound (27 mg, 57%) as white solid. ¹H NMR (400MHz, DMSO-*d*₆) δ 8.90 (s, 1H), 8.80 - 8.65 (s, 1H), 7.83 - 7.79 (m, 2H), 7.56 (s, 1H), 7.15 - 7.11 (m, 1H), 6.52 - 6.48 (m, 1H), 6.45 (d, *J* = 8.4 Hz, 1H), 5.64 (d, *J* = 5.2 Hz, 1H), 4.04 - 3.98 (m, 2H), 3.51 - 3.46 (m, 2H), 3.20 - 3.15 (m, 1H), 2.46 (s, 3H), 2.08 - 1.98 (m, 2H), 1.72 - 1.66 (m, 2H), 1.60 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 459.1 (M+H⁺).

Example 45: 2-(((*R*)-1-(2-cyclopropyl-7-methyl-3-((*R*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid & 2-(((*R*)-1-(2-cyclopropyl-7-methyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (Compound 72 and Compound 73)



Step 1 - Synthesis of *N*-methoxy-*N*-methyl-2-(tetrahydro-2*H*-pyran-3-yl)acetamide:

A mixture of 2-tetrahydropyran-3-ylacetic acid (5.1 g, 35.4 mmol), *N*-methoxymethanamine (4.14 g, 42.5 mmol), HATU (16.1 g, 42.5 mmol) in DMF (100 mL), then DIEA (13.72 g, 106.13 mmol, 18.49 mL) was added slowly under 0 °C. The mixture was stirred at room temperature for 16 h under N₂ atmosphere. The reaction mixture was quenched with water (50 mL), extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (30 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give crude. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (5.6 g, 85%) as colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 3.90 - 3.79 (m, 2H), 3.67 (s, 3H), 3.45 - 3.38 (m, 1H), 3.20 - 3.14 (m, 4H), 2.34 - 2.26 (m, 2H), 2.19 - 2.13 (m, 1H), 1.93 - 1.86 (m, 1H), 1.65 - 1.58 (m, 2H), 1.26 - 1.20 (m, 1H).

Step 2 – Synthesis of 1-cyclopropyl-2-(tetrahydro-2*H*-pyran-3-yl)ethan-1-one:

A solution of *N*-methoxy-*N*-methyl-2-(tetrahydro-2*H*-pyran-3-yl)acetamide (5.6 g, 22.43 mmol) in THF (80 mL), then bromo(cyclopropyl)magnesium (89.72 mL, 0.5 M) was added slowly under 0 °C under N₂ atmosphere. The reaction mixture was stirred at room temperature for 2 h under N₂ atmosphere. The reaction mixture was quenched with water (50 mL), extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (30 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give crude. The crude was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (4.1 g, 81%) as colorless oil. ¹H NMR (400MHz, CDCl₃) δ 3.84 - 3.80 (m, 2H), 3.44 - 3.37 (m, 1H), 3.15-3.10 (m, 1H), 2.50 - 2.34 (m, 2H), 2.20 - 2.16 (m, 1H), 1.94 - 1.88 (m, 1H), 1.88 - 1.82 (m, 1H), 1.65 - 1.57 (m, 2H), 1.28 - 1.19 (m, 1H), 1.01 - 0.99 (m, 2H), 0.88 - 0.83 (m, 2H).

Step 3 – Synthesis of 5-bromo-2-cyclopropyl-7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinoline:

A mixture of 2-amino-6-bromo-4-methyl-benzaldehyde (2.1 g, 9.9 mmol), 1-cyclopropyl-2-(tetrahydro-2*H*-pyran-3-yl)ethan-1-one (2 g, 11.9 mmol) and NaOH (792 mg, 19.8 mmol) in *n*-BuOH (40 mL) and H₂O (4 mL), the reaction mixture was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the mixture was concentrated under reduced pressure, then diluted with water (20 mL), extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (20 mL x 3), dried over anhydrous Na₂SO₄, filtered and

concentrated in vacuum to give crude. The crude was purified by reverse phase chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (1.3 g, 37%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.14 (s, 1H), 7.67 (s, 1H), 7.55 (s, 1H), 4.23 - 4.18 (m, 1H), 4.11 - 4.06 (m, 1H), 3.61 - 3.55 (m, 1H), 3.51 - 3.42 (m, 2H), 2.49 (s, 3H), 2.44 - 2.38 (m, 1H), 2.23 - 2.17 (m, 1H), 2.01 - 1.89 (m, 2H), 1.87 - 1.81 (m, 1H), 1.33 - 1.23 (m, 2H), 1.11 - 1.05 (m, 2H). MS: m/z 346.2 (M+H⁺).

Step 4 – Synthesis of 2-cyclopropyl-5-(1-ethoxyvinyl)-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinoline:

A mixture of 5-bromo-2-cyclopropyl-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinoline (1.26 g, 3.6 mmol), tributyl(1-ethoxyvinyl)stannane (2.6 g, 7.3 mmol) and Pd(dppf)Cl₂ (266 mg, 364 μmol) in dioxane (15 mL), then the mixture was stirred at 90 °C for 16 h under N₂ atmosphere. After cooling to room temperature, 10% KF solution (30 mL) was added and stirred for 2 h. The aqueous layers were extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to give the title compound (1.23 g, crude) as brown oil. MS: m/z 338.1 (M+H⁺).

Step 5 – Synthesis of 1-(2-cyclopropyl-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethan-1-one:

A solution of 2-cyclopropyl-5-(1-ethoxyvinyl)-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinoline (1.23 g, 3.6 mmol), HCl (2 M, 5 mL) in dioxane (5 mL), then the mixture was stirred at room temperature for 0.5 h. The reaction mixture was diluted with water (20 mL), extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give crude. The crude was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (1.1 g, 97%) as yellow oil. ¹H NMR (400MHz, CDCl₃) δ 8.93 (s, 1H), 7.88 (s, 1H), 7.79 (d, J = 1.2 Hz, 1H), 4.21 - 4.16 (m, 1H), 4.08 - 4.06 (m, 1H), 3.61 - 3.39 (m, 4H), 2.75 (s, 3H), 2.56 (s, 3H), 2.44 - 2.37 (m, 1H), 2.20 - 2.13 (m, 1H), 2.06 - 1.79 (m, 4H), 1.08 - 1.03 (m, 2H). MS: m/z 310.1 (M+H⁺).

Step 6 – Synthesis of (R)-N-((E)-1-(2-cyclopropyl-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide:

A mixture of 1-(2-cyclopropyl-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethan-1-one (500 mg, 1.6 mmol), (R)-2-methylpropane-2-sulfinamide (979 mg, 8.01 mmol),

Ti(*i*-PrO)₄ (1.4 g, 4.85 mmol) in THF (20 mL), the mixture was stirred for 16 h at 75 °C. After cooling to room temperature, the reaction mixture was quenched with H₂O (20 mL), then filtered, the filtrate was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give crude. The crude was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (315 mg, 47%) as yellow oil. ¹H NMR (400MHz, CDCl₃) δ 8.41 (s, 1H), 7.79-7.78 (m, 1H), 7.38 (s, 1H), 4.17 (d, J = 10.8 Hz, 1H), 4.06 (d, J = 10.0 Hz, 1H), 3.50 (d, J = 10.4 Hz, 2H), 3.36 (d, J = 2.8 Hz, 1H), 2.88 (s, 2H), 2.53 (s, 3H), 2.43 - 2.36 (m, 1H), 2.15 - 2.05 (m, 1H), 1.92 - 1.78 (m, 3H), 1.32 (s, 8H), 1.27 - 1.25 (m, 1H), 1.21 (s, 2H), 1.10 - 1.04 (m, 2H). MS: m/z 413.1 (M+H⁺).

Step 7 – Synthesis of (*R*)-*N*-((1*R*)-1-(2-cyclopropyl-7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide & (*R*)-*N*-((1*S*)-1-(2-cyclopropyl-7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide:

A solution of (*R*)-*N*-((*E*)-1-(2-cyclopropyl-7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide (315 mg, 764 μmol,) in THF (5 mL) was added NaBH₄ (87 mg, 2.30 mmol). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with H₂O (15 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (20 mL x 3) dried over with Na₂SO₄, filtered and concentrated under reduced pressure to give crude. The crude was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give (*R*)-*N*-((1*R*)-1-(2-cyclopropyl-7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (170 mg, 54%) and (*R*)-*N*-((1*S*)-1-(2-cyclopropyl-7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (80 mg, 25%) both as yellow oil. MS: m/z 415.1 (M+H⁺).

Step 8 – Synthesis of (1*R*)-1-(2-cyclopropyl-7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethan-1-amine:

A solution of (*R*)-*N*-((1*R*)-1-(2-cyclopropyl-7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (170 mg, 410 μmol) in MeOH (5 mL) was added HCl (12 M, 103 μL). The mixture was stirred at room temperature for 0.5 h. The mixture was quenched with sat. aq. NaHCO₃ (10 mL), then extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (15 mL x 3), dried over anhydrous Na₂SO₄,

filtered and concentrated in vacuum to give the title compound (127 mg, crude) as yellow oil. ¹H NMR (400MHz, CDCl₃) δ 8.15 (s, 1H), 7.62 (s, 1H), 7.41 (s, 1H), 4.90 - 4.88 (m, 1H), 4.23 - 4.18 (m, 1H), 4.10 - 4.03 (m, 1H), 3.61-3.55 (m, 1H), 3.52 - 3.43 (m, 2H), 2.50 (s, 3H), 2.42 - 2.35 (m, 1H), 2.21 - 2.15 (m, 1H), 1.84 - 1.81 (m, 1H), 1.55 (d, J = 6.4 Hz, 3H), 1.35 - 1.18 (m, 6H), 1.07 - 1.01 (m, 2H). MS: m/z 310.2 (M+H⁺).

Step 9 – Synthesis of *tert*-butyl 2-(((1*R*)-1-(2-cyclopropyl-7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate:

To a mixture of (1*R*)-1-(2-cyclopropyl-7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethan-1-amine (127 mg, 410 μmol), *tert*-butyl 2-iodobenzoate (249 mg, 818 μmol), Pd₂(dba)₃ (38 mg, 41 μmol), Xantphos (48 g, 82 μmol), Cs₂CO₃ (400 mg, 1.23 mmol) was added in dioxane (3 mL), then the mixture was stirred at 110 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was diluted with water (15 mL), extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (15 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give crude. The crude was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (190 mg, 95%) as yellow oil. MS: m/z 487.1 (M+H⁺).

Step 10 – Synthesis of 2-(((1*R*)-1-(2-cyclopropyl-7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid:

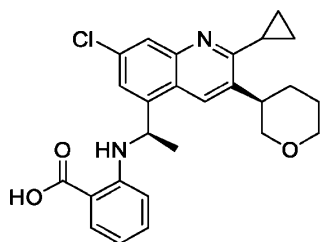
A solution of *tert*-butyl 2-(((1*R*)-1-(2-cyclopropyl-7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate (150 mg, 308 μmol) in DCM (3 mL) was added TFA (1 mL), the mixture was stirred at 40 °C for 16 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The residue was purified by reverse phase chromatography (acetonitrile 45% - 75% / 0.225% formic acid in water) to give the title compound (90 mg, 68%) as a yellow solid. MS: m/z 431.2 (M+H⁺).

Step 11 – Synthesis of 2-(((*R*)-1-(2-cyclopropyl-7-methyl-3-((*R*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid & 2-(((*R*)-1-(2-cyclopropyl-7-methyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid:

2-(((1*R*)-1-(2-cyclopropyl-7-methyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino) benzoic acid (90 mg, 210 μmol) was purified by using chiral SFC (DAICEL CHIRALPAK IC (250mm*30mm,10um); Supercritical CO₂ / *i*-PrOH + 0.1% NH₃•H₂O = 60/40; 80 mL/min) to afford 2-(((*R*)-1-(2-cyclopropyl-7-methyl-3-((*R*)-tetrahydro-2*H*-pyran-3-

yl)quinolin-5-yl)ethyl)amino)benzoic (22.6 mg, first peak) and 2-(((*R*)-1-(2-cyclopropyl-7-methyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (18 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. First peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.72 (s, 1H), 8.40 (d, *J* = 5.6 Hz, 1H), 8.30 (s, 1H), 7.82 - 7.78 (m, 1H), 7.49 (s, 1H), 7.30 (s, 1H), 7.23 - 7.17 (m, 1H), 6.55 - 6.49 (m, 2H), 5.43 - 5.36 (m, 1H), 4.00 - 3.95 (m, 1H), 3.94 - 3.89 (m, 1H), 3.46 - 3.39 (m, 3H), 2.46 - 2.42 (m, 1H), 2.39 (s, 3H), 2.04 - 1.99 (m, 1H), 1.89 - 1.81 (m, 1H), 1.77 - 1.66 (m, 2H), 1.61 (d, *J* = 6.8 Hz, 3H), 1.16 - 1.11 (m, 1H), 1.10 - 1.05 (m, 1H), 1.02 - 0.99 (m, 2H). MS: *m/z* 431.2 (*M*+*H*⁺). Second peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.71 (s, 1H), 8.40 (d, *J* = 5.6 Hz, 1H), 8.28 (s, 1H), 7.81 - 7.79 (m, 1H), 7.48 (s, 1H), 7.28 (s, 1H), 7.22 - 7.17 (m, 1H), 6.55 - 6.48 (m, 2H), 5.45 - 5.39 (m, 1H), 3.99 - 3.93 (m, 1H), 3.92 - 3.89 (m, 1H), 3.46 - 3.40 (m, 3H), 2.46 - 2.42 (m, 1H), 2.39 (s, 3H), 2.03 - 1.97 (m, 1H), 1.92 - 1.83 (m, 1H), 1.77 - 1.68 (m, 2H), 1.60 (d, *J* = 6.4 Hz, 3H), 1.13 - 1.08 (m, 1H), 1.07 - 1.05 (m, 1H), 1.04 - 0.99 (m, 2H). MS: *m/z* 431.2 (*M*+*H*⁺).

Example 46: 2-(((*R*)-1-(7-chloro-2-cyclopropyl-3-((*R*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (Compound 74)



Step 1 – Synthesis of 2-(2,6-dibromo-4-chloro-phenyl)-1,3-dioxolane:

A mixture of 2,6-dibromo-4-chloro-benzaldehyde (24 g, 80.44 mmol) (prepared according to the procedure in WO2021144439), ethylene glycol (11.5 g, 185.01 mmol), TsOH•H₂O (7.7 g, 40.22 mmol) in toluene (500 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 140 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was added NaOH (1M, 50 mL), and then diluted with water (200 mL) and extracted with EtOAc (300 mL x 3). The combined organic layers were washed with brine (500 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with petroleum ether at 0 °C for 30 min to give the title compound

(15 g, 54%) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.88 (s, 2H), 6.21 (s, 1H), 4.24 - 4.19 (m, 2H), 4.03 - 3.99 (m, 2H).

Step 2 – Synthesis of *N*-(3-bromo-5-chloro-2-(1,3-dioxolan-2-yl)phenyl)-1,1-diphenylmethanimine:

5 A mixture of 2-(2,6-dibromo-4-chloro-phenyl)-1,3-dioxolane (13 g, 37.97 mmol), diphenylmethanimine (6.9 g, 37.97 mmol), Pd(OAc)₂ (426 mg, 1.90 mmol), BINAP (2.36 g, 3.80 mmol) and Cs₂CO₃ (30.93 g, 94.92 mmol) in toluene (200 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 80 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was diluted with water (200 mL) and extracted with
10 EtOAc (300 mL x 3). The combined organic layers were washed with brine (300 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with petroleum ether (50 mL) at 0 °C for 30 min to give the title compound (13.5 g, 80%) as a yellow solid. MS: m/z 442.1 (M+H⁺).

Step 3 – Synthesis of 2-amino-6-bromo-4-chloro-benzaldehyde:

15 A mixture of *N*-(3-bromo-5-chloro-2-(1,3-dioxolan-2-yl)phenyl)-1,1-diphenylmethanimine (13.5 g, 30.49 mmol), HCl (1 M, 30 mL) in THF (200 mL) was degassed, and then the mixture was stirred at 80 °C for 2 h. After cooling to room temperature, the reaction mixture was added NaOH (1M, 30 mL), and then diluted with water (100 mL) and extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (300 mL), dried over
20 Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (5 g, 70%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.17 (s, 1H), 7.80 (s, 2H), 6.91 (d, *J* = 2.0 Hz, 1H), 6.88 (d, *J* = 1.6 Hz, 1H).

Step 4 - Synthesis of 5-bromo-7-chloro-2-cyclopropyl-3-tetrahydropyran-3-yl-quinoline:

25 A mixture of 2-amino-6-bromo-4-chloro-benzaldehyde (3.4 g, 7.13 mmol), 1-cyclopropyl-2-tetrahydropyran-3-yl-ethanone (800 mg, 4.76 mmol), NaOH (380 mg, 9.51 mmol) in *n*-BuOH (40 mL) and water (4 mL) was stirred at 100 °C for 1 h. After cooling to room temperature, the combined organic layers were washed with HCl (1 M, 10 mL), then extracted with EtOAc (50 mL
30 x 3), dried over Na₂SO₄, filtered and concentrated. The crude residue was purified by silica gel

chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (587 mg, 34%) as a yellow solid. MS: m/z 366.1 ($M+H^+$).

Step 5 - Synthesis of 1-(7-chloro-2-cyclopropyl-3-tetrahydropyran-3-yl-5-quinolyl)ethanone:

5 A mixture of 5-bromo-7-chloro-2-cyclopropyl-3-tetrahydropyran-3-yl-quinoline (586 mg, 1.60 mmol), tributyl(1-ethoxyvinyl)stannane (635 mg, 1.76 mmol), Pd(dppf)Cl₂ (117 mg, 160 μ mol) in dioxane (20 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 90 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was added HCl (1 M, 10 mL) and stirred at room temperature for 0.5 h. The reaction was
10 quenched with 10% KF solution (30 mL). The mixture was filtered and the filtrate was extracted with EtOAc (50 mL) and H₂O (20 mL). The organic layer was washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (345 mg, 66%) as a yellow solid. MS: m/z 330.1 ($M+H^+$).

15 **Step 6 - Synthesis of (R,E)-N-(1-(7-chloro-2-cyclopropyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide:**

A mixture of 1-(7-chloro-2-cyclopropyl-3-tetrahydropyran-3-yl-5-quinolyl)ethanone (198 mg, 600 μ mol), (R)-2-methylpropane-2-sulfinamide (728 mg, 6.00 mmol) and Ti(*i*-PrO)₄ (1.02 g, 3.60 mmol) in THF (20 mL) was degassed and purged with N₂ for 3 times, and then the mixture
20 was stirred at 75 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction was added water (10 mL) and filtered, then extracted with DCM (20 mL x 3). The organics were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (143 mg, 55%) as yellow oil. MS: m/z 433.1 ($M+H^+$).

25 **Step 7 – Synthesis of (R)-N-((1R)-1-(7-chloro-2-cyclopropyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide and (R)-N-[(1S)-1-(7-chloro-2-cyclopropyl-3-tetrahydro-2H-pyran-3-yl-5-quinolyl)ethyl]-2-methyl-propane-2-sulfinamide:**

A mixture of (R,E)-N-(1-(7-chloro-2-cyclopropyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide (143 mg, 330 μ mol) in THF (5 mL) was added
30 NaBH₄ (37 mg, 991 μ mol) at 0 °C, and the mixture was stirred at room temperature for 1 h. The

reaction was quenched with NH₄Cl (10 mL), extracted with DCM (20 mL x 3). The organics were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the (R)-N-(((1R)-1-(7-chloro-2-cyclopropyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)-2-methylpropane-2-sulfonamide (121 mg, 84%, first peak) and (R)-N-(((1S)-1-(7-chloro-2-cyclopropyl-3-(tetrahydro-2H-pyran-3-yl)-5-quinolyl)ethyl)-2-methylpropane-2-sulfonamide (39 mg, 27%, second peak) both as yellow solid. MS: m/z 435.1 (M+H⁺).

Step 8 – Synthesis of (1R)-1-(7-chloro-2-cyclopropyl-3-(tetrahydropyran-3-yl-5-quinolyl)ethanamine:

A mixture of (R)-N-(((1R)-1-(7-chloro-2-cyclopropyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)-2-methylpropane-2-sulfonamide (121 mg, 278 μmol) in MeOH (5 mL) was added HCl (12 M, 70 μL), and then the mixture was stirred at room temperature for 0.5 h. The reaction was quenched with sat. NaHCO₃ (10 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to give the title compound (83 mg, crude) as yellow oil that required no further purification. MS: m/z 331.1 (M+H⁺).

Step 9 – Synthesis of tert-butyl 2-(((1R)-1-(7-chloro-2-cyclopropyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate:

A mixture of (1R)-1-(7-chloro-2-cyclopropyl-3-(tetrahydropyran-3-yl-5-quinolyl)ethanamine (83 mg, 251 μmol), tert-butyl 2-iodobenzoate (153 mg, 502 μmol), Pd₂(dba)₃ (23 mg, 25 μmol), Xantphos (29 mg, 50 μmol) and Cs₂CO₃ (245 mg, 753 μmol) in dioxane (3 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The filtrate was concentrated to give a crude product. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (100 mg, 79%) as yellow oil. MS: m/z 507.2 (M+H⁺).

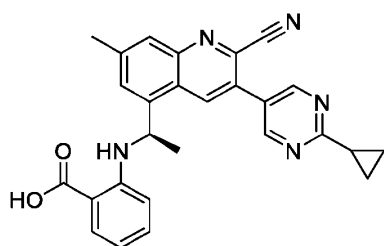
Step 10 – Synthesis of tert-butyl 2-(((R)-1-(7-chloro-2-cyclopropyl-3-((R)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate and tert-butyl 2-(((R)-1-(7-chloro-2-cyclopropyl-3-((S)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate:

tert-butyl 2-(((1*R*)-1-(7-chloro-2-cyclopropyl-3-(tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate (174 mg, 343 μ mol) was separated by using chiral SFC (DAICEL CHIRALPAK AD-3 (250mm*30mm,10 μ m); Supercritical CO₂ / EtOH+0.05% DEA = 40/60; 60 mL/min) to afford *tert*-butyl 2-(((*R*)-1-(7-chloro-2-cyclopropyl-3-((*R*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate (47 mg, first peak) and *tert*-butyl 2-(((*R*)-1-(7-chloro-2-cyclopropyl-3-((*S*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino) benzoate (52 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. MS: m/z 507.3 ($M+H^+$).

Step 11 – Synthesis of 2-(((*R*)-1-(7-chloro-2-cyclopropyl-3-((*R*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid:

A mixture of *tert*-butyl 2-(((*R*)-1-(7-chloro-2-cyclopropyl-3-((*R*)-tetrahydro-2*H*-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoate (47 mg, 93 μ mol) in DCM (3 mL) was added TFA (1.54 g, 13.46 mmol, 1 mL), and then the mixture was stirred at 40 °C for 16 h. After cooling to room temperature, the reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 75% - 100% / 0.225% formic acid in water) to give the title compound (26 mg, 62%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.81 (s, 1H), 8.44 - 8.37 (m, 2H), 7.84 - 7.81 (m, 1H), 7.72 (d, J = 1.6 Hz, 1H), 7.36 (d, J = 2.0 Hz, 1H), 7.23 - 7.17 (m, 1H), 6.58 - 6.54 (m, 1H), 6.43 (d, J = 8.4 Hz, 1H), 5.56 - 5.47 (m, 1H), 4.04 - 3.90 (m, 2H), 3.51 - 3.47 (m, 2H), 3.45 - 3.40 (m, 2H), 2.06 - 1.89 (m, 2H), 1.80 - 1.69 (m, 2H), 1.61 (d, J = 6.4 Hz, 3H), 1.29 - 1.20 (m, 1H), 1.20 - 1.03 (m, 4H). MS: m/z 451.2 ($M+H^+$).

Example 47: (*R*)-2-((1-(2-cyano-3-(2-cyclopropylpyrimidin-5-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid (Compound 75)



Step1 – Synthesis of 5-acetyl-3-(2-cyclopropylpyrimidin-5-yl)-7-methylquinoline-2-carbonitrile:

A mixture of (5-acetyl-2-cyano-7-methyl-3-quinolyl) trifluoromethanesulfonate (500 mg, 1.39 mmol), 2-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (411 mg, 1.67 mmol), Pd(PPh₃)₄ (81 mg, 70 μmol), K₂CO₃ (578 mg, 4.17 mmol) in dioxane (5 mL) and H₂O (0.5 mL) was stirred at 100 °C for 16 h under N₂ atmosphere. The reaction was quenched with water (20 mL). The mixture was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL x 2), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (392 mg, 86%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.20 (s, 1H), 9.00 (s, 2H), 8.39 (s, 1H), 8.21 (s, 1H), 2.78 (s, 3H), 2.66 (s, 3H), 2.38 - 2.31 (m, 1H), 1.18 - 1.11 (m, 4H). MS: m/z 329.1 (M+H⁺).

Step 2 – Synthesis of (*R,E*)-*N*-(1-(2-cyano-3-(2-cyclopropylpyrimidin-5-yl)-7-methylquinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide:

A mixture of 5-acetyl-3-(2-cyclopropylpyrimidin-5-yl)-7-methylquinoline-2-carbonitrile (300 mg, 914 μmol), (*R*)-2-methylpropane-2-sulfinamide (1.11 g, 9 mmol), Ti(*Oi*-Pr)₄ (1.56 g, 5 mmol, 1.62 mL) in THF (8 mL) was stirred at 75 °C for 16 h under N₂ atmosphere. The reaction was quenched with sat. aq. NaHCO₃ (10 mL). The mixture was extracted with DCM (30 mL x 3). The combined organic layers were washed with brine (30 mL x 2), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give the title compound (250 mg, 63%) as a white solid that required no further purification. MS: m/z 432.1 (M+H⁺).

Step 3 – Synthesis of (*R*)-*N*-((*R*)-1-(2-cyano-3-(2-cyclopropylpyrimidin-5-yl)-7-methylquinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide:

A mixture of (*R,E*)-*N*-(1-(2-cyano-3-(2-cyclopropylpyrimidin-5-yl)-7-methylquinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide (250 mg, 579 μmol), NaBH₄ (22 mg, 579 μmol) in THF (8 mL) was stirred at room temperature for 2 h. The reaction was quenched with sat. aq. NH₄Cl (10 mL). The mixture was extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by prep_TLC (petroleum ether /EtOAc = 1:1) to give the title compound (45 mg, 18%) as yellow solid. MS: m/z 456.1 (M+Na⁺).

Step 4 – Synthesis of (*R*)-5-(1-aminoethyl)-3-(2-cyclopropylpyrimidin-5-yl)-7-methylquinoline-2-carbonitrile:

A mixture of (*R*)-*N*-((*R*)-1-(2-cyano-3-(2-cyclopropylpyrimidin-5-yl)-7-methylquinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (45 mg, 104 μ mol) in MeOH (3 mL) was added HCl (12 M, 30 μ L) and the mixture was stirred at room temperature for 2 h. The mixture was diluted with water (10 mL), extracted with EtOAc (20 mL x 2). The combined organic layers were washed with
5 brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give the title compound (30 mg, 88%) as a white solid that required no further purification. MS: m/z 330.1 (M+H⁺).

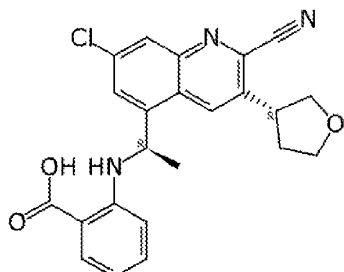
Step 5 - Synthesis of *tert*-butyl (*R*)-6-chloro-3-((1-(2-cyano-3-(2-cyclopropylpyrimidin-5-yl)-7-methylquinolin-5-yl)ethyl)amino)picolinate:

10 A mixture of (*R*)-5-(1-aminoethyl)-3-(2-cyclopropylpyrimidin-5-yl)-7-methylquinoline-2-carbonitrile (30 mg, 91 μ mol), *tert*-butyl 3-bromo-6-chloropicolinate (53 mg, 182 μ mol), Xantphos (21 mg, 36 μ mol), Cs₂CO₃ (89 mg, 273 μ mol), Pd₂(dba)₃ (17 mg, 18 μ mol) in dioxane (2 mL) was stirred at 100 °C for 16 h under N₂ atmosphere. The reaction was quenched with water (20 mL). The mixture was extracted with EtOAc (20 mL x 2). The combined organic layers were washed
15 with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by prep_TLC (petroleum ether / Ethyl acetate = 5:1) to give the title compound (40 mg, 54%) as a yellow solid. MS: m/z 541.1 (M+H⁺).

Step 6 – Synthesis of (*R*)-6-chloro-3-((1-(2-cyano-3-(2-cyclopropylpyrimidin-5-yl)-7-methylquinolin-5-yl)ethyl)amino)picolinic acid:

20 A mixture of *tert*-butyl (*R*)-6-chloro-3-((1-(2-cyano-3-(2-cyclopropylpyrimidin-5-yl)-7-methylquinolin-5-yl)ethyl)amino)picolinate (40 mg, 74 μ mol) in DCM (1.5 mL) was added TFA (767 mg, 6.73 mmol, 0.5 mL), the mixture was stirred at room temperature for 16 h. The reaction was quenched with water (10 mL). The mixture was extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered
25 and concentrated in vacuo. The resulting residue was purified by reverse phase chromatography (acetonitrile 58% - 88% / 0.225% formic acid in water) to give the title compound (9.32 mg, 26%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.14 (s, 1H), 9.11 (s, 2H), 9.09 (s, 1H), 8.45 (d, *J* = 6.4 Hz, 1H), 7.90 (s, 1H), 7.60 (s, 1H), 7.29 (d, *J* = 9.2 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 5.71 - 5.63 (m, 1H), 2.50 (s, 3H), 2.37 - 2.31 (m, 1H), 1.61 (d, *J* = 6.4 Hz, 3H), 1.20 - 1.09 (m,
30 4H). MS: m/z 485.1 (M+H⁺).

Example 48: 2-(((*R*)-1-(7-chloro-2-cyano-3-((*R*)-tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (Compound 425)



Step 1 - Synthesis of 1,3-dibromo-5-chloro-2-iodobenzene:

5 A mixture of 2,6-dibromo-4-chloro-aniline (100 g, 350.43 mmol, 1 *eq*), CuI (68.0 g, 357.05 mmol, 1.02 *eq*), *t*-BuONO (47.69 g, 462.42 mmol, 55.00 mL, 1.32 *eq*) in MeCN (1 L) was stirred at 60 °C for 16 h under N₂ atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The crude product was purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (120 g, 302.84
10 mmol, 86%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.58 (s, 2H).

Step 2 - Synthesis of 2,6-dibromo-4-chlorobenzaldehyde:

A mixture of 1,3-dibromo-5-chloro-2-iodobenzene (60 g, 151.42 mmol, 1 *eq*) in THF (2 L) was added *i*-PrMgCl·LiCl (1.3 M, 151.42 mL, 1.3 *eq*) at -78 °C under N₂ atmosphere, and the reaction mixture was stirred at the same temperature for 0.5 h. Anhydrous DMF (38.45 mL, 499.69
15 mmol, 3.3 *eq*) was added dropwise to the reaction mixture at -78 °C and stirred for 1 h. After completion (monitored by TLC), the reaction was quenched with saturated NH₄Cl (100 mL), then the mixture was warmed to room temperature. The mixture was diluted with water (100 mL) and extracted with EtOAc (500 mL x 2). The combined organic layers were washed with brine (500 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The
20 crude product was triturated with petroleum ether (300 mL) at 0 °C for 30 min, the suspension was filtered and the filter cake was dried in vacuo to give the title compound (40 g, 89%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.08 (s, 1H), 8.02 (s, 2H).

Step 3 - Synthesis of 2-(2,6-dibromo-4-chlorophenyl)-1,3-dioxolane:

A mixture of 2,6-dibromo-4-chloro-benzaldehyde (35 g, 117.31 mmol, 1 *eq*), ethylene
25 glycol (15.05 mL, 269.81 mmol, 2.3 *eq*) and TsOH·H₂O (11.16 g, 58.65 mmol, 0.5 *eq*) in

anhydrous toluene (500 mL) under N₂ atmosphere was stirred using DeanStark trap at 135 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the mixture was neutralized with 1M NaOH (150 mL) at 0 °C. Then the mixture was extracted with EtOAc (500 mL x 2), the combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude product was triturated with petroleum ether (200 mL), then filtered and the filter cake was dried in vacuo to give the title compound (35 g, 87%) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.89 (s, 2H), 6.22 (s, 1H), 4.23 - 4.20 (m, 2H), 4.03 - 3.99 (m, 2H).

Step 4 - Synthesis of *N*-(3-bromo-5-chloro-2-(1,3-dioxolan-2-yl)phenyl)-1,1-diphenylmethanimine:

To a solution of 2-(2,6-dibromo-4-chloro-phenyl)-1,3-dioxolane (16 g, 37.38 mmol, 1 *eq*), diphenylmethanimine (6.27 mL, 37.38 mmol, 1 *eq*), Cs₂CO₃ (30.45 g, 93.45 mmol, 2.5 *eq*) in toluene (500 mL) under N₂ atmosphere. Then BINAP (2.33 g, 3.74 mmol, 0.1 *eq*) and Pd(OAc)₂ (419.63 mg, 1.87 mmol, 0.05 *eq*) was added into the reaction. The mixture was stirred at 80 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the mixture was filtered and the filtrate was diluted with water (150 mL), then extracted with EtOAc (300 mL x 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude product was triturated with petroleum ether (150 mL), then filtered and the filter cake was dried in vacuo to give the title compound (11 g, 66%) as a yellow solid. LCMS: *m/z* 442.1 (M+H).

Step 5 - Synthesis of 2-amino-6-bromo-4-chlorobenzaldehyde:

A solution of *N*-(3-bromo-5-chloro-2-(1,3-dioxolan-2-yl)phenyl)-1,1-diphenylmethanimine (6 g, 13.55 mmol, 1 *eq*) in THF (100 mL) was added HCl (1 M, 13.55 mL, 1 *eq*). The mixture was stirred at 80 °C for 2 h. After cooling to 0 °C, the pH of the reaction mixture was adjusted to around 7 by progressively adding 1M NaOH. The mixture was extracted with EtOAc (200 mL x 2), and the combined organic layer were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (3.1 g, 97%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.17 (s, 1H), 7.80 (s, 2H), 6.91 (d, *J* = 2.0 Hz, 1H), 6.88 (d, *J* = 1.6 Hz, 1H).

Step 6 - Synthesis of 5-bromo-7-chloro-3-(tetrahydrofuran-3-yl)quinoline:

To a solution of 2-(tetrahydrofuran-3-yl)acetaldehyde (1.0 g, 8.76 mmol) (prepared according to the procedure in WO201283105) and 2-amino-6-bromo-4-chlorobenzaldehyde (2.05 g, 8.76 mmol) in *n*-BuOH (10 mL) and H₂O (1 mL) was added NaOH (0.7 g, 17.52 mmol). The reaction mixture was stirred at 110 °C for 1 h. After cooling to room temperature, the mixture was added water (15 mL) and extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (1.99 g, 73%) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.97 (d, *J* = 2.0 Hz, 1H), 8.28 (d, *J* = 2.0 Hz, 1H), 8.13 (d, *J* = 1.2 Hz, 1H), 8.08 (d, *J* = 2.0 Hz, 1H), 4.14 - 4.09 (m, 1H), 4.06 - 4.00 (m, 1H), 3.89 - 3.83 (m, 1H), 3.78 - 3.70 (m, 2H), 2.47 - 2.42 (m, 1H), 2.11 - 2.00 (m, 1H). MS: *m/z* 311.9 (M+H⁺).

Step 7 – Synthesis of 5-bromo-7-chloro-3-(tetrahydrofuran-3-yl)quinoline 1-oxide:

To a solution of 5-bromo-7-chloro-3-(tetrahydrofuran-3-yl)quinoline (1.5 g, 4.80 mmol) in DCM (15 mL) was added *m*-CPBA (2.07 g, 9.60 mmol, 80% purity) at 0°C and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched by sat. NaHCO₃ (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 80% EtOAc in petroleum ether) to give the title compound (1.23 g, 78%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.73 (d, *J* = 1.2 Hz, 1H), 8.53 (d, *J* = 1.2 Hz, 1H), 8.25 (d, *J* = 2.0 Hz, 1H), 7.85 (s, 1H), 4.07 - 3.96 (m, 2H), 3.85 - 3.78 (m, 1H), 3.76 - 3.71 (m, 1H), 3.68 - 3.58 (m, 1H), 2.45 - 2.36 (m, 1H), 2.10 - 1.99 (m, 1H). MS: *m/z* 327.8 (M+H⁺).

Step 8 - Synthesis of 5-bromo-7-chloro-3-(tetrahydrofuran-3-yl)quinoline-2-carbonitrile:

A mixture of 5-bromo-7-chloro-3-(tetrahydrofuran-3-yl)quinoline 1-oxide (1.23 g, 3.74 mmol), 1-ethoxyphosphonyloxyethane (0.96 mL, 7.49 mmol), TEA (1.04 mL 7.49 mmol), CCl₄ (0.72 mL, 7.49 mmol) and trimethylsilylformonitrile (0.51 mL, 4.03 mmol) in DCM (15 mL) was degassed and purged with N₂ atmosphere for 3 times, and then the mixture was stirred at room temperature for 16 h under N₂ atmosphere. The reaction mixture was diluted with DCM (30 mL) and washed with NaHCO₃ (35 mL x 2), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in

petroleum ether) to give the title compound (1.05 g, 83%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.56 (s, 1H), 8.13 (d, *J* = 1.2 Hz, 1H), 7.95 (d, *J* = 2.0 Hz, 1H), 4.29 - 4.15 (m, 2H), 4.10 - 3.98 (m, 3H), 2.70 - 2.62 (m, 1H), 2.18 - 2.05 (m, 1H). MS: *m/z* 336.9 (M+H⁺).

Step 9 - Synthesis of 5-acetyl-7-chloro-3-(tetrahydrofuran-3-yl)quinoline-2-carbonitrile:

A mixture of 5-bromo-7-chloro-3-(tetrahydrofuran-3-yl)quinoline-2-carbonitrile (1.05 g, 3.11 mmol), tributyl(1-ethoxyvinyl)stannane (1.86 g, 5.15 mmol) and Pd(dppf)Cl₂ (227 mg, 0.311 mmol) in dioxane (15 mL) was degassed and purged with N₂ atmosphere for 3 times. The reaction mixture was stirred at 90 °C for 16 h under N₂ atmosphere. After cooling to room temperature, HCl (3 mL, 1 M) was added. The mixture was stirred at room temperature for 0.5 h. The reaction mixture was added 20 mL 10% KF aqueous solution, stirred at room temperature for 2 h. The mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 100% EtOAc in petroleum ether) to give the title compound (0.27 g, 37%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) 9.32 (s, 1H), 8.30 (d, *J* = 1.6 Hz, 1H), 8.12 (d, *J* = 2.0 Hz, 1H), 4.29 - 4.17 (m, 2H), 4.08 - 4.00 (m, 2H), 3.95 - 3.90 (m, 1H), 2.79 (s, 3H), 2.67 - 2.56 (m, 1H), 2.23 - 2.12 (m, 1H). MS: *m/z* 300.9 (M+H⁺).

Step 10 - Synthesis of (*R*)-*N*-((*E*)-1-(7-chloro-2-cyano-3-(tetrahydrofuran-3-yl)quinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide:

To a solution of 5-acetyl-7-chloro-3-(tetrahydrofuran-3-yl)quinoline-2-carbonitrile (0.27 g, 0.89 mmol) in THF (6 mL) was added tetraisopropoxytitanium (0.79 mL, 2.69 mmol) and (*R*)-2-methylpropane-2-sulfinamide (0.54 g, 4.49 mmol). The mixture was stirred at 75 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was quenched by addition water (10 mL) at room temperature, and then extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 80% EtOAc in petroleum ether) to give the title compound (0.22 g, 61%) as yellow oil. ¹H NMR (400 MHz, CDCl₃) 8.82 (s, 1H), 8.20 (s, 1H), 7.73 (s, 1H), 4.24 - 4.17 (m, 1H), 4.16 - 4.11 (m, 1H), 4.06 - 3.96 (m, 2H), 3.90 - 3.82 (m, 1H), 2.90 (s, 3H), 2.65 - 2.57 (m, 1H), 2.11 - 2.04 (m, 1H), 1.30 (s, 9H). MS: *m/z* 404.0 (M+H⁺).

Step 11 - Synthesis of (*R*)-*N*-((1*R*)-1-(7-chloro-2-cyano-3-(tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide:

A mixture of (*R*)-*N*-((*E*)-1-(7-chloro-2-cyano-3-(tetrahydrofuran-3-yl)quinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide (220 mg, 544 μ mol) in THF (6 mL) was added
5 NaBH₄ (20 mg, 528 μ mol) at 0 °C, and then the mixture was stirred at 0 °C for 2h under N₂ atmosphere. The reaction was quenched with aq. sat. NH₄Cl (5 mL) and extracted with DCM (20 mL x 3). The organics were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to give mixture (200 mg, two isomers 5:1). The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 80% EtOAc in petroleum ether) to give the title
10 compound (135 mg, 61%) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.75 (s, 1H), 8.14 (d, *J* = 2.0 Hz, 1H), 7.91 (s, 1H), 6.03 - 5.98 (m, 1H), 5.35 - 5.25 (m, 1H), 4.17 - 4.11 (m, 1H), 4.09 - 4.01 (m, 1H), 3.94 - 3.84 (m, 3H), 2.48 - 2.44 (m, 1H), 2.29 - 2.17 (m, 1H), 1.55 (d, *J* = 6.8 Hz, 3H), 1.09 (s, 9H). MS: *m/z* 428.1 (M+Na⁺).

Step 12 - Synthesis of 5-((*R*)-1-aminoethyl)-7-chloro-3-(tetrahydrofuran-3-yl)quinoline-2-carbonitrile:

A solution of (*R*)-*N*-((1*R*)-1-(7-chloro-2-cyano-3-(tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (130 mg, 32 μ mol) in MeOH (1 mL) was added 12M HCl (18 mg, 522 μ mol). The reaction mixture was stirred at room temperature for 2 h. The reaction
mixture was adjusted to pH 8 with NaHCO₃ saturated solution, then diluted with water (20 mL)
20 and extracted with DCM (30 mL x 3). The organics were dried over Na₂SO₄, filtered and concentrated in vacuo to give the title compound (88 mg, crude) as a yellow solid that required no further purification. MS: *m/z* 302.1 (M+H⁺).

Step 13 - Synthesis of *tert*-butyl 2-(((1*R*)-1-(7-chloro-2-cyano-3-(tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzoate:

A mixture of 5-((*R*)-1-aminoethyl)-7-chloro-3-(tetrahydrofuran-3-yl)quinoline-2-carbonitrile (88 mg, 291 μ mol), *tert*-butyl 2-iodobenzoate (266 mg, 875 μ mol), Pd₂(dba)₃ (26.7 mg, 29.1 μ mol), XantPhos (34 mg, 58.3 μ mol) and Cs₂CO₃ (285 mg, 875 μ mol) in dioxane (2 mL) was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the mixture was quenched with water (10 mL), extracted with EtOAc (25 mL x 2). The combined organic
30 layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30%

EtOAc in petroleum ether) to give the title compound (45 mg, 32%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.84 - 8.78 (m, 1H), 8.21 - 8.16 (m, 1H), 8.14 - 8.12 (m, 1H), 7.82 - 7.76 (m, 1H), 7.68 - 7.64 (m, 1H), 7.23 - 7.17 (m, 1H), 6.62 - 6.55 (m, 1H), 6.47 - 6.41 (m, 1H), 5.68 - 5.55 (m, 1H), 4.21 - 4.11 (m, 1H), 4.07 - 3.97 (m, 1H), 3.95 - 3.81 (m, 3H), 2.42 - 2.35 (m, 1H), 2.26 - 2.16 (m, 1H), 1.63 (d, *J* = 6.8 Hz, 3H), 1.60 - 1.57 (m, 9H). MS: *m/z* 478.2 (M+H⁺).

Step 14 - Synthesis of 2-(((1*R*)-1-(7-chloro-2-cyano-3-(tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid:

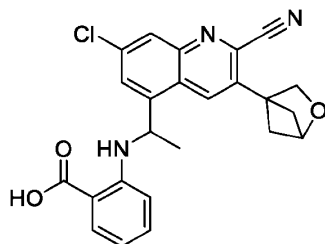
To a solution of *tert*-butyl 2-(((1*R*)-1-(7-chloro-2-cyano-3-(tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzoate (45 mg, 94 μmol) in DCM (3 mL) was added TFA (0.45 g, 6.06 mmol). The reaction mixture was stirred at 40 °C for 16 h. After cooling to room temperature, the reaction mixture was concentrated and the residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (38 mg, 96%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.97 (s, 1H), 8.82 (d, *J* = 8.8 Hz, 1H), 8.45 - 8.39 (m, 1H), 8.13 (s, 1H), 7.85 - 7.81 (m, 1H), 7.65 (s, 1H), 7.27 - 7.15 (m, 1H), 6.61 - 6.53 (m, 1H), 6.45 - 6.39 (m, 1H), 5.67 - 5.56 (m, 1H), 4.17 - 4.13 (m, 1H), 4.06 - 3.98 (m, 1H), 3.97 - 3.78 (m, 4H), 2.28 - 2.14 (m, 1H), 1.62 (d, *J* = 6.8 Hz, 3H). MS: *m/z* 422.0 (M+H⁺).

Step 15 - Synthesis of 2-(((*R*)-1-(7-chloro-2-cyano-3-((*R*)-tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid & 2-(((*R*)-1-(7-chloro-2-cyano-3-((*S*)-tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid:

2-(((1*R*)-1-(7-chloro-2-cyano-3-(tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (38 mg, 219 μmol) was separated by using chiral SFC (DAICEL CHIRALCEL OD (250mm*30mm,10um); Supercritical CO₂ / EtOH+0.1% NH₃•H₂O = 50/50; 80 mL/min) to afford 2-(((*R*)-1-(7-chloro-2-cyano-3-((*R*)-tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (13.86 mg, first peak) and 2-(((*R*)-1-(7-chloro-2-cyano-3-((*S*)-tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (10.83 mg, second peak) both as yellow solid. Absolute configuration was arbitrarily assigned to each enantiomer. First Peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.91 (s, 1H), 8.83 (s, 1H), 8.56 - 8.43 (m, 1H), 8.13 (d, *J* = 1.6 Hz, 1H), 7.85 - 7.80 (m, 1H), 7.65 (d, *J* = 2.0 Hz, 1H), 7.23 - 7.14 (m, 1H), 6.60 - 6.54 (m, 1H), 6.40 (d, *J* = 8.0 Hz, 1H), 5.68 - 5.55 (m, 1H), 4.18 - 4.12 (m, 1H), 4.05 - 3.97 (m, 1H), 3.97 - 3.85 (m, 3H), 2.47 - 2.45 (m, 1H), 2.25 - 2.15 (m, 1H), 1.61 (d, *J* = 6.8 Hz, 3H). MS: *m/z* 422.0 (M+H⁺). Second Peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.89 (s, 1H), 8.81 (s, 1H), 8.50 - 8.41 (m, 1H), 8.13 (d, *J* = 1.6 Hz, 1H), 7.83 (d, *J*

= 8.0 Hz, 1H), 7.65 (d, J = 2.0 Hz, 1H), 7.23 - 7.16 (m, 1H), 6.60 - 6.54 (m, 1H), 6.42 (d, J = 8.4 Hz, 1H), 5.68 - 5.57 (m, 1H), 4.18 - 4.12 (m, 1H), 4.07 - 4.00 (m, 1H), 3.93 - 3.79 (m, 3H), 2.47 - 2.43 (m, 1H), 2.30 - 2.20 (m, 1H), 1.61 (d, J = 6.8 Hz, 3H). MS: m/z 421.9 ($M+H^+$).

Example 49: 2-((1-(3-(2-oxabicyclo[2.1.1]hexan-4-yl)-7-chloro-2-cyanoquinolin-5-yl)ethyl)amino)benzoic acid (Compound 141)



Step 1 - Synthesis of 2-oxabicyclo[2.1.1]hexane-4-carbaldehyde:

To a solution of oxalyl dichloride (6.17 g, 48.62 mmol, 4.26 mL) in DCM (60 mL) was added DMSO (7.60 g, 97.25 mmol, 7.60 mL) at -78 °C under N₂ atmosphere. After 10 min 2-oxabicyclo[2.1.1]hexan-4-ylmethanol (3.7 g, 32.42 mmol) in DCM (30 mL) was added to the mixture at -78 °C. The mixture was stirred at this temperature for 30 min. To the mixture was added DIEA (23.04 g, 178 mmol, 31.05 mL) dropwise over 15 min at -78 °C. Then, the mixture was warmed to 0 °C and stirred for 1 h. The reaction mixture was adjusted to pH 4 with HCl (60 mL, 1 M), then diluted with water (50 mL) and extracted with DCM (80 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo to give the title compound (3.1, crude) as yellow oil that required no further purification. ¹H NMR (400 MHz, CDCl₃) δ 9.92 (s, 1H), 4.62 (s, 1H), 3.92 (s, 2H), 2.19 - 2.16 (m, 2H), 1.85 - 1.82 (m, 2H).

Step 2 - Synthesis of 4-(2-methoxyvinyl)-2-oxabicyclo[2.1.1]hexane:

To a mixture of (methoxymethyl)triphenylphosphonium chloride (18.95 g, 55.29 mmol) in THF (100 mL) was added *t*-BuOK (6.20 g, 55.29 mmol) in THF (30 mL) dropwise at -65 °C under N₂ atmosphere. After the addition, the reaction mixture was stirred at -65 °C for 30 min. To the mixture was added 2-oxabicyclo[2.1.1]hexane-4-carbaldehyde (3.1 g, 27.65 mmol) in THF (30 mL). The resulting mixture was stirred at 0 °C for 1 h. The mixture was added water (30 mL) and extracted with EtOAc (45 mL x 3). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give the title compound (3.8, crude) as yellow oil that required no further purification.

Step 3 - Synthesis of 2-(2-oxabicyclo[2.1.1]hexan-4-yl)acetaldehyde:

A solution of 4-(2-methoxyvinyl)-2-oxabicyclo[2.1.1]hexane (3.8, 27.1 mmol) in THF (30 mL) was added 2M HCl (13.5 mL, 27.1 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was adjusted to pH 8 with NaHCO₃ saturated solution, then diluted with water (20 mL) and extracted with DCM (30 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% EtOAc in petroleum ether) to give the title compound (0.78 g, 23%) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 9.82 (t, *J* = 2.0 Hz, 1H), 4.59 (s, 1H), 3.65 (s, 2H), 2.84 (d, *J* = 2.0 Hz, 2H), 1.87 - 1.78 (m, 2H), 1.69 - 1.63 (m, 2H).

Step 4 - Synthesis of 3-(2-oxabicyclo[2.1.1]hexan-4-yl)-5-bromo-7-chloroquinoline:

To a solution of 2-(2-oxabicyclo[2.1.1]hexan-4-yl)acetaldehyde (0.78 g, 6.18 mmol) and 2-amino-6-bromo-4-chlorobenzaldehyde (1.59 g, 6.80 mmol) in *n*-BuOH (10 mL) and H₂O (1 mL) was added NaOH (0.74 g, 18.5 mmol). The reaction mixture was stirred at 110 °C for 1 h. After cooling to room temperature, the mixture was added water (15 mL) and extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (0.88 g, 44%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.87 (d, *J* = 2.0 Hz, 1H), 8.32 (s, 1H), 8.16 (s, 1H), 7.87 (d, *J* = 2.0 Hz, 1H), 4.78 (s, 1H), 4.01 (s, 2H), 2.24 - 2.21 (m, 2H), 2.16 - 2.13 (m, 2H). MS: *m/z* 325.9 (M+H⁺).

Step 5 - Synthesis of 3-(2-oxabicyclo[2.1.1]hexan-4-yl)-5-bromo-7-chloroquinoline 1-oxide:

To a solution of 3-(2-oxabicyclo[2.1.1]hexan-4-yl)-5-bromo-7-chloroquinoline (0.88 g, 2.71 mmol) in DCM (15 mL) was added *m*-CPBA (1.1 g, 5.42 mmol, 85% purity) at 0°C and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched by sat. aq. Na₂S₂O₃ (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with 2M NaOH (40 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give the title compound (0.8 g, crude) as a yellow oil that required no further purification. ¹H NMR (400 MHz, CDCl₃) δ 8.74 (s, 1H), 8.49 (s, 1H), 7.91 (s, 1H), 7.82 (s, 1H), 4.75 (s, 1H), 3.95 (s, 2H), 2.19 - 2.14 (m, 2H), 2.11 - 2.09 (m, 2H). MS: *m/z* 341.9 (M+H⁺).

Step 6 - Synthesis of 3-(2-oxabicyclo[2.1.1]hexan-4-yl)-5-bromo-7-chloroquinoline-2-carbonitrile:

A mixture of 3-(2-oxabicyclo[2.1.1]hexan-4-yl)-5-bromo-7-chloroquinoline 1-oxide (0.8 g, 2.35 mmol), 1-ethoxyphosphonyloxyethane (0.61 mL, 4.7 mmol), TEA (0.65 mL 4.7 mmol),
5 CCl₄ (0.45 mL, 4.7 mmol) and trimethylsilylformonitrile (0.60 mL, 4.84 mmol) in DCM (15 mL) was degassed and purged with N₂ atmosphere for 3 times, and then the mixture was stirred at room temperature for 16 h under N₂ atmosphere. The reaction mixture was diluted with DCM (30 mL) and washed with NaHCO₃ (35 mL x 2), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in
10 petroleum ether) to give the title compound (0.5 g, 52%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.39 (s, 1H), 8.14 (d, *J* = 1.2 Hz, 1H), 7.96 (d, *J* = 1.6 Hz, 1H), 4.79 (s, 1H), 4.09 (s, 2H), 2.46 - 2.43 (m, 2H), 2.31 - 2.28 (m, 2H). MS: *m/z* 350.9 (M+H⁺).

Step 7 - Synthesis of 5-acetyl-3-(2-oxabicyclo[2.1.1]hexan-4-yl)-7-chloroquinoline-2-carbonitrile:

15 A mixture of 3-(2-oxabicyclo[2.1.1]hexan-4-yl)-5-bromo-7-chloroquinoline-2-carbonitrile (0.5 g, 1.22 mmol, 85% purity), tributyl(1-ethoxyvinyl)stannane (0.57 g, 1.58 mmol) and Pd(dppf)Cl₂ (88.9 mg, 0.121 mmol) in dioxane (8 mL) was degassed and purged with N₂ atmosphere for 3 times. The reaction mixture was stirred at 90 °C for 16 h under N₂ atmosphere. After cooling to room temperature, HCl (3 mL, 1 M) was added. The mixture was stirred at room
20 temperature for 0.5 h. The reaction mixture was added 20 mL 10% KF aqueous solution, stirred at room temperature for 2 h. The mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 100% EtOAc in petroleum ether) to give the title compound (0.2 g, 54%) as a yellow
25 solid. ¹H NMR (400 MHz, CDCl₃) 9.19 (s, 1H), 8.32 (d, *J* = 1.2 Hz, 1H), 8.14 (d, *J* = 2.0 Hz, 1H), 4.77 (s, 1H), 4.07 (s, 2H), 2.79 (s, 3H), 2.44 - 2.39 (m, 2H), 2.30 - 2.24 (m, 2H). MS: *m/z* 312.9 (M+H⁺).

Step 8 - Synthesis of (R,E)-N-(1-(3-(2-oxabicyclo[2.1.1]hexan-4-yl)-7-chloro-2-cyanoquinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide:

30 To a solution of 5-acetyl-3-(2-oxabicyclo[2.1.1]hexan-4-yl)-7-chloroquinoline-2-carbonitrile (0.2 g, 0.64 mmol) in THF (6 mL) was added tetraisopropoxytitanium (0.57 mL, 1.92

mmol) and (*R*)-2-methylpropane-2-sulfinamide (0.38 g, 4.49 mmol). The mixture was stirred at 75 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was quenched by addition water (10 mL) at room temperature, and then extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 80% EtOAc in petroleum ether) to give the title compound (0.2 g, 75%) as yellow oil. MS: m/z 416.1 (M+H⁺).

Step 9 - Synthesis of (*R*)-*N*-(1-(3-(2-oxabicyclo[2.1.1]hexan-4-yl)-7-chloro-2-cyanoquinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide:

A mixture of (*R,E*)-*N*-(1-(3-(2-oxabicyclo[2.1.1]hexan-4-yl)-7-chloro-2-cyanoquinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide (200 mg, 480 μmol) in THF (4 mL) was added NaBH₄ (60 mg, 1.59 mmol) at 0 °C, and then the mixture was stirred at 0 °C for 2 h under N₂ atmosphere. The reaction was quenched with sat. aq. NH₄Cl (5 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 80% EtOAc in petroleum ether) to give the title compound (120 mg, 60%, mixture *R*:*S* = 2:1) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 8.53 (s, 1H), 8.13 (d, *J* = 1.6 Hz, 1H), 7.74 (d, *J* = 2.0 Hz, 1H), 5.28 - 5.21 (m, 1H), 4.77 (s, 1H), 4.09 - 4.03 (m, 2H), 2.50 - 2.41 (m, 2H), 2.33 - 2.23 (m, 2H), 1.71 (d, *J* = 6.4 Hz, 3H), 1.23 (s, 9H). MS: m/z 442.0 (M+Na⁺).

Step 10 - Synthesis of 5-(1-aminoethyl)-3-(2-oxabicyclo[2.1.1]hexan-4-yl)-7-chloroquinoline-2-carbonitrile: A solution of (*R*)-*N*-(1-(3-(2-oxabicyclo[2.1.1]hexan-4-yl)-7-chloro-2-cyanoquinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (100 mg, 239 μmol) in MeOH (1 mL) was added 12M HCl (18 mg, 522 μmol). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was adjusted to pH 8 with NaHCO₃ saturated solution, then diluted with water (20 mL) and extracted with DCM (30 mL x 3). The organics were dried over Na₂SO₄, filtered and concentrated in vacuo to give the title compound (70 mg, crude) as a yellow solid that required no further purification. MS: m/z 314.0 (M+H⁺).

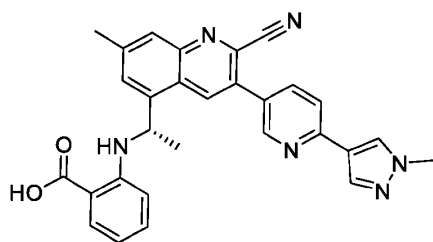
Step 11 - Synthesis of *tert*-butyl 2-(((1-(3-(2-oxabicyclo[2.1.1]hexan-4-yl)-7-chloro-2-cyanoquinolin-5-yl)ethyl)amino)benzoate:

A mixture of 5-(1-aminoethyl)-3-(2-oxabicyclo[2.1.1]hexan-4-yl)-7-chloroquinoline-2-carbonitrile (70 mg, 223 μ mol), *tert*-butyl 2-iodobenzoate (101 mg, 335 μ mol), Pd₂(dba)₃ (20.4 mg, 22.3 μ mol), XantPhos (26 mg, 44.6 μ mol) and Cs₂CO₃ (218 mg, 669 μ mol) in dioxane (2 mL) was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the mixture was quenched with water (10 mL), extracted with EtOAc (25 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (50 mg, 50% purity) as a yellow solid. MS: m/z 490.4 (M+H⁺).

Step 12 - Synthesis of 2-((1-(3-(2-oxabicyclo[2.1.1]hexan-4-yl)-7-chloro-2-cyanoquinolin-5-yl)ethyl)amino)benzoic acid:

To a solution of *tert*-butyl 2-((1-(3-(2-oxabicyclo[2.1.1]hexan-4-yl)-7-chloro-2-cyanoquinolin-5-yl)ethyl)amino)benzoate (50 mg, 50% purity) in DCM (3 mL) was added TFA (0.45 g, 6.06 mmol). The reaction mixture was stirred at 30 °C for 16 h. After cooling to room temperature, the reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 50% - 80% / 0.225% formic acid in water) to give the title compound (3.80 mg, 17%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.86 (s, 1H), 8.74 (s, 1H), 8.15 (d, *J* = 1.6 Hz, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 1.6 Hz, 1H), 7.21 - 7.10 (m, 1H), 6.58 - 6.54 (m, 1H), 6.45 - 6.38 (m, 1H), 5.67 - 5.54 (m, 1H), 4.71 (s, 1H), 3.93 (s, 2H), 2.32 - 2.22 (m, 4H), 1.63 (d, *J* = 6.8 Hz, 3H). MS: m/z 434.0 (M+H⁺).

Example 50: (S)-2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid (Compound 367)



Step 1 - Synthesis of 5-bromo-2-(1-methyl-1*H*-pyrazol-4-yl)pyridine:

To a solution of 5-bromo-2-iodo-pyridine (25 g, 88.06 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (24.92 g, 119 mmol) in dioxane (140 mL) and H₂O (65 mL) was added Cs₂CO₃ (86.08 g, 264 mmol), Na₂CO₃ (14.00 g, 132 mmol) and Pd(dppf)Cl₂

(3.22 g, 4.40 mmol). The mixture was evacuated and backfilled with N₂ for 3 times, and then it was stirred at 110 °C for 4 h under N₂ atmosphere. The reaction mixture was diluted with water (200 mL), extracted with EtOAc (200 mL x 2). The combined organic layers were washed with brine (30 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give crude. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (18 g, 86%) as colorless oil. MS: m/z 237.9 (M+H⁺).

Step 2 - Synthesis of (6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)boronic acid:

To a solution of 5-bromo-2-(1-methylpyrazol-4-yl)pyridine (18 g, 75.60 mmol) and B₂pin₂ (28.80 g, 113.41 mmol) in dioxane (200 mL) was added KOAc (22.26 g, 226.81 mmol) and Pd(dppf)Cl₂ (5.53 g, 7.56 mmol) under N₂ atmosphere, and then the mixture was stirred at 80 °C for 4 h under N₂ atmosphere. The reaction mixture was quenched with water (100 mL), extracted with EtOAc (100 mL x 2). The combined organic layers were washed with brine (50 mL x 2), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give the title compound (18 g, crude) as colorless oil that required no further purification. MS: m/z 204.0 (M+H⁺).

Step 3 - Synthesis of 5-acetyl-7-methyl-3-(6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)quinoline-2-carbonitrile:

A mixture of (6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)boronic acid (1.70 g, 3.35 mmol) and 5-acetyl-2-cyano-7-methylquinolin-3-yl trifluoromethanesulfonate (1.2 g, 3.35 mmol), Pd(PPh₃)₄ (387 mg, 334.92 μmol) and K₂CO₃ (1.39 g, 10.05 mmol) in dioxane (16 mL) and H₂O (2 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 2 h under N₂ atmosphere. After cooling to room temperature, the residue was diluted with EtOAc (40 mL), washed with H₂O (20 mL x 3) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude, which was purified by silica gel chromatography (solvent gradient: 0~10% EtOAc in petroleum ether) to give the title compound (900 mg, 73%) as a brown solid. ¹H NMR (400 MHz, CDCl₃) δ 9.46 (s, 1H), 8.84 (d, *J* = 2.0 Hz, 1H), 8.22 - 8.04 (m, 5H), 7.66 (d, *J* = 8.0 Hz, 1H), 4.02 (s, 3H), 2.81 (s, 3H), 2.71 (s, 3H). MS: m/z 368.2 (M+H⁺).

Step 4 - Synthesis of (R,E)-N-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide:

To a solution of 5-acetyl-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinoline-2-carbonitrile (580 mg, 1.58 mmol) in THF (5 mL) was added tetrakisopropoxytitanium (2.69 g, 9.47 mmol) and (*R*)-2-methylpropane-2-sulfinamide (1.91 g, 15.79 mmol). The mixture was stirred at 75 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was quenched by addition of water (40 mL) at room temperature, and then extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to give the title compound (600 mg, crude) as yellow oil that required no further purification. MS: m/z 471.2 (M+H⁺).

Step 5 - Synthesis of (*R*)-*N*-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide:

To a solution of (*R,E*)-*N*-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide (600 mg, 1.28 mmol) in THF (5 mL) was added NaBH₄ (48.24 mg, 1.28 mmol) at room temperature under N₂ atmosphere. The mixture was stirred at room temperature for 1 h under N₂ atmosphere. The reaction was quenched with sat. aq. NH₄Cl (20 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (40 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (450 mg, 60%) as a yellow solid. MS: m/z 473.5 (M+H⁺).

Step 6 - Synthesis of 5-(1-aminoethyl)-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinoline-2-carbonitrile:

To a solution of (*R*)-*N*-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (450 mg, 952 μmol) in MeCN (4 mL) was added concentrated HCl (238 μL, 12 M) at room temperature. The mixture was stirred at room temperature for 1 h. The reaction was quenched with sat. aq. NaHCO₃ (20 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (40 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 100% EtOAc in petroleum ether) to give the title compound (420 mg, 78%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.93 (s, 1H), 8.86 (d, *J* = 2.0 Hz, 1H), 8.41 (s, 1H), 8.22 - 8.16 (m, 1H), 8.11 (s, 1H), 7.88 - 7.85 (m, 3H), 4.93 - 4.88 (m, 1H), 3.93 (s, 3H), 2.58 (s, 3H), 1.40 (d, *J* = 6.4 Hz, 3H). MS: m/z 369.2 (M+H⁺).

Step 7 - Synthesis of *tert*-butyl 2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzoate:

A mixture of 5-(1-aminoethyl)-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinoline-2-carbonitrile (220 mg, 597 μ mol), *tert*-butyl 2-iodobenzoate (182 mg, 597 μ mol),
5 Cs₂CO₃ (584 mg, 1.79 mmol), Pd₂(dba)₃ (54.68 mg, 59.71 μ mol) and Xantphos (35 mg, 59.71 mmol) in dioxane (4 mL), the reaction mixture was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% EtOAc in petroleum ether) to give the title compound (160 mg, 49%) as a yellow solid. ¹H NMR
10 (400 MHz, DMSO-*d*₆) δ 9.07 (s, 1H), 8.91 (d, *J* = 1.6 Hz, 1H), 8.41 (s, 1H), 8.26 - 8.22 (m, 2H), 8.12 (s, 1H), 7.93 - 7.84 (m, 2H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.63 (s, 1H), 7.21 - 7.10 (m, 1H), 6.58 - 6.50 (m, 1H), 6.48 - 6.39 (m, 1H), 5.70 - 5.58 (m, 1H), 4.08 - 3.97 (m, 1H), 3.93 (s, 3H), 2.49 (s, 3H), 1.63 (d, *J* = 6.8 Hz, 3H), 1.57 (s, 9H). MS: *m/z* 545.3 (M+H⁺).

Step 8 - Synthesis of *tert*-butyl (*R*)-2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzoate & *tert*-butyl (*S*)-2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzoate:

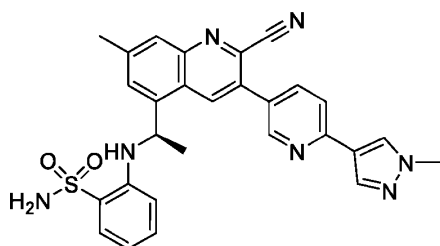
tert-butyl 2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzoate (180 mg, 330 μ mol) was separated by chiral SFC (DAICEL
20 CHIRALCEL OD (250mm*30mm,10 μ m); Supercritical CO₂ / EtOH+0.1% NH₃•H₂O = 60/40; 80 mL/min) to afford *tert*-butyl (*R*)-2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzoate (60 mg, 32%, first peak) and *tert*-butyl (*S*)-2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzoate (50 mg, 28%, second peak) both as white solid. Absolute configuration
25 was arbitrarily assigned to each enantiomer. MS: *m/z* 545.4 (M+H⁺).

Step 9 - Synthesis of (*S*)-2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid:

To a mixture of *tert*-butyl (*S*)-2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzoate (50 mg, 91.80 μ mol) in DCM (12 mL) was
30 added TFA (340 μ L, 4.59 mmol). The reaction mixture was stirred at room temperature for 16 h. The mixture was concentrated and the residue purified by silica gel chromatography (solvent

gradient: 0 - 50% EtOAc in petroleum ether) to give the title compound (39.75 mg, 88%) as white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.84 (s, 1H), 9.08 (s, 1H), 8.92 (d, *J* = 2.0 Hz, 1H), 8.50 (s, 1H), 8.42 (s, 1H), 8.25 - 8.22 (m, 1H), 8.12 (s, 1H), 7.91 - 7.86 (m, 2H), 7.83 - 7.81 (m, 1H), 7.61 (s, 1H), 7.19 - 7.12 (m, 1H), 6.57 - 6.50 (m, 1H), 6.41 (d, *J* = 8.4 Hz, 1H), 5.72 - 5.60 (m, 1H), 3.93 (s, 3H), 2.47 (s, 3H), 1.61 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 489.3 (M+H⁺).

Example 51: (*R*)-2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl) pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide (Compound 405)



Step 1 - Synthesis of 5-(1-hydroxyethyl)-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinoline-2-carbonitrile:

To a solution of 5-acetyl-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinoline-2-carbonitrile (500 mg, 1.36 mmol) in THF (7 mL) was added NaBH₄ (103 mg, 2.72 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction was quenched with sat. aq. NH₄Cl (10 mL) at 0 °C and extracted with DCM (20 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0~50% EtOAc in petroleum ether) to give the title compound (200 mg, 40%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.86 - 8.78 (m, 1H), 8.72 (s, 1H), 8.26 (s, 1H), 8.15 (s, 1H), 8.11 - 8.05 (m, 1H), 7.94 (s, 1H), 7.71 (s, 1H), 7.65 - 7.60 (m, 1H), 5.63 - 5.51 (m, 1H), 4.12 (s, 3H), 2.63 (s, 3H), 1.72 (d, *J* = 6.8 Hz, 3H).

Step 2 - Synthesis of 5-(1-bromoethyl)-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinoline-2-carbonitrile:

To a solution of 5-(1-hydroxyethyl)-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinoline-2-carbonitrile (200 mg, 541.39 μmol) in DCM (2 mL) was added phosphorus tribromide (176 mg, 61.70 μL). The mixture was stirred at 0 °C for 2 h. The mixture was quenched with NaHCO₃ (4 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were

washed with brine (30 mL x 2), dried over Na₂SO₄, filtered and concentrated in vacuo to give the title compound (234 mg, crude) as yellow oil that required no further purification. MS: m/z 432.1 (M+H⁺).

Step 3 - Synthesis of 2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide:

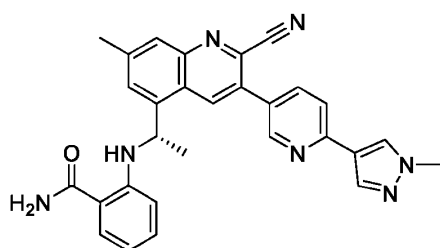
To a solution of 5-(1-bromoethyl)-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinoline-2-carbonitrile (234 mg, 541.27 μmol) in dioxane (3 mL) was added 2-aminobenzenesulfonamide (186 mg, 1.08 mmol). The mixture was heated to 90 °C and stirred for 16 h. After cooling to room temperature, the solvent was removed in vacuo to get crude residue. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to give the title compound (130 mg, 46%) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 8.77 (d, *J* = 2.0 Hz, 1H), 8.64 (s, 1H), 8.14 - 8.00 (m, 3H), 7.92 (s, 1H), 7.87 - 7.80 (m, 1H), 7.73 - 7.62 (m, 2H), 7.21 - 7.14 (m, 1H), 6.78 - 6.68 (m, 1H), 6.47 (d, *J* = 5.2 Hz, 1H), 6.35 (d, *J* = 8.4 Hz, 1H), 5.28 - 5.18 (m, 1H), 5.02 (s, 2H), 4.01 (s, 3H), 2.56 (s, 3H), 1.75 (d, *J* = 6.8 Hz, 3H). MS: m/z 524.2 (M+H⁺).

Step 4 - Synthesis of (*R*)-2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide & (*S*)-2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide:

2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide (130 mg, 248 μmol) was separated by using chiral SFC (DAICEL CHIRALPAK OJ (250mm x 30mm, 10μm); Supercritical CO₂ / EtOH + 0.1% NH₃•H₂O = 45/55; 80 mL/min to afford (*R*)-2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide (28.86 mg, first peak) and (*S*)-2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide (25.18 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. First Peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.08 (s, 1H), 8.96 - 8.90 (m, 1H), 8.41 (s, 1H), 8.27 - 8.21 (m, 1H), 8.15 - 8.11 (m, 1H), 7.91 - 7.87 (m, 2H), 7.79 - 7.73 (m, 1H), 7.66 - 7.62 (m, 1H), 7.18 - 7.10 (m, 1H), 6.68 - 6.57 (m, 1H), 6.49 - 6.42 (m, 1H), 5.65 (q, *J* = 6.8 Hz, 1H), 3.92 (s, 3H), 2.52 (s, 3H), 1.61 (d, *J* = 6.8 Hz, 3H). MS: m/z 524.3 (M+H⁺). Second peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.06 (s, 1H), 8.95 - 8.87

(m, 1H), 8.40 (s, 1H), 8.26 - 8.20 (m, 1H), 8.11 (s, 1H), 7.91 - 7.85 (m, 2H), 7.80 - 7.75 (m, 1H), 7.69 - 7.61 (m, 1H), 7.19 - 7.07 (m, 1H), 6.70 - 6.58 (m, 1H), 6.44 (d, $J = 8.4$ Hz, 1H), 5.64 (q, $J = 6.4$ Hz, 1H), 3.91 (s, 3H), 2.52 (s, 3H), 1.60 (d, $J = 6.4$ Hz, 3H). MS: m/z 524.3($M+H^+$).

5 **Example 52: (*S*)-2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzamide (Compound 355)**



Step 1 – Synthesis of 2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzamide:

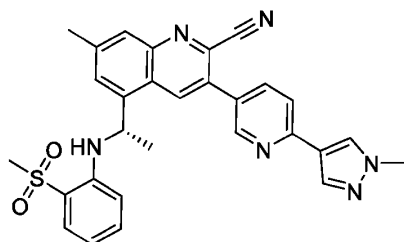
10 To a solution of 5-(1-bromoethyl)-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinoline-2-carbonitrile (150 mg, 347 μ mol) in dioxane (2 mL) was added 2-aminobenzenesulfonamide (57 mg, 417 μ mol). The mixture was stirred at 100 °C for 16 h. After cooling to room temperature, the solvent was removed in vacuo to get crude residue. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc/EtOH (v/v =
15 3:1) in petroleum ether) to give the title compound (40 mg, 23%) as a white solid. 1H NMR (400 MHz, DMSO- d_6) δ 9.07 (s, 1H), 8.92 (d, $J = 2.0$ Hz, 1H), 8.86 (d, $J = 6.0$ Hz, 1H), 8.42 (s, 1H), 8.23 (dd, $J_1 = 8.0$, $J_2 = 2.4$ Hz, 1H), 8.12 (s, 1H), 7.97 - 7.92 (m, 1H), 7.90 - 7.86 (m, 2H), 7.65 - 7.61 (m, 2H), 7.33 - 7.27 (m, 1H), 7.09 - 7.03 (m, 1H), 6.53 - 6.47 (m, 1H), 6.38 (d, $J = 8.4$ Hz, 1H), 5.60 - 5.53 (m, 1H), 3.93 (s, 3H), 2.54 (s, 3H), 1.57 (d, $J = 6.4$ Hz, 3H). MS: m/z 488.3
20 ($M+H^+$).

Step 2 – Synthesis of (*R*)-2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzamide and (*S*)-2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzamide:

25 2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzamide (45 mg, 92 μ mol) was separated by using chiral SFC (DAICEL CHIRALCEL OJ-H (250mm*30mm,10um); Supercritical CO₂ / EtOH + 0.1% NH₃·H₂O = 40/60;

80 mL/min) to afford (*R*)-2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzamide (2.4 mg, first peak) and (*S*)-2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzamide (6.0 mg, second peak) both as yellow solid. First peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.07 (s, 1H), 8.92 (d, *J* = 1.6 Hz, 1H), 8.86 (d, *J* = 6.4 Hz, 1H), 8.42 (s, 1H), 8.26 - 8.22 (m, 1H), 8.12 (s, 1H), 7.98 - 7.93 (m, 1H), 7.90 - 7.86 (m, 2H), 7.65 - 7.61 (m, 2H), 7.35 - 7.27 (m, 1H), 7.09 - 7.02 (m, 1H), 6.53 - 6.46 (m, 1H), 6.38 (d, *J* = 8.4 Hz, 1H), 5.60 - 5.53 (m, 1H), 3.93 (s, 3H), 2.53 (s, 3H), 1.57 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 488.3 (M+H⁺). Second peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.07 (s, 1H), 8.92 (d, *J* = 1.6 Hz, 1H), 8.86 (d, *J* = 6.4 Hz, 1H), 8.42 (s, 1H), 8.26 - 8.21 (m, 1H), 8.12 (s, 1H), 7.98 - 7.92 (m, 1H), 7.91 - 7.85 (m, 2H), 7.64 - 7.60 (m, 2H), 7.33 - 7.26 (m, 1H), 7.09 - 7.02 (m, 1H), 6.49 (m, 1H), 6.38 (d, *J* = 8.4 Hz, 1H), 5.60 - 5.54 (m, 1H), 3.93 (s, 3H), 2.53 (s, 3H), 1.57 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 488.3 (M+H⁺).

Example 53: (*S*)-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)-5-(1-((2-(methylsulfonyl)phenyl)amino)ethyl)quinoline-2-carbonitrile (Compound 289)



Step 1 - Synthesis of 7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)-5-(1-((2-(methylsulfonyl)phenyl)amino)ethyl)quinoline-2-carbonitrile:

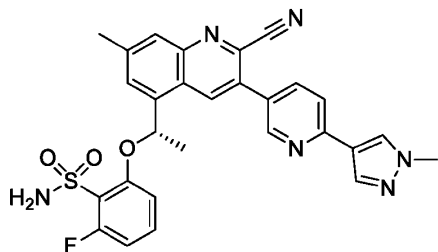
To a mixture of 5-(1-bromoethyl)-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinoline-2-carbonitrile (157 mg, 0.36 mmol) and 2-(methylsulfonyl)aniline (622 mg, 3.63 mmol) in DMF (5 mL) was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction was quenched with water (15 mL), extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 35% EtOAc in petroleum ether) to give the title compound (102 mg, 48%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.08 (s, 1H), 8.93 (d, *J* = 2.0 Hz, 1H), 8.42 (s,

1H), 8.29 - 8.18 (m, 1H), 8.13 (s, 1H), 7.93 - 7.84 (m, 2H), 7.72 - 7.62 (m, 2H), 7.33 - 7.24 (m, 1H), 6.79 - 6.68 (m, 2H), 6.53 (d, $J = 8.8$ Hz, 1H), 5.73 - 5.63 (m, 1H), 3.93 (s, 3H), 3.29 (s, 3H), 2.54 (s, 3H), 1.63 (d, $J = 6.8$ Hz, 3H). MS: m/z 523.2 ($M+H^+$).

Step 2 - Synthesis of (*R*)-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)-5-(1-((2-(methylsulfonyl)phenyl)amino)ethyl)quinoline-2-carbonitrile & (*S*)-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)-5-(1-((2-(methylsulfonyl)phenyl)amino)ethyl)quinoline-2-carbonitrile:

7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)-5-(1-((2-(methylsulfonyl)phenyl)amino)ethyl)quinoline-2-carbonitrile (100 mg, 191 μ mol) was purified by using chiral SFC (DAICEL CHIRALCEL OJ (250mm*30mm,10 μ m); Supercritical CO₂ / *i*-PrOH+0.1% NH₃•H₂O = 50/50; 80 mL/min) to afford (*R*)-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)-5-(1-((2-(methylsulfonyl)phenyl)amino)ethyl)quinoline-2-carbonitrile (24.4 mg, first peak) and (*S*)-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)-5-(1-((2-(methylsulfonyl)phenyl)amino)ethyl)quinoline-2-carbonitrile (22.5 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. First peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.08 (s, 1H), 8.93 (d, $J = 2.0$ Hz, 1H), 8.42 (s, 1H), 8.27 - 8.20 (m, 1H), 8.12 (s, 1H), 7.94 - 7.80 (m, 2H), 7.71 - 7.60 (m, 2H), 7.34 - 7.21 (m, 1H), 6.78 - 6.63 (m, 2H), 6.53 (d, $J = 8.8$ Hz, 1H), 5.74 - 5.60 (m, 1H), 3.93 (s, 3H), 3.28 (s, 3H), 2.50 (s, 3H), 1.63 (d, $J = 6.4$ Hz, 3H). MS: m/z 523.4 ($M+H^+$). Second peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.08 (s, 1H), 8.93 (d, $J = 2.0$ Hz, 1H), 8.42 (s, 1H), 8.29 - 8.20 (m, 1H), 8.13 (s, 1H), 7.92 - 7.83 (m, 2H), 7.72 - 7.59 (m, 2H), 7.33 - 7.23 (m, 1H), 6.79 - 6.63 (m, 2H), 6.53 (d, $J = 8.4$ Hz, 1H), 5.74 - 5.62 (m, 1H), 3.93 (s, 3H), 3.28 (s, 3H), 2.50 (s, 3H), 1.63 (d, $J = 6.4$ Hz, 3H). MS: m/z 523.3 ($M+H^+$).

Example 54: (*S*)-2-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)-6-fluorobenzenesulfonamide (Compound 317)



Step 1 – Synthesis of 2-fluoro-6-methoxybenzenesulfonamide:

To a solution of 2-fluoro-6-methoxybenzene-1-sulfonyl chloride (200 mg, 890 μ mol) and $\text{NH}_3 \cdot \text{H}_2\text{O}$ (312 mg, 8.90 mmol, 30% in water) in THF (2 mL), then the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 40% EtOAc in petroleum ether) to give the title compound (180 mg, 99%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.54 (m, 1H), 7.39 (s, 2H), 7.03 (d, J = 8.4 Hz, 1H), 6.93 - 6.86 (m, 1H), 3.90 (s, 3H).

Step 2 – Synthesis of 2-fluoro-6-hydroxybenzenesulfonamide:

A mixture of 2-fluoro-6-methoxy-benzenesulfonamide (180 mg, 877 μ mol) in DCM (2 mL) was degassed and purged with N_2 for 3 times, then BBr_3 (2.44 mL, 4.87 mmol, 2 M in DCM) was added and stirred at room temperature for 1 h under N_2 atmosphere. The reaction was quenched with MeOH (10 mL). The mixture was concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (150 mg, 89%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.64 (s, 1H), 7.58 (s, 2H), 7.45 - 7.37 (m, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.80 - 6.74 (m, 1H).

Step 3 - Synthesis of 2-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)-6-fluorobenzenesulfonamide:

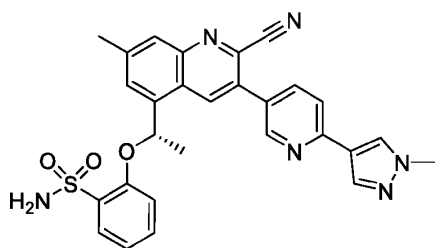
To a mixture of 2-fluoro-6-hydroxybenzenesulfonamide (66 mg, 0.35 mmol), 5-(1-bromoethyl)-7-methyl-3-(6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)quinoline-2-carbonitrile (150 mg, 0.35 mmol) and K_2CO_3 (144 mg, 1.04 mmol) in DMF (2 mL) was stirred at room temperature for 16 h under N_2 atmosphere. After cooling to room temperature, the reaction was quenched with water (15 mL), extracted with DCM (15 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by reverse phase chromatography (acetonitrile 43% - 73% / 0.225% formic acid in water) to give the title compound (78 mg, 41%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.09 (s, 1H), 8.93 (d, J = 2.0 Hz, 1H), 8.42 (s, 1H), 8.27 - 8.22 (m, 1H), 8.13 (s, 1H), 7.99 (s, 1H), 7.93 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.51 (s, 2H), 7.41 - 7.31 (m, 1H), 6.91 - 6.80 (m, 2H), 6.61 - 6.53 (m, 1H), 3.93 (s, 3H), 2.53 (s, 3H), 1.76 (d, J = 6.0 Hz, 3H). MS: m/z 543.2 ($\text{M}+\text{H}^+$).

Step 4 - Synthesis of (R)-2-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)-6-fluorobenzenesulfonamide & (S)-2-(1-(2-cyano-7-

methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)-6-fluorobenzenesulfonamide:

2-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)-6-fluorobenzenesulfonamide (78 mg, 144 μ mol) was separated by using chiral SFC (DAICEL CHIRALCEL OD (250mm*30mm,10 μ m); Supercritical CO₂ / *i*-PrOH+0.1% NH₃•H₂O = 40/60; 80 mL/min) to afford (*R*)-2-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)-6-fluorobenzenesulfonamide (5.7 mg, first peak) and (*S*)-2-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)-6-fluorobenzenesulfonamide (6.4 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. First peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.10 (s, 1H), 8.93 (d, *J* = 2.4 Hz, 1H), 8.42 (s, 1H), 8.27 - 8.22 (m, 1H), 8.13 (s, 1H), 7.99 (d, *J* = 1.2 Hz, 1H), 7.93 (s, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.52 (s, 2H), 7.40 - 7.32 (m, 1H), 6.91 - 6.81 (m, 2H), 6.62 - 6.53 (m, 1H), 3.93 (s, 3H), 2.53 (s, 3H), 1.76 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 543.1 (M+H⁺). Second peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.10 (s, 1H), 8.93 (d, *J* = 2.4 Hz, 1H), 8.42 (s, 1H), 8.28 - 8.22 (m, 1H), 8.13 (s, 1H), 7.99 (d, *J* = 1.2 Hz, 1H), 7.93 (s, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.52 (s, 2H), 7.41 - 7.32 (m, 1H), 6.91 - 6.81 (m, 2H), 6.61 - 6.54 (m, 1H), 3.93 (s, 3H), 2.53 (s, 3H), 1.76 (d, *J* = 6.0 Hz, 3H). MS: *m/z* 543.1 (M+H⁺).

Example 55: (*S*)-2-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)benzenesulfonamide (Compound 360)



Step 1 – Synthesis of 2-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)benzenesulfonamide:

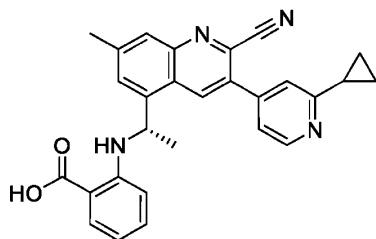
To a solution of 2-hydroxybenzenesulfonamide (20 mg, 116 μ mol) and K₂CO₃ (48 mg, 347 μ mol) in DMF (0.5 mL) was stirred at room temperature for 10 min under N₂ atmosphere. Then 5-(1-bromoethyl)-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinoline-2-

carbonitrile (50 mg, 116 μmol) was added to the mixture at room temperature. The mixture was stirred at room temperature for 16 h. The mixture was filtrated and the filtrate was purified by reverse phase chromatography (acetonitrile 40% - 70% / 0.225% formic acid in water) to give the title compound (6 mg, 9%) as a white solid. MS: m/z 525.2 ($M+H^+$).

Step 2 – Synthesis of (*R*)-2-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)benzenesulfonamide and (*S*)-2-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)benzenesulfonamide:

2-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)benzenesulfonamide (40 mg, 76.3 μmol) was separated by using chiral SFC (DAICEL CHIRALCEL OJ-H (250mm*30mm,10 μm); Supercritical CO_2 / EtOH + 0.1% $\text{NH}_3 \cdot \text{H}_2\text{O}$ = 50/50; 80 mL/min) to afford (*R*)-2-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)benzenesulfonamide (19.6 mg, first peak) and (*S*)-2-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)benzenesulfonamide (18.6 mg, second peak) both as yellow solid. First peak: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.12 (s, 1H), 8.93 (d, J = 2.0 Hz, 1H), 8.43 (s, 1H), 8.25 (dd, J_1 = 8.4, J_2 = 2.4 Hz, 1H), 8.13 (s, 1H), 7.99 (d, J = 1.2 Hz, 1H), 7.92 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.77 (dd, J_1 = 7.6, J_2 = 1.2 Hz, 1H), 7.40 - 7.34 (m, 1H), 7.20 (s, 2H), 7.05 (d, J = 8.4 Hz, 1H), 7.01 - 6.97 (m, 1H), 6.62 - 6.58 (m, 1H), 3.93 (s, 3H), 2.52 (s, 3H), 1.77 (d, J = 6.0 Hz, 3H). MS: m/z 525.2 ($M+H^+$). Second peak: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.12 (s, 1H), 8.93 (d, J = 2.4 Hz, 1H), 8.43 (s, 1H), 8.25 (dd, J_1 = 8.0, J_2 = 2.4 Hz, 1H), 8.13 (s, 1H), 7.99 (s, 1H), 7.91 (s, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.77 (dd, J_1 = 7.6, J_2 = 1.6 Hz, 1H), 7.40 - 7.34 (m, 1H), 7.20 (s, 2H), 7.05 (d, J = 8.0 Hz, 1H), 7.01 - 6.98 (m, 1H), 6.62 - 6.58 (m, 1H), 3.93 (s, 3H), 2.52 (s, 3H), 1.77 (d, J = 6.0 Hz, 3H). MS: m/z 525.3 ($M+H^+$).

Example 56: (*S*)-2-((1-(2-cyano-3-(2-cyclopropylpyridin-4-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid (Compound 389)



Step 1 – Synthesis of 5-acetyl-3-(2-cyclopropylpyridin-4-yl)-7-methylquinoline-2-carbonitrile:

To a mixture of 5-acetyl-2-cyano-7-methylquinolin-3-yl trifluoromethanesulfonate (300 mg, 837 μ mol), 2-cyclopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (410 mg, 1.67 mmol), Pd(PPh₃)₄ (97 mg, 84 μ mol), K₂CO₃ (347 mg, 2.51 mmol) in dioxane (3 mL) and H₂O (0.3 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 80 °C for 2 h under N₂ atmosphere. The mixture was cooled to room temperature, diluted with H₂O (10 mL), extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 15% EtOAc in petroleum ether) to afford title compound (175 mg, 64%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 9.43 (s, 1H), 8.63 (d, *J* = 5.2 Hz, 1H), 8.17 (s, 1H), 8.11 (s, 1H), 7.43 (s, 1H), 7.36 (d, *J* = 4.8 Hz, 1H), 2.80 (s, 3H), 2.70 (s, 3H), 2.24 - 2.14 (m, 1H), 1.19 - 1.13 (m, 2H), 1.13 - 1.06 (m, 2H). MS: *m/z* 328.1 (M+H⁺).

Step 2 – Synthesis of 5-(1-aminoethyl)-3-(2-cyclopropylpyridin-4-yl)-7-methylquinoline-2-carbonitrile:

To a solution of 5-acetyl-3-(2-cyclopropylpyridin-4-yl)-7-methylquinoline-2-carbonitrile (175 mg, 534 μ mol), NH₄OAc (824 mg, 10.69 mmol) and AcOH (3 mg, 53 μ mol) in MeOH (2 mL). The mixture was stirred at room temperature for 1 h. Then NaBH₃CN (101 mg, 1.60 mmol) was added to the reaction mixture. After the addition, the reaction mixture was stirred at 60 °C for 4 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (20 mL x 3). The mixture was washed with saturated NaHCO₃ solution (20 mL x 3) and brine (20 mL), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated to give the title compound (143 mg, crude) as a brown solid that required no further purification. MS: *m/z* 329.2 (M+H⁺).

Step 3 – Synthesis of *tert*-butyl 2-((1-(2-cyano-3-(2-cyclopropylpyridin-4-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoate:

A mixture of 5-(1-aminoethyl)-3-(2-cyclopropylpyridin-4-yl)-7-methylquinoline-2-carbonitrile (143 mg, 435 μ mol), *tert*-butyl 2-iodobenzoate (265 mg, 871 μ mol), Pd₂(dba)₃ (40 mg, 44 μ mol), XantPhos (50 mg, 87 μ mol) and Cs₂CO₃ (426 mg, 1.31 mmol) in dioxane (2 mL) was degassed with N₂ for 3 times and stirred at 100 °C for 16 h. The mixture was cooled to room temperature, diluted with water (10 mL), extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum.

The residue was purified by chromatography on silica (solvent gradient: 0 - 20% EtOAc in petroleum ether) to afford title compound (113 mg, 51%) as a yellow solid. MS: m/z 505.3 (M+H⁺).

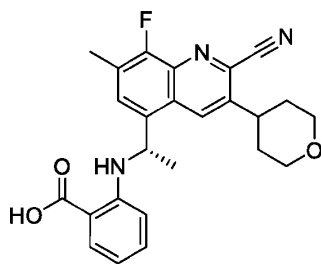
Step 4 – Synthesis of (*R*)-tert-butyl 2-((1-(2-cyano-3-(2-cyclopropylpyridin-4-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoate & (*S*)-tert-butyl 2-((1-(2-cyano-3-(2-cyclopropylpyridin-4-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoate:

Tert-butyl 2-((1-(2-cyano-3-(2-cyclopropylpyridin-4-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoate (100 mg, 198 μmol) was separated by using chiral SFC (DAICEL CHIRALCEL OD(250mm*30mm,10um); Supercritical CO₂ / EtOH + 0.1% NH₃•H₂O = 30/70; 150 mL/min) to afford (*R*)-tert-butyl 2-((1-(2-cyano-3-(2-cyclopropylpyridin-4-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoate (50 mg, first peak) and (*S*)-tert-butyl 2-((1-(2-cyano-3-(2-cyclopropylpyridin-4-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoate (39 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. MS: m/z 505.2 (M+H⁺).

Step 5 – Synthesis of (*S*)-2-((1-(2-cyano-3-(2-cyclopropylpyridin-4-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid:

To a mixture of (*S*)-tert-butyl 2-((1-(2-cyano-3-(2-cyclopropylpyridin-4-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoate (39 mg, 77 μmol) in DCM (0.6 mL) was added TFA (307 mg, 2.69 mmol). The reaction was stirred at 40 °C for 1 h. After cooling to room temperature, the reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 37% - 67% / 0.225% formic acid in water) to give the title compound (9.3 mg, 27%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.03 (s, 1H), 8.75 - 8.62 (m, 1H), 8.60 (d, *J* = 5.2 Hz, 1H), 7.89 (s, 1H), 7.85 - 7.79 (m, 1H), 7.70 (s, 1H), 7.63 (s, 1H), 7.59 - 7.54 (m, 1H), 7.17 - 7.07 (m, 1H), 6.56 - 6.47 (m, 1H), 6.39 (d, *J* = 8.4 Hz, 1H), 5.69 - 5.55 (m, 1H), 2.27 - 2.18 (m, 1H), 1.60 (d, *J* = 6.4 Hz, 3H), 1.08 - 0.98 (m, 4H). MS: m/z 449.2 (M+H⁺).

Example 57: (*S*)-2-((1-(2-cyano-8-fluoro-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoic acid (Compound 366)



Step 1 - Synthesis of (*E*)-*N*-(5-bromo-2-fluoro-3-methylphenyl)-2-(hydroxyimino)acetamide:

A mixture of 2,2,2-trichloroethane-1,1-diol (8.92 g, 53.91 mmol) and Na₂SO₄ (69.62 g, 490.10 mmol) in water (80 mL) was heated to 55 °C and then 5-bromo-2-fluoro-3-methyl-aniline (5 g, 24.51 mmol) in water (40 mL) was added, followed concentrated HCl (9 mL, 107.70 mmol, 12 M) and NH₂OH•HCl (11.07 g, 159.28 mmol) in water (20 mL) were added to the reaction mixture. The resulting mixture was stirred at 90 °C for 3 h. The suspension solution was filtered and the filter cake was washed with water (20 mL x 3) to give the title compound (6 g, 89%) was obtained as yellow solid that required no further purification. MS: m/z 274.9 (M+H⁺).

Step 2 - Synthesis of 4-bromo-7-fluoro-6-methylindoline-2,3-dione:

A mixture of (*E*)-*N*-(5-bromo-2-fluoro-3-methylphenyl)-2-(hydroxyimino)acetamide (6 g, 21.81 mmol) and H₂SO₄ (1.19 mL, 21.81 mmol, 98% purity) was stirred at 90 °C for 4 h. The reaction mixture was poured into ice water (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (2.5 g, 44%) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.64 (s, 1H), 7.18 (d, *J* = 5.6 Hz, 1H), 2.29 (s, 3H).

Step 3 - Synthesis of 2-amino-6-bromo-3-fluoro-4-methylbenzoic acid:

To a solution of 4-bromo-7-fluoro-6-methyl-indoline-2,3-dione (2.5 g, 9.69 mmol) in NaOH (35 mL, 2 M) was added H₂O₂ (6 mL, 62.44 mmol, 30% purity) at 0 °C and then the mixture was stirred at room temperature for 16 h. The mixture was quenched with sat. aq. Na₂SO₃ (20 mL), and then the mixture was acidified with conc. HCl to adjust pH to 2. The precipitate was collected by filtration and dried to give the title compound (1.9 g, 79%) as a gray solid that required no further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.74 (d, *J* = 6.4 Hz, 1H), 2.16 (s, 3H). MS : 247.7 (M+H⁺).

Step 4 - Synthesis of (2-amino-6-bromo-3-fluoro-4-methylphenyl) methanol:

A mixture of 2-amino-6-bromo-3-fluoro-4-methylbenzoic acid (0.5 g, 2.02 mmol) in THF (6 mL) was degassed and purged with N₂ for 3 times, and then added BH₃•THF (16.05 mL, 1M in THF), the mixture was stirred at room temperature for 16 h under N₂ atmosphere. The mixture was quenched with MeOH (50 mL) under N₂ atmosphere. The reaction mixture was poured into water (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo to give the title compound (0.42 g, crude) as a white solid that required no further purification. MS: m/z 234.0 (M+H⁺).

Step 5 – Synthesis of 2-amino-6-bromo-3-fluoro-4-methylbenzaldehyde:

To a solution of (2-amino-6-bromo-3-fluoro-4-methylphenyl)methanol (1.8 g, 7.69 mmol) in DCM (20 mL) was added MnO₂ (3.34 g, 38.45 mmol) at room temperature. The mixture was stirred at room temperature for 2 h. The reaction mixture was filtered and the filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (1.1 g, 61%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.13 (d, *J* = 1.8 Hz, 1H), 7.51 (s, 2H), 6.82 (d, *J* = 6.4 Hz, 1H), 2.21 (d, *J* = 2.4 Hz, 3H). MS: m/z 232.0 (M+H⁺).

Step 6 – Synthesis of 5-bromo-8-fluoro-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline:

To a solution of 2-amino-6-bromo-3-fluoro-4-methylbenzaldehyde (420 mg, 1.81 mmol) and 2-(tetrahydro-2H-pyran-4-yl)acetaldehyde (348 mg, 2.71 mmol) in *n*-BuOH (5 mL) and H₂O (0.5 mL) was added NaOH (217 mg, 5.43 mmol). The reaction mixture was stirred at 110 °C for 1 h. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to give the title compound (252 mg, 43%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.96 (s, 1H), 8.15 (s, 1H), 7.90 (d, *J* = 6.4 Hz, 1H), 4.10 - 3.97 (m, 2H), 3.58 - 3.44 (m, 2H), 3.19 - 3.04 (m, 1H), 2.43 (s, 3H), 1.92 - 1.70 (m, 4H). MS: m/z 323.9 (M+H⁺).

Step 7 – Synthesis of 5-bromo-8-fluoro-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline 1-oxide:

To a solution of 5-bromo-8-fluoro-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline (252 mg, 777 μmol) in DCM (5 mL) was added *m*-CPBA (268 mg, 1.55 mmol, 85% purity) at 0°C and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched

with sat. aq. Na₂SO₃ (20 mL) and sat. aq. NaHCO₃ (20 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc/EtOH (v/v = 3:1) in petroleum ether) to give the title compound (180 mg, 68%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.59 (d, *J* = 1.2 Hz, 1H), 8.03 (d, *J* = 5.6 Hz, 1H), 7.71 (s, 1H), 4.06 - 3.91 (m, 2H), 3.51 - 3.39 (m, 2H), 3.07 - 2.93 (m, 1H), 2.38 (d, *J* = 3.2 Hz, 3H), 1.87 - 1.68 (m, 4H). MS: *m/z* 340.0 (M+H⁺).

Step 8 – Synthesis of 5-bromo-8-fluoro-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline-2-carbonitrile:

A mixture of 5-bromo-8-fluoro-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline 1-oxide (1.6 g, 4.70 mmol), 1-ethoxyphosphonyloxyethane (1.21 mL, 9.41 mmol), TEA (1.31 mL, 9.41 mmol), CCl₄ (0.91 mL, 9.41 mmol) and trimethylsilylformonitrile (0.88 mL, 7.05 mmol) in DCM (20 mL) was degassed and purged with N₂ atmosphere for 3 times, and then the mixture was stirred at room temperature for 16 h under N₂ atmosphere. The reaction mixture was diluted with DCM (50 mL) and washed with NaHCO₃ (30 mL x 3), dried over Na₂SO₄, filtered and concentrated in vacuo. The reaction residue was dissolved in MeOH (5 mL) and stirred at room temperature for 30 min, then filtered and filter cake concentrated under reduced pressure to give the title compound (1.23 g, 75%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.41 (s, 1H), 8.16 (d, *J* = 6.4 Hz, 1H), 4.20 - 3.94 (m, 2H), 3.66 - 3.45 (m, 2H), 3.39 - 3.34 (m, 1H), 2.47 (d, *J* = 2.0 Hz, 3H), 2.01 - 1.76 (m, 4H). MS: *m/z* 349.0 (M+H⁺).

Step 9 – Synthesis of 5-acetyl-8-fluoro-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline-2-carbonitrile:

A mixture of 5-bromo-8-fluoro-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline-2-carbonitrile (1.23 g, 3.52 mmol), tributyl(1-ethoxyvinyl)stannane (2.54 g, 7.04 mmol) and Pd(dppf)Cl₂ (257 mg, 354 μ mol) in dioxane (12 mL) was degassed and purged with N₂ atmosphere for 3 times. The reaction mixture was stirred at 90 °C for 16 h under N₂ atmosphere. After cooling to room temperature, HCl (5 mL, 1 M) was added. The mixture was stirred at room temperature for 0.5 h. The reaction mixture was added 20 mL 10% KF aqueous solution, stirred at room temperature for 1 h. The mixture was extracted with DCM (3 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in

petroleum ether) to give the title compound (773 mg, 70%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.23 (s, 1H), 8.48 (d, *J* = 6.8 Hz, 1H), 4.11 - 3.97 (m, 2H), 3.60 - 3.46 (m, 2H), 3.31 - 3.24 (m, 1H), 2.75 (s, 3H), 2.52 (d, *J* = 2.0 Hz, 3H), 1.92 - 1.85 (m, 2H), 1.82 - 1.70 (m, 2H). MS: *m/z* 312.9 (M+H⁺).

5 **Step 10 – Synthesis of 5-(1-aminoethyl)-8-fluoro-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinoline-2-carbonitrile:**

A mixture of 5-acetyl-8-fluoro-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinoline-2-carbonitrile (673 mg, 2.15 μmol) in MeOH (30 mL) was added NH₄OAc (2.49 g, 32.32 mmol) and AcOH (130 mg, 2.15 μmol). The reaction mixture was stirred at room temperature for 1 h. Then
10 NaBH₃CN (406 mg, 6.46 μmol) was added to the reaction mixture. After the addition, the reaction mixture was stirred at 60 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with DCM (30 mL). The mixture was washed with saturated NaHCO₃ solution (10 mL x 3), brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 80% EtOAc in petroleum
15 ether) to give the title compound (379 mg, 56%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.77 (s, 1H), 7.83 (d, *J* = 7.2 Hz, 1H), 4.86 - 4.73 (m, 1H), 4.14 - 3.97 (m, 2H), 3.65 - 3.45 (m, 2H), 3.31 - 3.21 (m, 1H), 2.46 (d, *J* = 1.6 Hz, 3H), 2.03 - 1.88 (m, 2H), 1.87 - 1.79 (m, 2H), 1.36 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 314.2 (M+H⁺).

20 **Step 11 – Synthesis of *tert*-butyl 2-((1-(2-cyano-8-fluoro-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoate:**

A mixture of 5-(1-aminoethyl)-8-fluoro-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinoline-2-carbonitrile (300 mg, 957 μmol) and *tert*-butyl 2-iodobenzoate (436 mg, 1.44 mmol) in dioxane (5 mL) was added XantPhos (111 mg, 191 μmol), Cs₂CO₃ (936 mg, 2.87 mmol) and Pd₂(dba)₃ (88 mg, 96 μmol) under N₂ atmosphere. The reaction mixture was stirred at 100 °C for 16 h under N₂
25 atmosphere. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 15% EtOAc in petroleum ether) to give the title compound (300 mg, 64%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.81 (s, 1H), 8.18 (d, *J* = 6.0 Hz, 1H), 7.85 - 7.74 (m, 1H), 7.64 (d, *J* = 6.8 Hz, 1H), 7.25 - 7.13 (m, 1H), 6.61 - 6.51 (m, 1H), 6.50 - 6.40 (m, 1H), 5.61 - 5.53 (m, 1H),
30 4.10 - 3.98 (m, 2H), 3.63 - 3.51 (m, 2H), 3.31 - 3.24 (m, 1H), 2.40 (d, *J* = 1.6 Hz, 3H), 2.08 - 1.90 (m, 2H), 1.88 - 1.79 (m, 2H), 1.60 (d, *J* = 6.4 Hz, 3H), 1.57 (s, 9H). MS: *m/z* 490.2 (M+H⁺).

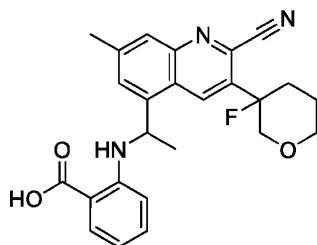
Step 12 – Synthesis of *tert*-butyl (*R*)-2-((1-(2-cyano-8-fluoro-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoate & *tert*-butyl (*S*)-2-((1-(2-cyano-8-fluoro-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoate:

tert-butyl 2-((1-(2-cyano-8-fluoro-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoate (300 mg, 613 μ mol) was purified by using chiral SFC (DAICEL CHIRALCEL OD (250mm*30mm,10 μ m); Supercritical CO₂ / EtOH + 0.1% NH₃•H₂O = 30/70; 80 mL/min) to afford *tert*-butyl (*R*)-2-((1-(2-cyano-8-fluoro-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoate (153 mg, first peak) and *tert*-butyl (*S*)-2-((1-(2-cyano-8-fluoro-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoate (147 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. MS: *m/z* 490.2 (M+H⁺).

Step 13 – Synthesis of (*S*)-2-((1-(2-cyano-8-fluoro-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoic acid:

A mixture of *tert*-butyl (*S*)-2-((1-(2-cyano-8-fluoro-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoate (70 mg, 143 μ mol) in DCM (1 mL) was added TFA (0.2 mL, 2.7 mmol) and then the mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 51% - 81% / 0.225% formic acid in water) to give the title compound (22.02 mg, 36%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.81 (s, 1H), 8.81 (s, 1H), 8.42 (d, *J* = 5.2 Hz, 1H), 7.87 - 7.75 (m, 1H), 7.62 (d, *J* = 6.8 Hz, 1H), 7.24 - 7.13 (m, 1H), 6.62 - 6.51 (m, 1H), 6.48 - 6.40 (m, 1H), 5.67 - 5.52 (m, 1H), 4.12 - 3.90 (m, 2H), 3.61-3.47 (m, 2H), 3.31 - 3.23 (m, 1H), 2.40 (s, 3H), 2.06 - 1.89 (m, 2H), 1.87 - 1.78 (m, 2H), 1.59 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 434.2 (M+H⁺).

Example 58: 2-((1-(2-cyano-3-(3-fluorotetrahydro-2*H*-pyran-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid (Compound 353)



Step 1 - Synthesis of 5-chloro-7-methylquinoline and 7-chloro-5-methylquinoline:

A mixture of 3-chloro-5-methyl-aniline (10 g, 70.62 mmol), sodium 3-nitrobenzenesulfonate (7.95 g, 35.31 mmol) and glycerol (26.42 mL, 353.11 mmol) in concentrated H₂SO₄ (80 mL) was stirred at 140 °C for 6 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was quenched with sat. aq. NaHCO₃ solution (2 L) and the water layer was extracted with EtOAc (300 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the mixture compound (3.7 g, 30%, mixture 1:1) as a yellow solid. The mixture compound was further purified by reverse phase chromatography (acetonitrile 40% - 60% / 0.05% NH₃H₂O + 10 mM NH₄HCO₃ in water) to give 5-chloro-7-methylquinoline (1.5 g, 41%, which was further confirmed by NOESY) and 7-chloro-5-methylquinoline (1.5 g, 41%) both as yellow solid, 5-chloro-7-methylquinoline: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.79 (d, *J* = 2.8 Hz, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 7.75 (s, 1H), 7.45-7.40 (m, 1H), 7.33 (s, 1H), 2.51 (s, 3H). MS: *m/z* 178.1 (M+H⁺). 7-chloro-5-methylquinoline: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.93 (d, *J* = 2.4 Hz, 1H), 8.46 (d, *J* = 8.8 Hz, 1H), 7.80 (s, 1H), 7.64 (s, 1H), 7.61-7.57 (m, 1H), 2.52 (s, 3H). MS: *m/z* 178.1 (M+H⁺).

Step 2 - Synthesis of 5-chloro-3-iodo-7-methylquinoline and 7-chloro-3-iodo-5-methylquinoline:

To a solution of 5-chloro-7-methylquinoline and 7-chloro-5-methylquinoline (870 mg, 4.90 mmol) and I₂ (2.49 g, 9.80 mmol) in DCE (20 mL) was added TBHP (1.89 g, 14.69 mmol) was stirred at 90 °C for 16 h under N₂ atmosphere. The reaction was quenched by addition sat. aq. NaHCO₃ and extracted with DCM (40 mL x 3). The combined organic layers were washed with sat. aq. Na₂SO₃ (40 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a crude. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% EtOAc in petroleum ether) to give the title compound (300 mg, 20%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.17 - 8.99 (m, 1H), 8.90 - 8.67 (m, 1H), 7.84 - 7.74 (m, 1H), 7.73 - 7.60 (m, 1H), 2.49 - 2.43 (m, 3H). MS: *m/z* 303.7 (M+H⁺).

Step 3 - Synthesis of 3-(5-chloro-7-methylquinolin-3-yl)tetrahydro-2H-pyran-3-ol:

To a solution of 5-chloro-3-iodo-7-methylquinoline (4.9 g, 16.14 mmol) and dihydro-2H-pyran-3(4H)-one in THF (50 mL) was added *i*-PrMgCl (3.32 g, 32.29 mmol, 2M in THF) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h under N₂ atmosphere. The reaction was quenched

with sat. aq. NH_4Cl (30 mL), extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 80% EtOAc in petroleum ether) to give the title compound (1.2 g, 27%) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.13 (d, J = 2.0 Hz, 1H), 8.59 (d, J = 1.6 Hz, 1H), 7.82 (s, 1H), 7.68 (d, J = 1.2 Hz, 1H), 5.59 (s, 1H), 3.90 - 3.82 (m, 1H), 3.81 - 3.73 (m, 1H), 3.67 - 3.59 (m, 1H), 3.56 - 3.49 (m, 1H), 2.52 (s, 3H), 2.27 - 2.15 (m, 1H), 1.99 - 1.90 (m, 1H), 1.89 - 1.78 (m, 1H), 1.50 - 1.36 (m, 1H). MS: m/z 278.0 ($\text{M}+\text{H}^+$).

Step 4 - Synthesis of 5-chloro-3-(3-fluorotetrahydro-2H-pyran-3-yl)-7-methylquinoline:

To a solution of 3-(5-chloro-7-methylquinolin-3-yl)tetrahydro-2H-pyran-3-ol (1.2 g, 4.39 mmol) in DCM (100 mL) was added DAST (1.4 g, 8.79 mmol) at -78°C . After the addition, the reaction mixture was stirred at room temperature for 1 h. The mixture was quenched with sat. aq. NaHCO_3 (50 mL), extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (930 mg, 75%) as a yellow solid. MS: m/z 280.1 ($\text{M}+\text{H}^+$).

Step 5 - Synthesis of 5-chloro-3-(3-fluorotetrahydro-2H-pyran-3-yl)-7-methylquinoline 1-oxide:

To a solution of 5-chloro-3-(3-fluorotetrahydro-2H-pyran-3-yl)-7-methylquinoline (930 mg, 3.32 mmol) in DCM (30 mL) was added *m*-CPBA (1.15 g, 6.65 mmol, 85% purity) at 0°C and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with sat. aq. Na_2SO_3 (20 mL) and sat. aq. NaHCO_3 (20 mL), extracted with DCM (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 60% EtOAc in petroleum ether) to give the title compound (858 mg, 87%) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.81 (s, 1H), 8.29 (s, 1H), 7.97 (s, 1H), 7.82 (s, 1H), 3.93 - 3.73 (m, 3H), 3.66 - 3.52 (m, 1H), 2.53 (s, 3H), 2.46 - 2.26 (m, 1H), 2.17 - 2.05 (m, 1H), 1.96 - 1.86 (m, 1H), 1.65 - 1.54 (m, 1H). MS: m/z 296.0 ($\text{M}+\text{H}^+$).

Step 6 - Synthesis of 5-chloro-3-(3-fluorotetrahydro-2H-pyran-3-yl)-7-methylquinoline-2-carbonitrile:

A mixture of 5-chloro-3-(3-fluorotetrahydro-2H-pyran-3-yl)-7-methylquinoline 1-oxide (850 mg, 2.90 mmol), 1-ethoxyphosphonyloxyethane (0.75 mL, 5.80 mmol), TEA (0.81 mL, 5.80 mmol), CCl₄ (0.56 mL, 5.80 mmol) and trimethylsilylformonitrile (0.54 mL, 4.35 mmol) in DCM (10 mL) was degassed and purged with N₂ atmosphere for 3 times, and then the mixture was stirred at room temperature for 16 h under N₂ atmosphere. The reaction mixture was diluted with DCM (50 mL) and washed with NaHCO₃ (30 mL x 2), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc/EtOH (v/v = 3:1) in petroleum ether) to give the title compound (850 mg, 96%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.71 (s, 1H), 7.98 (s, 1H), 7.96 (s, 1H), 4.19 - 4.12 (m, 1H), 3.96 - 3.84 (m, 2H), 3.68 - 3.61 (m, 1H), 2.74 - 2.61 (m, 1H), 2.57 (s, 3H), 2.40 - 2.23 (m, 1H), 2.07 - 1.88 (m, 1H), 1.72 - 1.57 (m, 1H). MS: m/z 305.1 (M+H⁺).

Step 7 - Synthesis of 3-(3-fluorotetrahydro-2H-pyran-3-yl)-7-methyl-5-(1-nitroethyl)quinoline-2-carbonitrile:

To a solution of 5-chloro-3-(3-fluorotetrahydro-2H-pyran-3-yl)-7-methylquinoline-2-carbonitrile (100 mg, 328 μ mol), nitroethane (73.9 mg, 984 μ mol) in dioxane (2 mL) was added Cs₂CO₃ (320 mg, 984 μ mol), Pd₂(dba)₃ (30 mg, 32 μ mol) and di-tert-butyl-[2-(*o*-tolyl)phenyl]phosphine (10 mg, 33 μ mol). The reaction was stirred at 60 °C for 3 h under N₂ atmosphere. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% MeOH in DCM) to give the title compound (120 mg, crude) as a yellow solid. MS: m/z 344.1 (M+H⁺).

Step 8 - Synthesis of 5-(1-aminoethyl)-3-(3-fluorotetrahydro-2H-pyran-3-yl)-7-methylquinoline-2-carbonitrile:

To a solution of 3-(3-fluorotetrahydro-2H-pyran-3-yl)-7-methyl-5-(1-nitroethyl)quinoline-2-carbonitrile (120 mg, 394 μ mol) and NH₄Cl (373 mg, 6.99 mmol) in EtOH (6 mL) and H₂O (2 mL) was added iron powder (195 mg, 3.49 mmol). The reaction mixture was stirred at 80 °C for 1 h. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% MeOH in DCM) to give the title compound (50 mg, 45%) as a white solid. MS: m/z 313.9 (M+H⁺).

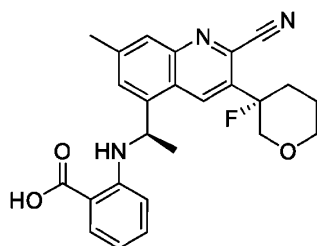
Step 9 - Synthesis of *tert*-butyl 2-((1-(2-cyano-3-(3-fluorotetrahydro-2*H*-pyran-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoate:

A mixture of 5-(1-aminoethyl)-3-(3-fluorotetrahydro-2*H*-pyran-3-yl)-7-methylquinoline-2-carbonitrile (50 mg, 159 μ mol), *tert*-butyl 2-iodobenzoate (73 mg, 239 μ mol), Cs₂CO₃ (156 mg, 478 μ mol), Pd₂(dba)₃ (15 mg, 16 μ mol) and XantPhos (19 mg, 32 μ mol) in dioxane (2 mL), the reaction mixture was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% EtOAc in petroleum ether) to give the title compound (22 mg, 28%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.96 - 8.73 (m, 1H), 8.22 - 8.14 (m, 1H), 7.85 (s, 1H), 7.82 - 7.76 (m, 1H), 7.68 - 7.59 (m, 1H), 7.22 - 7.14 (m, 1H), 6.61 - 6.51 (m, 1H), 6.50 - 6.39 (m, 1H), 5.64 - 5.50 (m, 1H), 4.15 - 4.01 (m, 1H), 3.99 - 3.82 (m, 2H), 3.61 - 3.49 (m, 1H), 2.49 - 2.46 (m, 3H), 2.38 - 2.23 (m, 1H), 2.05 - 1.90 (m, 1H), 1.78 - 1.66 (m, 1H), 1.65 - 1.63 (m, 3H), 1.59 - 1.54 (m, 9H), 1.52 - 1.43 (m, 1H). MS: *m/z* 490.4 (M+H⁺).

Step 10 - Synthesis of 2-((1-(2-cyano-3-(3-fluorotetrahydro-2*H*-pyran-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid:

To a mixture of *tert*-butyl 2-((1-(2-cyano-3-(3-fluorotetrahydro-2*H*-pyran-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoate (22 mg, 45 μ mol) in DCM (1 mL) was added TFA (0.2 mL). The reaction mixture was stirred at 30 °C for 16 h. After cooling to room temperature, the reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 45% - 75% / 0.225% formic acid in water) to give the title compound (13.72 mg, 34%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.85 (s, 1H), 8.83 (d, *J* = 8.4 Hz, 1H), 8.47 (s, 1H), 7.89 - 7.79 (m, 2H), 7.68 - 7.58 (m, 1H), 7.24 - 7.13 (m, 1H), 6.62 - 6.51 (m, 1H), 6.49 - 6.37 (m, 1H), 5.69 - 5.48 (m, 1H), 4.19 - 4.05 (m, 1H), 4.04 - 3.81 (m, 2H), 3.66 - 3.50 (m, 1H), 2.65 - 2.53 (m, 1H), 2.50 - 2.42 (m, 3H), 2.32 - 2.18 (m, 1H), 2.05 - 1.91 (m, 1H), 1.71 - 1.56 (m, 4H). MS: *m/z* 434.1 (M+H⁺).

Example 59: 2-(((*R*)-1-(2-cyano-3-((*S*)-3-fluorotetrahydro-2*H*-pyran-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid (Compound 328)

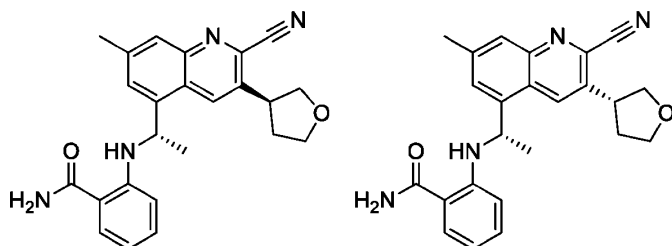


Step 1 – Synthesis of 2-(((R)-1-(2-cyano-3-((R)-3-fluorotetrahydro-2H-pyran-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid & 2-(((S)-1-(2-cyano-3-((R)-3-fluorotetrahydro-2H-pyran-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid & 2-(((S)-1-(2-cyano-3-((S)-3-fluorotetrahydro-2H-pyran-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid & 2-(((R)-1-(2-cyano-3-((S)-3-fluorotetrahydro-2H-pyran-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid:

2-(((1-(2-cyano-3-(3-fluorotetrahydro-2H-pyran-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid (50 mg, 115.3 μmol) was separated by using chiral SFC (DAICEL CHIRALPAK AD (250mm*30mm,10 μm); Supercritical CO_2 / MeOH + 0.1% $\text{NH}_3 \cdot \text{H}_2\text{O}$ = 70/30; 80 mL/min) to afford 2-(((1-(2-cyano-3-(3-fluorotetrahydro-2H-pyran-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid (16 mg, mixture of first peak, second peak and third peak) and 2-(((R)-1-(2-cyano-3-((R)-3-fluorotetrahydro-2H-pyran-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid (3 mg, fourth peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. 2-(((1-(2-cyano-3-(3-fluorotetrahydro-2H-pyran-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid (16 mg, 37.0 μmol , mixture of first peak, second peak and third peak) was separated by using chiral SFC (DAICEL CHIRALPAK OD (250mm*30mm,10 μm); Supercritical CO_2 / MeOH + 0.1% $\text{NH}_3 \cdot \text{H}_2\text{O}$ = 60/40; 80 mL/min) to afford 2-(((S)-1-(2-cyano-3-((R)-3-fluorotetrahydro-2H-pyran-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid (1.13 mg, first peak), 2-(((S)-1-(2-cyano-3-((S)-3-fluorotetrahydro-2H-pyran-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid (1.77 mg, second peak) and 2-(((R)-1-(2-cyano-3-((S)-3-fluorotetrahydro-2H-pyran-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid (0.89 mg, third peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. First peak: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.83 (s, 1H), 8.65 (s, 1H), 7.85 - 7.80 (m, 2H), 7.62 (s, 1H), 7.17 - 7.10 (m, 1H), 6.52 (m, 1H), 6.39 (d, J = 9.2 Hz, 1H), 5.60 - 5.50 (m, 1H), 4.14 - 4.06 (s, 1H), 3.94 - 3.90 (m, 2H), 3.63 - 3.57 (m, 2H), 2.48 (s,

3H), 2.29 - 2.21 (m, 1H), 2.00 - 1.96 (m, 1H), 1.68 - 1.63 (m, 1H), 1.61 (d, $J = 6.4$ Hz, 3H). MS: m/z 434.2 ($M+H^+$). Second peak: 1H NMR (400 MHz, DMSO- d_6) δ 8.80 (s, 1H), 8.50 (s, 1H), 7.86 - 7.79 (m, 2H), 7.64 (s, 1H), 7.20 - 7.13 (m, 1H), 6.55 - 6.49 (m, 1H), 6.45 (d, $J = 8.4$ Hz, 1H), 5.57 - 5.50 (m, 1H), 4.12 - 4.03 (m, 1H), 4.02 - 3.87 (m, 2H), 3.60 - 3.54 (m, 2H), 2.49 - 2.48 (m, 3H), 2.31 - 2.25 (m, 1H), 2.03 - 1.92 (m, 1H), 1.68 - 1.62 (s, 1H), 1.62 (d, $J = 6.4$ Hz, 3H). MS: m/z 434.2 ($M+H^+$). Third peak: 1H NMR (400 MHz, DMSO- d_6) δ 8.83 (s, 1H), 8.60 (s, 1H), 7.86 - 7.80 (m, 2H), 7.61 (s, 1H), 7.18 - 7.09 (m, 1H), 6.55 - 6.49 (m, 1H), 6.39 (d, $J = 8.4$ Hz, 1H), 5.61 - 5.52 (m, 1H), 4.15 - 4.05 (m, 1H), 4.00 - 3.88 (m, 2H), 3.62 - 3.55 (m, 2H), 2.48 (s, 3H), 2.30 - 2.23 (m, 1H), 2.03 - 1.94 (m, 1H), 1.71 - 1.65 (s, 1H), 1.61 (d, $J = 6.4$ Hz, 3H). MS: m/z 434.3 ($M+H^+$). Fourth peak: 1H NMR (400 MHz, DMSO- d_6) δ 8.82 (s, 1H), 7.85 - 7.78 (m, 2H), 7.66 (s, 1H), 7.16 - 7.03 (m, 1H), 6.53 - 6.45 (m, 1H), 6.39 (d, $J = 8.8$ Hz, 1H), 5.55 - 5.44 (m, 1H), 4.11 - 4.03 (m, 1H), 4.01 - 3.88 (m, 2H), 3.61 - 3.53 (m, 2H), 2.44 (s, 3H), 2.31 - 2.22 (m, 1H), 2.03 - 1.92 (m, 1H), 1.69 - 1.64 (m, 1H), 1.61 (d, $J = 6.0$ Hz, 3H). MS: m/z 434.3 ($M+H^+$).

Example 60: 2-(((S)-1-(2-cyano-7-methyl-3-((S)-tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzamide (Compound 430) & 2-(((S)-1-(2-cyano-7-methyl-3-((R)-tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzamide (Compound 431)



Step 1 - Synthesis of 5-bromo-7-methyl-3-(tetrahydrofuran-3-yl)quinoline:

To a solution of 2-(tetrahydrofuran-3-yl)acetaldehyde (7.23 g, 63.33 mmol) (prepared according to the procedure in WO201283105) and 2-amino-6-bromo-4-methylbenzaldehyde (13.5 g, 143.94 mmol) in *n*-BuOH (130 mL) and H₂O (13 mL) was added NaOH (5.76 g, 18.5 mmol). The reaction mixture was stirred at 110 °C for 1 h. After cooling to room temperature, the mixture was concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (17 g, 89%) as a yellow solid. 1H NMR (400 MHz, DMSO- d_6) δ 8.98 (d, $J = 2.0$ Hz, 1H), 8.28 (s, 1H), 8.14 (s, 1H), 8.10

(d, $J = 1.6$ Hz, 1H), 4.14 - 4.08 (m, 1H), 4.07 - 3.98 (m, 1H), 3.90 - 3.81 (m, 1H), 3.79 - 3.68 (m, 2H), 2.49 - 2.40 (m, 1H), 2.14 - 2.00 (m, 1H). MS: m/z 311.9 ($M+H^+$).

Step 2 - Synthesis of 5-bromo-7-methyl-3-(tetrahydrofuran-3-yl)quinoline 1-oxide:

To a solution of 5-bromo-7-methyl-3-(tetrahydrofuran-3-yl)quinoline (25 g, 79.98 mmol) in DCM (100 mL) was added *m*-CPBA (16.24 g, 79.98 mmol, 80% purity) at 0°C and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched by sat. $NaHCO_3$ (100 mL) and extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give the title compound (28.91 g, crude) as yellow solid that required no further purification. 1H NMR (400 MHz, $DMSO-d_6$) δ 8.98 (d, $J = 2.0$ Hz, 1H), 8.28 (s, 1H), 8.14 (s, 1H), 8.10 (d, $J = 1.6$ Hz, 1H), 4.14 - 4.08 (m, 2H), 4.07 - 3.98 (m, 1H), 3.90 - 3.81 (m, 1H), 3.79 - 3.68 (m, 1H), 2.49 - 2.40 (m, 1H), 2.14 - 2.00 (m, 1H). MS: m/z 328.0 ($M+H^+$).

Step 3 - Synthesis of 5-bromo-7-methyl-3-(tetrahydrofuran-3-yl)quinoline-2-carbonitrile:

A mixture of 5-bromo-7-methyl-3-(tetrahydrofuran-3-yl)quinoline 1-oxide (15.2 g, 46.26 mmol), 1-ethoxyphosphonyloxyethane (11.92 mL, 92.53 mmol), TEA (12.88 mL 92.52 mmol), CCl_4 (8.92 mL, 92.52 mmol) and $TMSCN$ (8.68 mL, 69.39 mmol) in DCM (150 mL) was degassed and purged with N_2 atmosphere for 3 times, and then the mixture was stirred at room temperature for 16 h under N_2 atmosphere. The reaction mixture was diluted with DCM (300 mL) and washed with $NaHCO_3$ (100 mL x 2), dried over Na_2SO_4 , filtered and concentrated in vacuo. The reaction was filtered and the filter cake was concentrated in vacuo to give the title compound (11.4 g, crude) as a yellow solid that required no further purification. 1H NMR (400 MHz, $DMSO-d_6$) δ 8.49 (s, 1H), 8.29 - 8.27 (m, 2H), 4.13 - 4.05 (m, 1H), 3.96 - 3.85 (m, 3H), 3.17 - 2.99 (m, 1H), 2.61 - 2.51 (m, 1H), 2.20 - 2.03 (m, 1H). MS: m/z 337.0 ($M+H^+$).

Step 4 - Synthesis of 5-acetyl-7-methyl-3-(tetrahydrofuran-3-yl)quinoline-2-carbonitrile:

A mixture of 5-bromo-7-methyl-3-(tetrahydrofuran-3-yl)quinoline-2-carbonitrile (8 g, 23.70 mmol), tributyl(1-ethoxyvinyl)stannane (8.99 g, 8.41 mmol) and $Pd(dppf)Cl_2$ (8.67 mg, 1.18 mmol) in dioxane (80 mL) was degassed and purged with N_2 atmosphere for 3 times. The reaction mixture was stirred at 90 °C for 16 h under N_2 atmosphere. After cooling to room temperature, HCl (15 mL, 1 M) was added. The mixture was stirred at room temperature for 0.5 h. The reaction

mixture was added 100 mL 10% KF aqueous solution, stirred at room temperature for 2 h. The mixture was extracted with EtOAc (80 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to give the title compound (6 g, 85%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.06 (s, 1H), 8.46 - 8.42 (m, 2H), 4.13 - 4.08 (m, 1H), 4.05 - 3.96 (m, 1H), 3.93 - 3.86 (m, 2H), 3.86 - 3.81 (m, 1H), 2.78 (s, 3H), 2.56 - 2.52 (m, 1H), 2.09 - 1.98 (m, 1H). MS: m/z 301.1 (M+H⁺).

Step 5 - Synthesis of 5-(1-hydroxyethyl)-7-methyl-3-(tetrahydrofuran-3-yl)quinoline-2-carbonitrile:

To a solution of 5-acetyl-7-methyl-3-(tetrahydrofuran-3-yl)quinoline-2-carbonitrile (0.80 g, 2.85 mmol) in DCM (5 mL) and MeOH (5 mL) was added NaBH₄ (324 mg, 8.56 mmol) at 0 °C, and then the mixture was stirred at 0 °C for 15 min under N₂ atmosphere. The reaction was quenched with sat. aq. NH₄Cl (10 mL) and extracted with DCM (20 mL x 3). The organics were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 25% - 50% EtOAc in petroleum ether) to give the title compound (282 mg, 82%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.67 (d, *J* = 2.8 Hz, 1H), 7.77 (s, 1H), 7.69 (s, 1H), 5.56 - 5.51 (m, 1H), 5.50 - 5.41 (m, 1H), 4.17 - 4.09 (m, 1H), 4.07 - 3.97 (m, 1H), 3.95 - 3.80 (m, 3H), 2.54 (s, 3H), 2.52 - 2.43 (m, 1H), 2.20 - 2.04 (m, 1H), 1.47 (d, *J* = 6.0 Hz, 3H). MS: m/z 283.2 (M+H⁺).

Step 6 - Synthesis of 5-(1-bromoethyl)-7-methyl-3-(tetrahydrofuran-3-yl)quinoline-2-carbonitrile:

To a solution of 5-(1-hydroxyethyl)-7-methyl-3-(tetrahydrofuran-3-yl)quinoline-2-carbonitrile (670 mg, 2.37 mmol) in DCM (10 mL) was added PBr₃ (963 mg, 3.56 mmol). The mixture was stirred at 0 °C for 0.5 h. The mixture was quenched with sat. aq. NaHCO₃ (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (20 mL x 2), dried over Na₂SO₄, filtered and concentrated in vacuo to remove EtOAc and give the title compound (581 mg, 70% yield) as colorless oil that required no further purification. MS: m/z 347.1 (M+H⁺).

Step 7 - Synthesis of 2-((1-(2-cyano-7-methyl-3-(tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzamide:

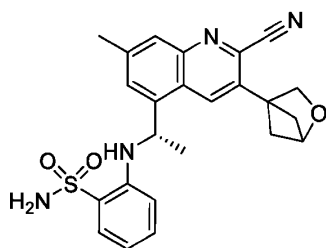
To a solution of 5-(1-bromoethyl)-7-methyl-3-(tetrahydrofuran-3-yl)quinoline-2-carbonitrile (581 mg, 1.68 mmol) in DMF (8 mL) was added 2-aminobenzamide (344 mg, 2.52 mmol). The mixture was stirred at room temperature for 5 h. The mixture was quenched with water (10 mL), extracted with EtOAc (20 mL x 2). The combined organic layers were washed with
5 brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude was purified by flash silica gel chromatography (solvent gradient: 25% - 35% EtOAc in petroleum ether) to give the title compound (200 mg, 26%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.85 - 8.81 (m, 1H), 8.75 - 8.72 (m, 1H), 7.98 - 7.87 (m, 1H), 7.78 (s, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.59 (s, 1H), 7.27 (s, 1H), 7.12 - 7.01 (m, 1H), 6.54 - 6.45 (m, 1H), 6.42 - 6.38 (m, 1H),
10 5.47 - 5.43 (m, 1H), 4.18 - 4.10 (m, 1H), 4.06 - 3.95 (m, 2H), 3.93 - 3.77 (m, 3H), 2.46 (s, 3H), 2.23 - 2.13 (m, 1H), 1.56 (d, *J* = 6.4 Hz, 3H). *m/z* 401.2 (M+H⁺).

Step 8 - Synthesis of 2-(((*R*)-1-(2-cyano-7-methyl-3-((*S*)-tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzamide & 2-(((*R*)-1-(2-cyano-7-methyl-3-((*R*)-tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzamide & 2-(((*S*)-1-(2-cyano-7-methyl-3-((*S*)-tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzamide & 2-(((*S*)-1-(2-cyano-7-methyl-3-((*R*)-tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzamide
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2-(((1-(2-cyano-7-methyl-3-(tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzamide (200 mg, 499 μmol) was separated by using chiral SFC (DAICEL CHIRALPAK OD (250mm*30mm,10um); Supercritical CO₂-MeOH + 0.1% NH₃•H₂O = 40/60; 80 mL/min) to
20 afford 2-(((1*R*)-1-(2-cyano-7-methyl-3-(tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzamide (50 mg, mixture of first peak and second peak), 2-(((*S*)-1-(2-cyano-7-methyl-3-((*S*)-tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzamide (13.2 mg, third peak) and
2-(((*S*)-1-(2-cyano-7-methyl-3-((*R*)-tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzamide (9.1 mg, fourth peak) both as white solid. Absolute configuration was
25 arbitrarily assigned to each enantiomer. 2-(((1*R*)-1-(2-cyano-7-methyl-3-(tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzamide (50 mg, mixture of first peak and second peak) was separated by using chiral SFC (DAICEL CHIRALPAK AD (250mm*30mm,10um); Supercritical CO₂-EtOH + 0.1% NH₃•H₂O = 60/40; 80 mL/min) to afford 2-(((*R*)-1-(2-cyano-7-methyl-3-((*S*)-tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzamide (5.1 mg, first peak) and 2-(((*R*)-1-(2-cyano-7-methyl-3-((*R*)-tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzamide (5.3 mg,
30 second peak) both as white solid. Absolute configuration was arbitrarily assigned to each

enantiomer. First peak: ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.82 (d, $J = 6.4$ Hz, 1H), 8.72 (s, 1H), 7.92 (s, 1H), 7.78 (s, 1H), 7.65 - 7.60 (m, 2H), 7.26 (s, 1H), 7.09 (t, $J = 7.6$ Hz, 1H), 6.50 (t, $J = 7.6$ Hz, 1H), 6.41 (d, $J = 8.4$ Hz, 1H), 5.50 - 5.40 (m, 1H), 4.20 - 4.08 (m, 1H), 4.04 - 3.94 (m, 1H), 3.93 - 3.76 (m, 3H), 2.46 (s, 3H), 2.48 - 2.41 (m, 1H), 2.24 - 2.13 (m, 1H), 1.56 (d, $J = 6.4$ Hz, 3H). MS: m/z 401.0 ($\text{M}+\text{H}^+$). Second peak: ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.84 (d, $J = 6.4$ Hz, 1H), 8.75 (s, 1H), 7.92 (s, 1H), 7.78 (s, 1H), 7.66 - 7.60 (m, 2H), 7.27 (s, 1H), 7.07 (t, $J = 7.6$ Hz, 1H), 6.50 (t, $J = 7.6$ Hz, 1H), 6.39 (d, $J = 8.8$ Hz, 1H), 5.45 (t, $J = 6.4$ Hz, 1H), 4.18 - 4.10 (m, 1H), 4.04 - 3.98 (m, 1H), 3.93 - 3.82 (m, 3H), 2.46 (s, 3H), 2.48 - 2.38 (m, 1H), 2.22 - 2.12 (m, 1H), 1.56 (d, $J = 6.4$ Hz, 3H). MS: m/z 401.2 ($\text{M}+\text{H}^+$). Third peak: ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.84 (d, $J = 6.0$ Hz, 1H), 8.75 (s, 1H), 7.92 (s, 1H), 7.78 (s, 1H), 7.65 - 7.59 (m, 2H), 7.27 (s, 1H), 7.09 - 7.05 (m, 1H), 6.52 - 6.48 (m, 1H), 6.40 (d, $J = 8.4$ Hz, 1H), 5.51 - 5.38 (m, 1H), 4.17 - 4.10 (m, 1H), 4.05 - 3.97 (m, 1H), 3.94 - 3.81 (m, 3H), 2.46 (s, 3H), 2.48 - 2.41 (m, 1H), 2.24 - 2.11 (m, 1H), 1.56 (d, $J = 6.4$ Hz, 3H). MS: m/z 401.1 ($\text{M}+\text{H}^+$). Fourth peak: ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.82 (d, $J = 6.4$ Hz, 1H), 8.72 (s, 1H), 7.92 (s, 1H), 7.78 (s, 1H), 7.65 - 7.59 (m, 2H), 7.25 (s, 1H), 7.11 - 7.07 (m, 1H), 6.52 - 6.48 (m, 1H), 6.41 (d, $J = 8.4$ Hz, 1H), 5.47 - 5.43 (m, 1H), 4.16 - 4.12 (m, 1H), 4.02 - 3.95 (m, 1H), 3.92 - 3.76 (m, 3H), 2.46 (s, 3H), 2.48 - 2.41 (m, 1H), 2.25 - 2.14 (m, 1H), 1.57 (d, $J = 6.8$ Hz, 3H). MS: m/z 401.0 ($\text{M}+\text{H}^+$).

Example 61: (*S*)-2-((1-(3-(2-oxabicyclo[2.1.1]hexan-4-yl)-2-cyano-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (Compound 344)



Step 1 - 3-(2-oxabicyclo[2.1.1]hexan-4-yl)-5-bromo-7-methylquinoline:

To a solution of 2-(2-oxabicyclo[2.1.1]hexan-4-yl)acetaldehyde (1.6 g, 12.68 mmol) and 2-amino-6-bromo-4-methylbenzaldehyde (3.26 g, 15.22 mmol) in *n*-BuOH (20 mL) and H_2O (2 mL) was added NaOH (1.01 g, 25.37 mmol). The reaction mixture was stirred at 110 °C for 1 h. After cooling to room temperature, the mixture was added water (20 mL) and extracted with

EtOAc (50 mL x 2). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% EtOAc in petroleum ether) to give the title compound (2.8 g, 73%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.80 (d, *J* = 2.0 Hz, 1H), 8.25 (d, *J* = 2.0 Hz, 1H), 7.86 (s, 1H), 7.71 (d, *J* = 1.2 Hz, 1H), 4.76 (s, 1H), 4.00 (s, 2H), 2.55 (s, 3H), 2.23 - 2.18 (m, 2H), 2.14 - 2.11 (m, 2H). MS: *m/z* 304.0 (M+H⁺).

Step 2 - 3-(2-oxabicyclo[2.1.1]hexan-4-yl)-5-bromo-7-methylquinoline 1-oxide:

To a solution of 3-(2-oxabicyclo[2.1.1]hexan-4-yl)-5-bromo-7-methylquinoline (2.8 g, 9.21 mmol) in DCM (30 mL) was added *m*-CPBA (3.97 g, 18.41 mmol, 80% purity) at 0 °C and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched by sat. aq. Na₂S₂O₃ (30 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with 2M NaOH (40 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give the title compound (2.9 g, crude) as yellow oil that required no further purification. ¹H NMR (400 MHz, CDCl₃) δ 8.52 - 8.49 (m, 2H), 7.88 - 7.75 (m, 2H), 4.74 (s, 1H), 3.95 (s, 2H), 2.58 (s, 3H), 2.19 - 2.14 (m, 2H), 2.11 - 2.06 (m, 2H). MS: *m/z* 320.0 (M+H⁺).

Step 3 - 3-(2-oxabicyclo[2.1.1]hexan-4-yl)-5-bromo-7-methylquinoline-2-carbonitrile:

A mixture of 3-(2-oxabicyclo[2.1.1]hexan-4-yl)-5-bromo-7-methylquinoline 1-oxide (2.9 g, 9.06 mmol), 1-ethoxyphosphonyloxyethane (2.5 g, 18.11 mmol), TEA (1.83 g, 18.11 mmol), CCl₄ (2.79 g, 18.11 mmol) and TMSCN (1.70 mL, 13.59 mmol) in DCM (30 mL) was degassed and purged with N₂ atmosphere for 3 times, and then the mixture was stirred at room temperature for 16 h under N₂ atmosphere. The reaction mixture was diluted with DCM (30 mL) and washed with NaHCO₃ (35 mL x 2), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was triturated with petroleum ether (50 mL) at room temperature to give the title compound (2.9 g, 97%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.35 (s, 1H), 7.89 (s, 1H), 7.82 (s, 1H), 4.77 (s, 1H), 4.08 (s, 2H), 2.58 (s, 3H), 2.44 - 2.41 (m, 2H), 2.30 - 2.27 (m, 2H). MS: *m/z* 329.0 (M+H⁺).

Step 4 - 5-acetyl-3-(2-oxabicyclo[2.1.1]hexan-4-yl)-7-methylquinoline-2-carbonitrile

A mixture of 3-(2-oxabicyclo[2.1.1]hexan-4-yl)-5-bromo-7-methylquinoline-2-carbonitrile (1.5 g, 4.56 mmol), tributyl(1-ethoxyvinyl)stannane (1.65 g, 4.56 mmol) and Pd(dppf)Cl₂ (333 mg, 456 μmol) in dioxane (15 mL) was degassed and purged with N₂ atmosphere for 3 times. The reaction mixture was stirred at 90 °C for 16 h under N₂ atmosphere. After cooling

to room temperature, HCl (5 mL, 1 M) was added. The mixture was stirred at room temperature for 0.5 h. The reaction mixture was added 50 mL 10% KF aqueous solution, stirred at room temperature for 2 h. The mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 21% EtOAc in petroleum ether) to give the title compound (325 mg, 27%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 9.20 (s, 1H), 8.13 - 8.02 (m, 2H), 4.76 (s, 1H), 4.06 (s, 2H), 2.78 (s, 3H), 2.66 (s, 3H), 2.43 - 2.38 (m, 2H), 2.29 - 2.25 (m, 2H). MS: m/z 293.1 (M+H⁺).

Step 5 - 3-(2-oxabicyclo[2.1.1]hexan-4-yl)-5-(1-hydroxyethyl)-7-methylquinoline-2-carbonitrile:

A mixture of 5-acetyl-3-(2-oxabicyclo[2.1.1]hexan-4-yl)-7-methylquinoline-2-carbonitrile (325 mg, 1.11 mmol) in THF (4 mL) was added NaBH₄ (63 mg, 1.67 mmol) at 0 °C, and then the mixture was stirred at 0 °C for 1 h under N₂ atmosphere. The reaction was quenched with sat. aq. NH₄Cl (5 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give the title compound (325 mg, crude) as a yellow solid that required no further purification. ¹H NMR (400 MHz, CDCl₃) δ 8.44 (s, 1H), 7.86 (s, 1H), 7.64 (s, 1H), 5.58 - 5.49 (m, 1H), 4.76 (s, 1H), 4.06 (s, 2H), 2.59 (s, 3H), 2.44 - 2.38 (m, 2H), 2.28 - 2.23 (m, 2H), 1.69 (d, J = 6.4 Hz, 3H). MS: m/z 295.1 (M+H⁺).

Step 6 - 3-(2-oxabicyclo[2.1.1]hexan-4-yl)-5-(1-bromoethyl)-7-methylquinoline-2-carbonitrile:

A solution of 3-(2-oxabicyclo[2.1.1]hexan-4-yl)-5-(1-hydroxyethyl)-7-methylquinoline-2-carbonitrile (277 mg, 941 μmol) in DCM (4 mL) was added PBr₃ (382 mg, 1.41 mmol). The reaction mixture was stirred at room temperature for 1 h under N₂ atmosphere. The reaction mixture was adjusted to pH = 8 with NaHCO₃ saturated solution, then diluted with water (20 mL) and extracted with DCM (30 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo to give the title compound (280 mg, crude) as a yellow solid that required no further purification. MS: m/z 357.0 (M+H⁺).

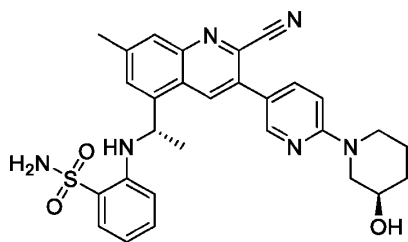
Step 7 - 2-((1-(3-(2-oxabicyclo[2.1.1]hexan-4-yl)-2-cyano-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide:

A mixture of 3-(2-oxabicyclo[2.1.1]hexan-4-yl)-5-(1-bromoethyl)-7-methylquinoline-2-carbonitrile (280 mg, 784 μ mol), 2-aminobenzenesulfonamide (1.35 g, 7.84 mmol) in dioxane (4 mL) was stirred at 100 °C for 16 h. After cooling to room temperature, the reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 45%-75% / 0.225% formic acid in water) to give the title compound (60 mg, 17%) as a white solid. MS: m/z 449.1 (M+H⁺).

Step 8 - (*R*)-2-((1-(3-(2-oxabicyclo[2.1.1]hexan-4-yl)-2-cyano-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide & (*S*)-2-((1-(3-(2-oxabicyclo[2.1.1]hexan-4-yl)-2-cyano-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide:

2-((1-(3-(2-oxabicyclo[2.1.1]hexan-4-yl)-2-cyano-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (60 mg, 134 μ mol) was separated by using chiral SFC (DAICEL CHIRALCEL OJ (250mm*30mm,10 μ m); Supercritical CO₂ / EtOH+0.1% NH₃•H₂O = 70/30; 80 mL/min) to afford (*R*)-2-((1-(3-(2-oxabicyclo[2.1.1]hexan-4-yl)-2-cyano-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (24.7 mg, first peak) and (*S*)-2-((1-(3-(2-oxabicyclo[2.1.1]hexan-4-yl)-2-cyano-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (28.5 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. First peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.63 (s, 1H), 7.81 (s, 1H), 7.73 (s, 1H), 7.67 - 7.63 (m, 1H), 7.57 (s, 2H), 7.21 - 7.12 (m, 1H), 6.69 - 6.60 (m, 1H), 6.46 (d, *J* = 8.4 Hz, 1H), 6.39 (d, *J* = 5.6 Hz, 1H), 5.62 - 5.49 (m, 1H), 4.69 (s, 1H), 3.92 (s, 2H), 2.46 (s, 3H), 2.30 - 2.20 (m, 4H), 1.61 (d, *J* = 6.4 Hz, 3H). MS: m/z 449.2 (M+H⁺). Second peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.63 (s, 1H), 7.81 (s, 1H), 7.73 (s, 1H), 7.68 - 7.61 (m, 1H), 7.58 (s, 2H), 7.21 - 7.11 (m, 1H), 6.70 - 6.60 (m, 1H), 6.46 (d, *J* = 8.4 Hz, 1H), 6.39 (d, *J* = 6.0 Hz, 1H), 5.60 - 5.54 (m, 1H), 4.69 (s, 1H), 3.92 (s, 2H), 2.46 (s, 3H), 2.30 - 2.20 (m, 4H), 1.61 (d, *J* = 6.8 Hz, 3H). MS: m/z 449.2 (M+H⁺).

Example 62: 2-(((*S*)-1-(2-cyano-3-(6-((*R*)-3-hydroxypiperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (Compound 291)



Step 1 - Synthesis of 5-acetyl-3-(6-chloropyridin-3-yl)-7-methylquinoline-2-carbonitrile:

A mixture of (6-chloropyridin-3-yl)boronic acid (18.8 g, 119.72 mmol), 5-acetyl-2-cyano-7-methylquinolin-3-yl trifluoromethanesulfonate (28.6 g, 79.84 mmol), Pd(dppf)Cl₂ (5.8 g, 7.98 mmol), K₂CO₃ (33.1 g, 239.48 mmol) in dioxane (300 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by flash silica gel column (0-100% DCM in petroleum ether) to afford the title compound (15 g, 58%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.19 (s, 1H), 8.76 (d, *J* = 2.4 Hz, 1H), 8.39 (d, *J* = 1.6 Hz, 1H), 8.28 - 8.24 (m, 1H), 8.19 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 2.77 (s, 3H), 2.65 (s, 3H). MS: *m/z* 322.0 (M+H⁺).

Step 2 - Synthesis of 3-(6-chloropyridin-3-yl)-5-(1-hydroxyethyl)-7-methylquinoline-2-carbonitrile:

The 5-acetyl-3-(6-chloropyridin-3-yl)-7-methylquinoline-2-carbonitrile (15.0 g, 46.64 mmol) was suspended in DCM (600 mL) and the mixture was cooled to 0 °C, NaBH₄ (3.6 g, 93.24 mmol) was added slowly at 0 °C, MeOH (120 mL) was added until the reaction was completely clear at 0 °C under N₂ atmosphere. The resulting reaction was kept stirring for 0.5 h at 0 °C. The reaction was quenched with NH₄Cl saturated aqueous solution (300 mL) at 0 °C, the mixture was extracted with DCM (200 mL × 3), the combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to afford the title compound (15 g, 99%) as a yellow solid, which was used in the next step without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.89 (s, 1H), 8.80 (d, *J* = 2.4 Hz, 1H), 8.33 - 8.29 (m, 1H), 7.88 (s, 1H), 7.82 - 7.75 (m, 2H), 5.63 - 5.48 (m, 2H), 2.59 (s, 3H), 1.48 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 324.0 (M+H⁺).

Step 3 - Synthesis of 5-(1-bromoethyl)-3-(6-chloropyridin-3-yl)-7-methylquinoline-2-carbonitrile:

To a solution of 3-(6-chloropyridin-3-yl)-5-(1-hydroxyethyl)-7-methylquinoline-2-carbonitrile (15.0 g, 46.34 mmol) in DCM (150 mL) was added PPh₃ (36.3 g, 139.02 mmol) and CBr₄ (46.1 g, 139.02 mmol) at 0 °C, the resulting mixture was stirred at room temperature for 1 h. The mixture was concentrated and the filtered to remove the solid precipitate. After filtration, the filtrate was continued to concentrate in vacuo. The residue was purified by flash silica gel column (0-40% DCM in petroleum) to afford the title compound (17.0 g, 95%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.02 (s, 1H), 8.84 (d, *J* = 2.4 Hz, 1H), 8.37 - 8.33 (m, 1H), 8.06 - 7.96 (m, 2H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.70 - 7.46 (m, 2H), 6.47 (q, *J* = 6.8 Hz, 1H), 2.62 (s, 3H), 2.21 (d, *J* = 6.8 Hz, 3H). MS: *m/z* 386.0 (M+H⁺).

Step 4 - Synthesis of 2-((1-(3-(6-chloropyridin-3-yl)-2-cyano-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide

A mixture of 2-aminobenzenesulfonamide (17.8 g, 103.45 mmol) and 5-(1-bromoethyl)-3-(6-chloropyridin-3-yl)-7-methylquinoline-2-carbonitrile (4.0 g, 10.34 mmol) in dioxane (40 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 16 h under N₂ atmosphere. The reaction was cooled to room temperature, the reaction solvent was removed under vacuum. The crude was dissolved in methanol (20 mL), and added into water (200 mL). After filtration, the solid was collected. The crude product was triturated with MeOH (80 mL) at room temperature for 20 min, the mixture was filtered and the filter cake was washed with methanol (20 mL), collected and dried under vacuum to afford the title compound (4 g, 81%) as a pink solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.12 (s, 1H), 8.88 (d, *J* = 2.4 Hz, 1H), 8.39 - 8.35 (m, 1H), 7.89 (s, 1H), 7.85 - 7.74 (m, 2H), 7.67 - 7.63 (m, 1H), 7.61 (s, 2H), 7.15 - 7.12 (m, 1H), 6.65 - 6.62 (m, 1H), 6.46 - 6.38 (m, 2H), 5.69 - 5.59 (m, 1H), 2.49 (s, 3H), 1.61 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 478.1 (M+H⁺).

Step 5 – Synthesis of 2-((1-(2-cyano-3-(6-((*R*)-3-hydroxypiperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide:

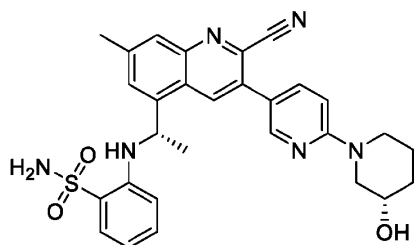
To a solution of 2-((1-(3-(6-chloropyridin-3-yl)-2-cyano-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (300 mg, 627 μmol) and DIEA (406 mg, 3.14 mmol) in NMP (5 mL) was added (*R*)-piperidin-3-ol (64 mg, 633 μmol). The reaction mixture was stirred at 140 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with water (10 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was

purified by silica gel chromatography (solvent gradient: 0 - 10% MeOH in DCM) to give the title compound (132 mg, 39%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.93 (s, 1H), 8.50 (d, *J* = 2.4 Hz, 1H), 8.05 - 7.93 (m, 1H), 7.82 (s, 1H), 7.74 (d, *J* = 1.2 Hz, 1H), 7.67 - 7.62 (m, 1H), 7.61 (s, 2H), 7.16 - 7.10 (m, 1H), 7.01 (d, *J* = 9.2 Hz, 1H), 6.70 - 6.58 (m, 1H), 6.49 - 6.35 (m, 2H), 5.72 - 5.56 (m, 1H), 4.91 (d, *J* = 4.4 Hz, 1H), 4.36 - 4.24 (m, 1H), 4.14 - 4.03 (m, 1H), 3.60 - 3.45 (m, 1H), 3.12 - 3.01 (m, 1H), 2.95 - 2.82 (m, 1H), 1.98 - 1.89 (m, 1H), 1.81 - 1.70 (m, 1H), 1.60 (d, *J* = 6.4 Hz, 3H), 1.51 - 1.38 (m, 2H). MS: *m/z* 543.3 (M+H⁺).

Step 6 – Synthesis of 2-(((*R*)-1-(2-cyano-3-(6-((*R*)-3-hydroxypiperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide & 2-(((*S*)-1-(2-cyano-3-(6-((*R*)-3-hydroxypiperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide:

2-(((1-(2-cyano-3-(6-((*R*)-3-hydroxypiperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (132 mg, 243 μmol) was separated by using chiral SFC (Daicel ChiralPak IG (250mm*30mm,10um); Supercritical CO₂ / EtOH+0.1% NH₃•H₂O = 60/40; 80 mL/min) to afford 2-(((*R*)-1-(2-cyano-3-(6-((*R*)-3-hydroxypiperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (18.4 mg, first peak) and 2-(((*S*)-1-(2-cyano-3-(6-((*R*)-3-hydroxypiperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (15.7 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. First peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.93 (s, 1H), 8.50 (d, *J* = 2.4 Hz, 1H), 8.02 - 7.93 (m, 1H), 7.82 (s, 1H), 7.74 (d, *J* = 1.2 Hz, 1H), 7.68 - 7.63 (m, 1H), 7.61 (s, 2H), 7.19 - 7.07 (m, 1H), 7.01 (d, *J* = 8.8 Hz, 1H), 6.66 - 6.59 (m, 1H), 6.49 - 6.36 (m, 2H), 5.71 - 5.58 (m, 1H), 4.91 (d, *J* = 4.4 Hz, 1H), 4.35 - 4.23 (m, 1H), 4.15 - 4.02 (m, 1H), 3.61 - 3.49 (m, 1H), 3.14 - 3.02 (m, 1H), 2.93 - 2.80 (m, 1H), 2.46 (s, 3H), 1.98 - 1.89 (m, 1H), 1.82 - 1.72 (m, 1H), 1.60 (d, *J* = 6.4 Hz, 3H), 1.52 - 1.35 (m, 2H). MS: *m/z* 543.2 (M+H⁺). Second peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.93 (s, 1H), 8.50 (d, *J* = 2.4 Hz, 1H), 8.00 - 7.93 (m, 1H), 7.82 (s, 1H), 7.74 (d, *J* = 1.2 Hz, 1H), 7.68 - 7.63 (m, 1H), 7.61 (s, 2H), 7.18 - 7.08 (m, 1H), 7.01 (d, *J* = 9.2 Hz, 1H), 6.68 - 6.58 (m, 1H), 6.49 - 6.36 (m, 2H), 5.71 - 5.64 (m, 1H), 4.91 (d, *J* = 4.4 Hz, 1H), 4.33 - 4.24 (m, 1H), 4.13 - 4.03 (m, 1H), 3.58 - 3.47 (m, 1H), 3.12 - 3.02 (m, 1H), 2.94 - 2.80 (m, 1H), 2.46 (s, 3H), 1.99 - 1.89 (m, 1H), 1.83 - 1.71 (m, 1H), 1.60 (d, *J* = 6.4 Hz, 3H), 1.52 - 1.33 (m, 2H). MS: *m/z* 543.2 (M+H⁺).

Example 63: 2-(((*S*)-1-(2-cyano-3-(6-((*S*)-3-hydroxypiperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (Compound 290)



Step 1 - Synthesis of 2-(((*S*)-1-(2-cyano-3-(6-((*S*)-3-hydroxypiperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide:

To a mixture of (*S*)-piperidin-3-ol (84.7 mg, 0.84 mmol), 2-((1-(3-(6-chloropyridin-3-yl)-2-cyano-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (100 mg, 0.21 mmol) in NMP (7 mL) was added DIEA (0.18 mL, 1.05 mmol). The mixture was stirred at 140 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was quenched with water (10 mL), extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (10 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give crude. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% MeOH in DCM) to give the title compound (100 mg, 88%) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.93 (s, 1H), 8.50 (d, *J* = 2.4 Hz, 1H), 8.01 - 7.93 (m, 1H), 7.82 (s, 1H), 7.74 (s, 1H), 7.70 - 7.62 (m, 1H), 7.61 (s, 2H), 7.18 - 7.10 (m, 1H), 7.01 (d, *J* = 8.8 Hz, 1H), 6.65 - 6.61 (m, 1H), 6.47 - 6.38 (m, 2H), 5.70 - 5.60 (m, 1H), 4.92 (d, *J* = 4.4 Hz, 1H), 4.33 - 4.25 (m, 1H), 4.13 - 4.04 (m, 1H), 3.60 - 3.47 (m, 1H), 3.12 - 3.02 (m, 1H), 2.94 - 2.82 (m, 1H), 2.54 (s, 3H), 1.99 - 1.92 (m, 1H), 1.80 - 1.72 (m, 1H), 1.60 (d, *J* = 6.4 Hz, 3H), 1.52 - 1.38 (m, 2H). MS: *m/z* 543.1 (M+H⁺).

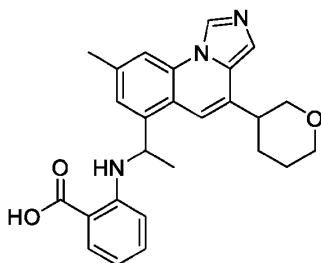
Step 2 - Synthesis of 2-(((*R*)-1-(2-cyano-3-(6-((*S*)-3-hydroxypiperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide & 2-(((*S*)-1-(2-cyano-3-(6-((*S*)-3-hydroxypiperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide:

2-((1-(2-cyano-3-(6-((*S*)-3-hydroxypiperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (100 mg, 184 μmol) was purified by using chiral SFC (DAICEL ChiralPak IG (250mm*30mm,10um); Supercritical CO₂ / EtOH+0.1% NH₃•H₂O = 70/30; 80 mL/min) to afford 2-(((*R*)-1-(2-cyano-3-(6-((*S*)-3-hydroxypiperidin-1-yl)pyridin-3-yl)-

7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (18.4 mg, first peak) and 2-(((*S*)-1-(2-cyano-3-(6-((*S*)-3-hydroxypiperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (14.4 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. First peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.93 (s, 1H), 8.50 (d, *J* = 2.4 Hz, 1H), 8.00 - 7.93 (m, 1H), 7.82 (s, 1H), 7.74 (s, 1H), 7.67 - 7.62 (m, 1H), 7.61 (s, 2H), 7.17 - 7.10 (m, 1H), 7.01 (d, *J* = 9.2 Hz, 1H), 6.65 - 6.61 (m, 1H), 6.48 - 6.38 (m, 2H), 5.69 - 5.58 (m, 1H), 4.91 (d, *J* = 4.4 Hz, 1H), 4.34 - 4.24 (m, 1H), 4.14 - 4.03 (m, 1H), 3.58 - 3.47 (m, 1H), 3.12 - 3.02 (m, 1H), 2.92 - 2.80 (m, 1H), 2.46 (s, 3H), 1.97 - 1.89 (m, 1H), 1.81 - 1.73 (m, 1H), 1.60 (d, *J* = 6.8 Hz, 3H), 1.50 - 1.40 (m, 2H). MS: *m/z* 543.1 (M+H⁺).

Second peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.93 (s, 1H), 8.50 (d, *J* = 2.4 Hz, 1H), 8.00 - 7.94 (m, 1H), 7.82 (s, 1H), 7.74 (d, *J* = 1.2 Hz, 1H), 7.67 - 7.62 (m, 1H), 7.61 (s, 2H), 7.20 - 7.09 (m, 1H), 7.01 (d, *J* = 8.8 Hz, 1H), 6.65 - 6.61 (m, 1H), 6.46 - 6.39 (m, 2H), 5.70 - 5.60 (m, 1H), 4.91 (d, *J* = 4.4 Hz, 1H), 4.33 - 4.24 (m, 1H), 4.12 - 4.03 (m, 1H), 3.59 - 3.47 (m, 1H), 3.13 - 3.03 (m, 1H), 2.93 - 2.80 (m, 1H), 2.46 (s, 3H), 1.98 - 1.89 (m, 1H), 1.81 - 1.71 (m, 1H), 1.60 (d, *J* = 6.4 Hz, 3H), 1.50 - 1.37 (m, 2H). MS: *m/z* 543.1 (M+H⁺).

Example 64: 2-(((1-(8-methyl-4-(tetrahydro-2*H*-pyran-3-yl)imidazo[1,5-*a*]quinolin-6-yl)ethyl)amino)benzoic acid (Compound 440)



Step 1 – Synthesis of (*E*)-*N*-((3-(benzyloxy)-5-bromo-7-methylquinolin-2-yl)methylene)-2-methylpropane-2-sulfinamide:

To a solution of 3-benzyloxy-5-bromo-7-methyl-quinoline-2-carbaldehyde (0.6 g, 1.68 mmol) in DCM (10 mL) was added Cs₂CO₃ (1.65 g, 5.05 mmol) and 2-methylpropane-2-sulfinamide (306.22 mg, 2.53 mmol). The mixture was stirred at room temperature for 16 h.

The reaction was diluted with water (10 mL). The aqueous phase was extracted with DCM (15 mL x 3). The combined organic phase was washed with brine (20 mL), dried with anhydrous

Na₂SO₄, filtered and concentrated in vacuum. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 25% EtOAc in petroleum ether) to give the title compound (500 mg, 65%) as a yellow solid. MS: m/z 459.0 (M+H⁺).

Step 2 – Synthesis of *N*-((3-(benzyloxy)-5-bromo-7-methylquinolin-2-yl)methyl)-2-methylpropane-2-sulfinamide:

To a solution of (*E*)-*N*-((3-(benzyloxy)-5-bromo-7-methylquinolin-2-yl)methylene)-2-methylpropane-2-sulfinamide (1.8 g, 3.9 mmol) in MeOH (20 mL) was added NaBH₄ (300 mg, 7.9 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h. The reaction was quenched with sat. aq. NH₄Cl (5 mL), diluted with water (10 mL), extracted with EtOAc (15 mL x 2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (60 mg, 85%) as colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.78 (s, 2H), 7.74 (s, 1H), 7.60 - 7.56 (m, 2H), 7.45 - 7.34 (m, 3H), 5.67 (t, *J* = 5.6 Hz, 1H), 5.37 (s, 2H), 4.54 - 4.40 (m, 2H), 2.48 (s, 3H), 1.11 (s, 9H). MS: m/z 461.2 (M+H⁺).

Step 3 – Synthesis of (3-(benzyloxy)-5-bromo-7-methylquinolin-2-yl)methanamine:

To a solution of *N*-((3-(benzyloxy)-5-bromo-7-methylquinolin-2-yl)methyl)-2-methylpropane-2-sulfinamide (1.6 g, 3.5 mmol) in dioxane (10 mL) was added HCl (10 mL, 2M in dioxane) at room temperature. The reaction mixture was stirred at room temperature for 1 h. The mixture was quenched with sat. aq. NaHCO₃ (50 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc/EtOH (v/v = 3:1) in petroleum ether) to give the title compound (1.1 g, 89%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.48 (s, 2H), 7.85 - 7.80 (m, 3H), 7.59 (d, *J* = 7.2 Hz, 2H), 7.49 - 7.35 (m, 3H), 5.43 (s, 2H), 4.40 (s, 2H), 2.52 - 2.51 (m, 3H). MS: m/z 357.1 (M+H⁺).

Step 4 – Synthesis of 4-(benzyloxy)-6-bromo-8-methylimidazo[1,5-*a*]quinoline:

A mixture of (3-(benzyloxy)-5-bromo-7-methylquinolin-2-yl)methanamine (1.1 g, 3.1 mmol) in triethoxymethane (35.6 g, 240 mmol) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 110 °C for 1 h under N₂ atmosphere. After cooling to room temperature, the mixture was concentrated directly to give a residue. The crude residue was

purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (900 mg, 80%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.13 (s, 1H), 8.24 (s, 1H), 7.61 (s, 1H), 7.59 - 7.50 (m, 3H), 7.46 - 7.41 (m, 2H), 7.40 - 7.34 (m, 1H), 6.73 (s, 1H), 5.38 (s, 2H), 2.45 (s, 3H). MS: m/z 367.1 (M+H⁺).

5 **Step 5 – Synthesis of 4-(benzyloxy)-6-(1-ethoxyvinyl)-8-methylimidazo[1,5-*a*]quinoline:**

A mixture of 4-(benzyloxy)-6-bromo-8-methylimidazo[1,5-*a*]quinoline (700 mg, 1.9 mmol), tributyl(1-ethoxyvinyl)stannane (1.87 g, 5.2 mmol) and Pd(dppf)Cl₂ (140 mg, 190 μmol) in dioxane (15 mL) was stirred at 90 °C for 16 h under N₂ atmosphere. After cooling to room
10 temperature, the reaction was quenched with 10% KF solution (30 mL). The mixture was filtered and the filtrate was separated between EtOAc (50 mL) and H₂O (30 mL). The organic layer was washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give the title compound (650 mg, crude) as brown oil that required no further purification. MS: m/z 359.2 (M+H⁺).

15 **Step 6 – Synthesis of 1-(4-(benzyloxy)-8-methylimidazo[1,5-*a*]quinolin-6-yl)ethan-1-one:**

To a solution of 4-(benzyloxy)-6-(1-ethoxyvinyl)-8-methylimidazo[1,5-*a*]quinoline (650 mg, 1.8 mmol) in THF (6 mL) was added HCl (6 mL, 1M in water) at room temperature. The reaction mixture was stirred at room temperature for 1 h. The mixture was quenched with saturated
20 NaHCO₃ (10 mL), extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to give the title compound (380 mg, 63%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.18 (s, 1H), 8.43 (s, 1H), 7.85 (s, 1H), 7.58 - 7.52 (m, 2H), 7.52 - 7.47 (m, 1H), 7.46
25 - 7.40 (m, 3H), 7.39 - 7.33 (m, 1H), 5.29 (s, 2H), 2.68 (s, 3H), 2.53 (s, 3H). MS: m/z 331.2 (M+H⁺).

Step 7 – Synthesis of 1-(4-(benzyloxy)-8-methylimidazo[1,5-*a*]quinolin-6-yl)ethan-1-amine:

A mixture of 1-(4-(benzyloxy)-8-methylimidazo[1,5-*a*]quinolin-6-yl)ethan-1-one (380 mg, 1.15 mmol), NH₄OAc (1.35 g, 17.5 mmol) and AcOH (26 mg, 435 μmol) in MeOH (10 mL)
30 was stirred at room temperature for 1 h. Then NaBH₃CN (220 mg, 3.5 mmol) was added to the reaction mixture. After the addition, the reaction mixture was stirred at 60 °C for 16 h. After

cooling to room temperature, the reaction mixture was diluted with DCM (30 mL). The mixture was washed with saturated NaHCO₃ solution (30 mL x 3), brine (20 mL), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% MeOH in DCM) to give the title compound (110 mg, 29%) as a yellow solid MS: m/z 332.2 (M+H⁺).

Step 8 – Synthesis of *tert*-butyl 2-((1-(4-(benzyloxy)-8-methylimidazo[1,5-*a*]quinolin-6-yl)ethyl)amino)benzoate:

A mixture of *tert*-butyl 2-iodobenzoate (112 mg, 368 μmol), 1-(4-(benzyloxy)-8-methylimidazo[1,5-*a*]quinolin-6-yl)ethan-1-amine (90 mg, 271 μmol), Pd₂(dba)₃ (27 mg, 29 μmol), XantPhos (31 mg, 53 μmol) and Cs₂CO₃ (300 mg, 920 μmol) in dioxane (6 mL). The reaction mixture was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to give the title compound (100 mg, 72%) as a yellow solid. MS: m/z 508.3 (M+H⁺).

Step 9 – Synthesis of *tert*-butyl 2-((1-(4-hydroxy-8-methylimidazo[1,5-*a*]quinolin-6-yl)ethyl)amino)benzoate:

To a solution of *tert*-butyl 2-((1-(4-(benzyloxy)-8-methylimidazo[1,5-*a*]quinolin-6-yl)ethyl)amino)benzoate (60 mg, 118 μmol) in MeOH (4 mL) was added wet Pd on carbon (290 mg, 10% Pd, 50% wet with water). The mixture was stirred at room temperature for 1 h. The mixture was filtered, and the filtrate was concentrated to give the title compound (40 mg, 81%) as a green solid. MS: m/z 418.3 (M+H⁺).

Step 10 – Synthesis of *tert*-butyl 2-((1-(8-methyl-4-(((trifluoromethyl)sulfonyl)oxy)imidazo[1,5-*a*]quinolin-6-yl)ethyl)amino)benzoate:

To a solution of *tert*-butyl 2-((1-(4-hydroxy-8-methylimidazo[1,5-*a*]quinolin-6-yl)ethyl)amino)benzoate (60 mg, 143.71 μmol) in DCM (3 mL) was added Py (17 mg, 212 μmol), then trifluoromethanesulfonic anhydride (51 mg, 182 μmol) was added. The mixture was stirred at room temperature for 1 h. The mixture was diluted with DCM (10 mL) and washed with 10% aq. citric acid (10 mL) and sat. aq. NaHCO₃ (10 mL), dried over Na₂SO₄ and concentrated to give the title compound (60 mg, crude) as yellow oil that required no further purification. MS: m/z 550.2 (M+H⁺).

Step 11 – Synthesis of *tert*-butyl 2-((1-(4-(3,4-dihydro-2*H*-pyran-5-yl)-8-methylimidazo[1,5-*a*]quinolin-6-yl)ethyl)amino)benzoate:

A mixture of *tert*-butyl 2-((1-(8-methyl-4-(((trifluoromethyl)sulfonyl)oxy)imidazo[1,5-*a*]quinolin-6-yl)ethyl)amino)benzoate (60 mg, 109 μ mol), Pd(PPh₃)₄ (13 mg, 11 μ mol), 2-(5,6-dihydro-2*H*-pyran-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (30 mg, 143 μ mol) and K₂CO₃ (45 mg, 325 μ mol) in dioxane (2 mL) and H₂O (0.5 mL). The reaction mixture was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to give the title compound (30 mg, 57%) as a yellow solid. MS: *m/z* 484.3 (M+H⁺).

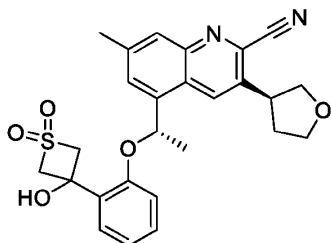
Step 12 – Synthesis of *tert*-butyl 2-((1-(8-methyl-4-(tetrahydro-2*H*-pyran-3-yl)imidazo[1,5-*a*]quinolin-6-yl)ethyl)amino)benzoate:

To a solution of *tert*-butyl 2-((1-(4-(3,4-dihydro-2*H*-pyran-5-yl)-8-methylimidazo[1,5-*a*]quinolin-6-yl)ethyl)amino)benzoate (30 mg, 62 μ mol) in MeOH (3 mL) was added wet Pd on carbon (30 mg, 10% Pd, 50% wet with water). The mixture was stirred at room temperature for 1 h. The mixture was filtered, and the filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 35% EtOAc in petroleum ether) to give the title compound (20 mg, 66%) as a yellow solid. MS: *m/z* 486.2 (M+H⁺).

Step 13 – Synthesis of 2-((1-(8-methyl-4-(tetrahydro-2*H*-pyran-3-yl)imidazo[1,5-*a*]quinolin-6-yl)ethyl)amino)benzoic acid:

To a mixture of *tert*-butyl 2-((1-(8-methyl-4-(tetrahydro-2*H*-pyran-3-yl)imidazo[1,5-*a*]quinolin-6-yl)ethyl)amino)benzoate (20 mg, 41 μ mol) in DCM (3 mL) was added TFA (1 mL, 13.5 mmol). The reaction mixture was stirred at 40 °C for 16 h. After cooling to room temperature, the reaction mixture was concentrated and the residue was purified by reverse phase chromatography (acetonitrile 25% - 55% / 0.225% formic acid in water) to give the title compound (1.3 mg, 7%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.27 (s, 1H), 9.11 (s, 1H), 8.43 (s, 1H), 8.11 (s, 1H), 7.85 - 7.76 (m, 1H), 7.60 (s, 1H), 7.35 - 7.31 (m, 1H), 7.28 - 7.24 (m, 1H), 7.22 - 7.18 (m, 1H), 6.55 - 6.51 (m, 1H), 6.46 - 6.41 (m, 1H), 5.51 - 5.18 (m, 1H), 4.02 - 3.86 (m, 2H), 3.56 - 3.45 (m, 2H), 3.15 - 3.06 (m, 1H), 2.41 (s, 3H), 2.06 - 1.98 (m, 1H), 1.97 - 1.84 (m, 1H), 1.81 - 1.64 (m, 2H), 1.58 (d, *J* = 6.8 Hz, 3H). MS: *m/z* 430.2 (M+H⁺).

Example 65: 5-((*S*)-1-(2-(3-hydroxy-1,1-dioxidothietan-3-yl)phenoxy)ethyl)-7-methyl-3-((*S*)-tetrahydrofuran-3-yl)quinoline-2-carbonitrile (Compound 365)



Step 1 - Synthesis of 3-(2-hydroxyphenyl)thietan-3-ol:

To a solution of *n*-BuLi (25.43 mL, 63.58 mmol, 2.5 M in THF) in THF (100 mL) was added 2-bromophenol (5 g, 28.90 mmol) at 0°C under N₂ and then ice bath was removed, the mixture was stirred at room temperature for 30 min, thietan-3-one (3.06 g, 34.68 mmol) in THF (30 mL) was added at -78 °C, and then the reaction was warmed to room temperature and stirred for 16 h under N₂ atmosphere. The reaction mixture was quenched with sat. aq. NH₄Cl (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to get crude. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% EtOAc in petroleum ether) to give the title compound (860 mg, 16%) was obtained as yellow oil. ¹H NMR (400 MHz, CD₃OD) δ 7.55 - 7.43 (m, 1H), 7.21 - 7.14 (m, 1H), 6.93 - 6.79 (m, 2H), 3.75 - 3.55 (m, 4H).

Step 2 - Synthesis of 5-(1-(2-(3-hydroxythietan-3-yl)phenoxy)ethyl)-7-methyl-3-(tetrahydrofuran-3-yl)quinoline-2-carbonitrile:

To a solution of 5-(1-bromoethyl)-7-methyl-3-(tetrahydrofuran-3-yl)quinoline-2-carbonitrile (800 mg, 70% purity, 1.62 mmol) in DMF (10 mL) was added 3-(2-hydroxyphenyl)thietan-3-ol (325 mg, 1.78 mmol) and K₂CO₃ (1.12 g, 8.11 mmol). The mixture was stirred at room temperature for 16 hr. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to get crude residue. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to give the title compound (350 mg, 48%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.77 (s, 1H), 7.94 (s, 1H), 7.84 (s, 1H), 7.43 - 7.38 (m, 1H), 7.18 - 7.08 (m, 1H), 6.94 - 6.81 (m, 2H), 6.39 - 6.30 (m, 1H), 6.09 - 6.06 (m, 1H), 4.18 - 4.12 (m, 1H), 4.03 - 3.99 (m, 3H), 3.93 -

3.82 (m, 3H), 3.42 - 3.37 (m, 2H), 3.30 - 3.27 (m, 1H), 2.54 (s, 3H), 2.47 - 2.43 (m, 1H), 2.30 - 2.18 (m, 1H), 1.72 (d, $J = 5.6$ Hz, 3H). MS: m/z 447.3 ($M+H^+$).

Step 3 - Synthesis of 5-((*R*)-1-(2-(3-hydroxythietan-3-yl)phenoxy)ethyl)-7-methyl-3-((*S*)-tetrahydrofuran-3-yl)quinoline-2-carbonitrile & 5-((*R*)-1-(2-(3-hydroxythietan-3-yl)phenoxy)ethyl)-7-methyl-3-((*R*)-tetrahydrofuran-3-yl)quinoline-2-carbonitrile & 5-((*S*)-1-(2-(3-hydroxythietan-3-yl)phenoxy)ethyl)-7-methyl-3-((*S*)-tetrahydrofuran-3-yl)quinoline-2-carbonitrile & 5-((*S*)-1-(2-(3-hydroxythietan-3-yl)phenoxy)ethyl)-7-methyl-3-((*R*)-tetrahydrofuran-3-yl)quinoline-2-carbonitrile:

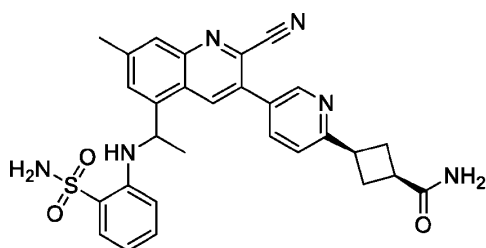
5-((*S*)-1-(2-(3-hydroxythietan-3-yl)phenoxy)ethyl)-7-methyl-3-((*R*)-tetrahydrofuran-3-yl)quinoline-2-carbonitrile (300 mg, 671 μ mol) was separated by using chiral SFC (DAICEL CHIRALCEL OD (250mm*30mm,10 μ m); Supercritical CO₂ / EtOH+0.1% NH₃•H₂O = 70/30; 120 mL/min) to afford 5-((*R*)-1-(2-(3-hydroxythietan-3-yl)phenoxy)ethyl)-7-methyl-3-((*S*)-tetrahydrofuran-3-yl)quinoline-2-carbonitrile (30 mg, first peak), 5-((*R*)-1-(2-(3-hydroxythietan-3-yl)phenoxy)ethyl)-7-methyl-3-((*R*)-tetrahydrofuran-3-yl)quinoline-2-carbonitrile (35 mg, second peak), 5-((*S*)-1-(2-(3-hydroxythietan-3-yl)phenoxy)ethyl)-7-methyl-3-((*S*)-tetrahydrofuran-3-yl)quinoline-2-carbonitrile (40 mg, third peak) and 5-((*S*)-1-(2-(3-hydroxythietan-3-yl)phenoxy)ethyl)-7-methyl-3-((*R*)-tetrahydrofuran-3-yl)quinoline-2-carbonitrile (40 mg, fourth peak). Absolute configuration was arbitrarily assigned to each enantiomer. MS: m/z 447.3 ($M+H^+$).

Step 4 - Synthesis of 5-((*S*)-1-(2-(3-hydroxy-1,1-dioxidothietan-3-yl)phenoxy)ethyl)-7-methyl-3-((*S*)-tetrahydrofuran-3-yl)quinoline-2-carbonitrile:

To a solution of 5-((*S*)-1-(2-(3-hydroxythietan-3-yl)phenoxy)ethyl)-7-methyl-3-((*S*)-tetrahydrofuran-3-yl)quinoline-2-carbonitrile (40 mg, 89.57 μ mol) in THF (2 mL) and H₂O (1 mL) was added Oxone (220 mg, 0.35 mmol). The mixture was stirred at room temperature for 16 hr. The reaction mixture was quenched with water (5 mL) and extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to get crude residue. The crude residue was purified by reverse phase chromatography (acetonitrile 50% - 70% / 0.225% formic acid in water) to give the title compound (21 mg, 49%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.71 (s, 1H), 7.85 (s, 1H), 7.77 (d, $J = 1.6$ Hz, 1H), 7.51 - 7.44 (m, 1H), 7.18 - 7.09 (m, 1H), 6.94 - 6.91 (m, 1H), 6.74 (d, $J = 8.4$ Hz, 1H), 6.56 (s, 1H), 6.42 - 6.34 (m, 1H), 5.05 - 4.86 (m, 2H), 4.35 - 4.28 (m, 1H), 4.25 - 4.18

(m, 1H), 4.16 - 4.10 (m, 1H), 4.05 - 3.95 (m, 1H), 3.95 - 3.82 (m, 3H), 2.49 (s, 3H), 2.48 - 2.44 (m, 1H), 2.25 - 2.16 (m, 1H), 1.75 (d, $J = 6.4$ Hz, 3H). MS: m/z 479.2 ($M+H^+$).

Example 66: *cis*-3-(5-(2-cyano-7-methyl-5-(1-((2-sulfamoylphenyl)amino)ethyl)quinolin-3-yl)pyridin-2-yl)cyclobutanecarboxamide (Compound 280)



Step 1 - Synthesis of methyl (1*r*,3*r*)-3-(5-chloropyridin-2-yl)cyclobutane-1-carboxylate and methyl (1*s*,3*s*)-3-(5-chloropyridin-2-yl)cyclobutane-1-carboxylate:

To a mixture of 3-hydroxycyclobutanecarboxylate (4.94 g, 37.99 mmol) and NHC-1 (14.13 g, 35.75 mmol) in *t*-BuOMe (100 mL) was added pyridine (2.83 g, 35.75 mmol). The reaction mixture was stirred at room temperature for 10 min under N_2 atmosphere. The mixture was filtered and filter liquor was added to a solution of 2-bromo-5-chloro-pyridine (4.3 g, 22.34 mmol), $NiBr_2 \cdot dtbbpy$ (544 mg, 1.12 mmol), quinuclidine (3.73 g, 35.52 mmol), $Ir(ppy)_2(dtbbpy)PF_6$ (306 mg, 335 μ mol) in DMA (100 mL) under N_2 atmosphere. The mixture was stirred and irradiated under blue LED at room temperature for 16 h. MTBE (100 mL) was added to the mixture, and the mixture was washed with brine (100 mL x 3). The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give *trans*-isomers (1.0 g, 20%) and *cis*-isomers (1.1 g, 22%) both as yellow oil. The *cis*-isomers was further confirmed by NOE. *trans*-isomers: 1H NMR (400 MHz, CD_3OD) δ 8.50 (d, $J = 2.4$ Hz, 1H), 7.80 - 7.70 (m, 1H), 7.29 (d, $J = 8.0$ Hz, 1H), 3.84 - 3.76 (m, 1H), 3.73 (s, 3H), 3.28 - 3.18 (m, 1H), 2.69 - 2.51 (m, 4H). MS: m/z 225.8 ($M+H^+$). *cis*-isomers: 1H NMR (400 MHz, CD_3OD) δ 8.46 (d, $J = 2.4$ Hz, 1H), 7.78 - 7.75 (m, 1H), 7.30 (d, $J = 8.0$ Hz, 1H), 3.68 (s, 3H), 3.66 - 3.52 (m, 1H), 3.27 - 3.14 (m, 1H), 2.63 - 2.55 (m, 2H), 2.54 - 2.44 (m, 2H). MS: m/z 225.8 ($M+H^+$).

Step 2 - Synthesis of (5-acetyl-2-cyano-7-methylquinolin-3-yl)boronic acid:

To a solution of 5-acetyl-2-cyano-7-methylquinolin-3-yl trifluoromethanesulfonate (1 g, 2.79 mmol) in dioxane (30 mL) was added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.06 g, 4.19 mmol), KOAc (821.73 mg, 8.37 mmol, 3 eq) and Pd(dppf)Cl₂ (204 mg, 279 μmol). The mixture was degassed and purged with N₂ for 3 times, and then was stirred at 100 °C for 2 h under N₂ atmosphere. The reaction mixture was used for the next step directly without further purification. MS: m/z 254.9 (M+H⁺).

Step 3 - Synthesis of *cis*-methyl 3-(5-(5-acetyl-2-cyano-7-methylquinolin-3-yl)pyridin-2-yl)cyclobutanecarboxylate:

To a solution of (5-acetyl-2-cyano-7-methyl-3-quinolyl)boronic acid (700 mg, 2.76 mmol) in dioxane (25 mL) and H₂O (2.5 mL) was added *cis*-3-(5-chloropyridin-2-yl)cyclobutanecarboxamide (933 mg, 4.13 mmol), XPhos (263 mg, 551 μmol), Pd₂(dba)₃ (252 mg, 275 μmol) and CsF (1.67 g, 11.02 mmol). The mixture was stirred at 100 °C for 3 h under N₂ atmosphere. After cooling to room temperature, the mixture was concentrated in vacuo. The residue was purified by silica gel chromatography (solvent gradient: 0 - 10% MeOH in DCM) to give the title compound (600 mg, 54%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 9.41 (s, 1H), 8.82 (d, *J* = 2.4 Hz, 1H), 8.16 (s, 1H), 8.09 (d, *J* = 1.6 Hz, 1H), 8.01 - 7.96 (m, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 3.73 (s, 3H), 3.71 - 3.68 (m, 1H), 3.23 - 3.20 (m, 1H), 2.79 (s, 3H), 2.74 - 2.71 (m, 2H), 2.69 (s, 3H), 2.68 - 2.66 (m, 2H). MS: m/z 400.1 (M+H⁺).

Step 4 - Synthesis of *cis*-methyl 3-(5-(2-cyano-5-(1-hydroxyethyl)-7-methylquinolin-3-yl)pyridin-2-yl)cyclobutanecarboxylate:

To a solution of *cis*-methyl 3-(5-(5-acetyl-2-cyano-7-methylquinolin-3-yl)pyridin-2-yl)cyclobutanecarboxylate (0.6 g, 1.50 mmol) in THF (10 mL) was added NaBH₄ (63 mg, 1.65 mmol). The mixture was degassed and purged with N₂ for 3 times, the mixture was stirred at 0 °C for 1 h under N₂ atmosphere. The reaction was quenched with sat. aq. NH₄Cl (20 mL). The mixture was extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (20 mL x 2), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (solvent gradient: 0 - 10% MeOH in DCM) to give the title compound (530 mg, 88%) as a yellow solid. MS: m/z 402.1 (M+H⁺).

Step 5 - Synthesis of *cis*-methyl 3-(5-(5-(1-bromoethyl)-2-cyano-7-methylquinolin-3-yl)pyridin-2-yl)cyclobutanecarboxylate:

To a solution of *cis*-methyl 3-(5-(2-cyano-5-(1-hydroxyethyl)-7-methylquinolin-3-yl)pyridin-2-yl)cyclobutanecarboxylate (100 mg, 249 μ mol) in DCM (3 mL) was added PBr₃ (135 mg, 498 μ mol). The mixture was stirred at 0 °C for 1 h under N₂ atmosphere. The reaction mixture was quenched with sat. aq. NaHCO₃ (10 mL), extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (10 mL x 2), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give the title compound (110 mg, crude) as a yellow solid that required no further purification. MS: m/z 464.0 (M+H⁺).

Step 6 - Synthesis of *cis*-methyl 3-(5-(2-cyano-7-methyl-5-(1-((2-sulfamoylphenyl)amino)ethyl)quinolin-3-yl)pyridin-2-yl)cyclobutanecarboxylate:

To a solution of *cis*-methyl 3-(5-(5-(1-bromoethyl)-2-cyano-7-methylquinolin-3-yl)pyridin-2-yl)cyclobutanecarboxylate (100 mg, 215 μ mol) in dioxane (3 mL) was added 2-aminobenzenesulfonamide (371 mg, 2.15 mmol). The mixture was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the mixture was concentrated in vacuo. The residue was purified by silica gel chromatography (solvent gradient: 0 - 100% EtOAc in petroleum ether) to give the title compound (70 mg, 59%) as a yellow solid. MS: m/z 556.1 (M+H⁺).

Step 7 - Synthesis of *cis*-3-(5-(2-cyano-7-methyl-5-(1-((2-sulfamoylphenyl)amino)ethyl)quinolin-3-yl)pyridin-2-yl)cyclobutanecarboxylic acid:

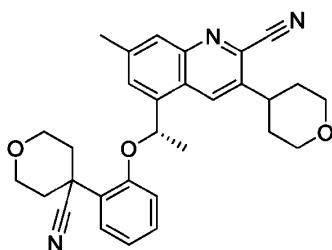
To a solution of *cis*-methyl 3-(5-(2-cyano-7-methyl-5-(1-((2-sulfamoylphenyl)amino)ethyl)quinolin-3-yl)pyridin-2-yl)cyclobutanecarboxylate (40 mg, 71.99 μ mol) in THF (2 mL), H₂O (1 mL) and MeOH (2 mL) was added LiOH·H₂O (30 mg, 719 μ mol). The mixture was stirred at room temperature for 1 h. The mixture was acidified to pH 6 with HCl (1 M) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give the title compound (38 mg, crude) as a yellow solid that required no further purification. MS: m/z 542.1 (M+H⁺).

Step 8 - Synthesis of *cis*-3-(5-(2-cyano-7-methyl-5-(1-((2-sulfamoylphenyl)amino)ethyl)quinolin-3-yl)pyridin-2-yl)cyclobutanecarboxamide:

To a solution of *cis*-3-(5-(2-cyano-7-methyl-5-(1-((2-sulfamoylphenyl)amino)ethyl)quinolin-3-yl)pyridin-2-yl)cyclobutanecarboxylic acid (38 mg, 70 μ mol) in THF (5 mL) was added EDCI (20 mg, 105 μ mol) and HOBt (14 mg, 105 μ mol). The mixture was stirred at room temperature for 20 min, NH₃·H₂O (51.76 mg, 1.40 mmol, 28% in

water) was added. The mixture was stirred at room temperature for 12 h under N₂ atmosphere. The mixture was concentrated in vacuo. The residue was purified by reverse phase chromatography (acetonitrile 25% - 55% / 0.225% formic acid in water) to give the title compound (12 mg, 29%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.07 (s, 1H), 8.93 (d, *J* = 2.0 Hz, 1H), 8.21 - 8.17 (m, 1H), 7.88 (s, 1H), 7.78 (s, 1H), 7.66 - 7.63 (m, 1H), 7.61 (s, 2H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.30 - 7.21 (m, 1H), 7.18 - 7.09 (m, 1H), 6.77 - 6.76 (m, 1H), 6.65 - 6.61 (m, 1H), 6.47 - 6.39 (m, 2H), 5.71 - 5.59 (m, 1H), 3.66 - 3.61 (m, 1H), 3.05 - 2.99 (m, 1H), 2.49 (s, 3H), 2.48 - 2.41 (m, 4H), 1.60 (d, *J* = 6.8 Hz, 3H). MS: *m/z* 541.1 (M+H⁺).

Example 67: (S)-5-(1-(2-(4-cyanotetrahydro-2H-pyran-4-yl)phenoxy)ethyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline-2-carbonitrile (Compound 356)



Step1 – Synthesis of 2-(2-(benzyloxy)phenyl)acetonitrile:

To a solution of 2-(2-hydroxyphenyl)acetonitrile (3 g, 22.53 mmol) and K₂CO₃ (9.34 g, 69.59 mmol) in DMF (30 mL) was added BnBr (4.05 g, 23.66 mmol). The reaction mixture was stirred at 80 °C for 1 h under N₂ atmosphere. After cooling to room temperature, the mixture was quenched with water (30 mL) and extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 5% EtOAc in petroleum ether) to give the title compound (3 g, 59%) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.54 - 7.50 (m, 2H), 7.44 - 7.38 (m, 2H), 7.37 - 7.28 (m, 3H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.00 - 6.95 (m, 1H), 5.20 (s, 2H), 3.90 (s, 2H). MS: *m/z* 224.0 (M+H⁺).

Step 2 - Synthesis of 4-(2-(benzyloxy)phenyl)tetrahydro-2H-pyran-4-carbonitrile:

To a solution of NaH (627 mg, 15.68 mmol, 60% purity) in THF (5 mL) at 0 °C under N₂ atmosphere, 2-(2-(benzyloxy)phenyl)acetonitrile (1 g, 4.48 mmol) and 1-bromo-2-(2-bromoethoxy)ethane (1.16 g, 5.02 mmol) in THF (5 mL) was added dropwise at 0 °C. The reaction

mixture was stirred at room temperature for 16 h under N₂ atmosphere. The reaction was quenched with sat. aq. NH₄Cl (20 mL) and extracted with DCM (30 mL x 3). The combined organic layers were washed with brine (40 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to give the title compound (467 mg, 36%) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.58 - 7.54 (m, 2H), 7.43 - 7.38 (m, 2H), 7.37 - 7.29 (m, 3H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.08 - 6.97 (m, 1H), 5.27 (s, 2H), 4.05 - 3.97 (m, 2H), 3.72 - 3.67 (m, 2H), 2.34 - 2.30 (m, 2H), 2.15 - 1.96 (m, 2H). MS: *m/z* 294.1 (M+H⁺).

Step 3 - Synthesis of 4-(2-(benzyloxy)phenyl)tetrahydro-2H-pyran-4-carbonitrile:

To a solution of 4-(2-(benzyloxy)phenyl)tetrahydro-2H-pyran-4-carbonitrile (230 mg, 0.78 mmol) in THF (4 mL) was added wet Pd on carbon (417 mg, 10% Pd, 50% wet with water). The reaction was stirred at room temperature for 2 h under H₂ atmosphere (15 psi). The reaction was filtered through diatomaceous earth and the filtrate was concentrated to afford the title compound (170 mg, crude) as yellow oil that required no further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.13 (s, 1H), 7.32 - 7.12 (m, 2H), 7.00 - 6.74 (m, 2H), 4.05 - 3.95 (m, 2H), 3.71 - 3.65 (m, 2H), 2.30 - 2.26 (m, 2H), 2.06 - 2.02 (m, 2H).

Step 4 - Synthesis of 5-(1-hydroxyethyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline-2-carbonitrile:

To a solution of 5-acetyl-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline-2-carbonitrile (4.3 g, 14.61 mmol) in THF (50 mL) was added NaBH₄ (1.11 g, 29.22 mmol) at room temperature for 1 h. The mixture was quenched with aq. sat. NH₄Cl (80 mL), extracted with EtOAc (80 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 100% EtOAc in petroleum ether) to give the title compound (4 g, 92 %) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.66 (s, 1H), 7.76 (s, 1H), 7.70 (s, 1H), 5.53 - 5.47 (m, 2H), 4.07 - 4.00 (m, 2H), 3.59 - 3.49 (m, 2H), 3.31 - 3.22 (m, 1H), 2.53 (s, 3H), 1.99 - 1.78 (m, 4H), 1.47 (d, *J* = 6.0 Hz, 3H). MS: *m/z* 297.2 (M+H⁺).

Step 5 - Synthesis of 5-(1-bromoethyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline-2-carbonitrile:

To a solution of 5-(1-hydroxyethyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline-2-carbonitrile (400 mg, 1.35 mmol) in DCM (3 mL) was added PBr₃ (438 mg, 1.62 mmol), The

reaction mixture was stirred at room temperature for 0.5 h under N₂ atmosphere. The mixture was quenched with saturated NaHCO₃ (20 mL) and extracted with DCM (30 mL x 2). The combined organic layers were washed with brine (20 mL x 2), dried over Na₂SO₄, filtered and concentrated in vacuo to remove DCM and give the title compound (400 mg, 82%) as yellow oil that required no further purification. MS: m/z 359.0 (M+H⁺).

Step 6 - Synthesis of 5-(1-(2-(4-cyanotetrahydro-2H-pyran-4-yl)phenoxy)ethyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline-2-carbonitrile:

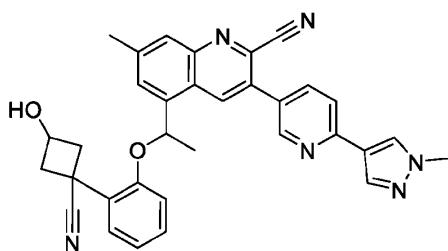
To a mixture of 4-(2-hydroxyphenyl)tetrahydro-2H-pyran-4-carbonitrile (170 mg, 0.83 mmol), K₂CO₃ (289 mg, 2.09 mmol) and 5-(1-bromoethyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline-2-carbonitrile (250 mg, 0.69 mmol) in DMF (2 mL). The reaction mixture was heated to 30 °C and stirred for 16 h under N₂ atmosphere. After cooling to room temperature. The reaction was diluted with water (30 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by reverse phase chromatography (acetonitrile 60% - 90% / 0.225% formic acid in water) to give the title compound (40 mg, 20%) as a white solid. MS: m/z 482.3. (M+H⁺).

Step 7 - Synthesis of (R)-5-(1-(2-(4-cyanotetrahydro-2H-pyran-4-yl)phenoxy)ethyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline-2-carbonitrile & (S)-5-(1-(2-(4-cyanotetrahydro-2H-pyran-4-yl)phenoxy)ethyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline-2-carbonitrile:

5-(1-(2-(4-cyanotetrahydro-2H-pyran-4-yl)phenoxy)ethyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline-2-carbonitrile (40 mg, 83 μmol) was separated by using chiral SFC (DAICEL CHIRALPAK IC (250mm*30mm,10um); Supercritical CO₂ / MeOH + 0.1% NH₃•H₂O = 80/20; 80 mL/min) to afford (R)-5-(1-(2-(4-cyanotetrahydro-2H-pyran-4-yl)phenoxy)ethyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline-2-carbonitrile (2 mg, first peak) and (S)-5-(1-(2-(4-cyanotetrahydro-2H-pyran-4-yl)phenoxy)ethyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline-2-carbonitrile (6 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. First peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.79 (s, 1H), 7.92 (s, 1H), 7.85 (s, 1H), 7.39 - 7.31 (m, 1H), 7.27 - 7.20 (m, 1H), 7.02 - 6.91 (m, 2H), 6.62-6.53 (m, 1H), 4.09 - 4.01 (m, 4H), 3.84 - 3.75 (m, 2H), 3.61 - 3.49 (m, 2H), 3.31 - 3.25 (m, 1H), 2.48 (s, 3H), 2.46 - 2.39 (m, 2H), 2.15 - 2.00 (m, 4H), 1.87 - 1.80 (m, 2H), 1.70 (d, *J* = 6.4 Hz, 3H).

MS: m/z 482.3 (M+H⁺). Second peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.79 (s, 1H), 7.92 (s, 1H), 7.85 (s, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.27 - 7.19 (m, 1H), 7.02 - 6.88 (m, 2H), 6.62 - 6.53 (m, 1H), 4.10 - 3.98 (m, 4H), 3.87 - 3.72 (m, 2H), 3.65 - 3.50 (m, 2H), 3.31 - 3.24 (m, 1H), 2.48 (s, 3H), 2.46 - 2.39 (m, 2H), 2.13 - 1.99 (m, 4H), 1.88 - 1.79 (m, 2H), 1.70 (d, *J* = 6.4 Hz, 3H). MS: m/z 482.3 (M+H⁺).

Example 68: 5-(1-(2-(1-cyano-3-hydroxycyclobutyl)phenoxy)ethyl)-7-methyl-3-(6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)quinoline-2-carbonitrile (Compound 340)



Step1 – Synthesis of 1-(2-(benzyloxy)phenyl)-3-hydroxycyclobutane-1-carbonitrile:

To a solution of 2-(2-benzyloxyphenyl)acetonitrile (2 g, 8.96 mmol) in THF (28 mL) was added methyl lithium (5.88 mL, 9.41 mmol, 1.6 M) dropwise and the resulting solution was stirred for 1 h at -78 °C under N₂ atmosphere. To the solution was added 2-(bromomethyl)oxirane (1.23 g, 8.96 mmol) in THF (10 mL) dropwise over 30 min and the reaction mixture was stirred for 1 h at -78 °C under N₂ atmosphere. A solution of methyl magnesium bromide (2.99 mL, 8.96 mmol, 3 M in THF) was added into the reaction mixture and the resulting mixture was stirred for 12 h at room temperature under N₂ atmosphere. The reaction was quenched with NH₄Cl (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% EtOAc in petroleum ether) to give the title compound (1.6 mg, 64%) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.55 - 7.49 (m, 2H), 7.45 - 7.31 (m, 5H), 7.19 - 7.12 (m, 1H), 7.03 - 6.96 (m, 1H), 5.48 - 5.42 (m, 1H), 5.23 - 5.19 (m, 2H), 4.05 - 3.94 (m, 1H), 3.09 - 2.92 (m, 2H), 2.60 - 2.55 (m, 1H), 2.35 - 2.25 (m, 1H). MS: m/z 280.1 (M+H⁺).

Step 2 - Synthesis of 3-hydroxy-1-(2-(hydroxyphenyl)cyclobutane-1-carbonitrile:

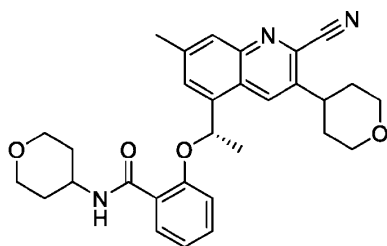
To a solution of 1-(2-(benzyloxy)phenyl)-3-hydroxycyclobutane-1-carbonitrile (1 g, 3.58 mmol) in MeOH (20 mL) was added wet Pd/C (380 mg, 10% Pd, 50% wet with water). The

reaction was stirred at room temperature for 2 h under H₂ atmosphere (15 psi). The reaction was filtered through diatomaceous earth and the filtrate was concentrated to afford the title compound (600 mg, crude) as yellow oil that required no further purification. MS: m/z 212.1 (M+Na⁺).

Step 3 - Synthesis of 5-(1-(2-(1-cyano-3-hydroxycyclobutyl)phenoxy)ethyl)-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinoline-2-carbonitrile:

To a solution of 3-hydroxy-1-(2-hydroxyphenyl)cyclobutane-1-carbonitrile (100 mg, 0.58 mmol) in DMF (2 mL) was added 5-(1-bromoethyl)-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinoline-2-carbonitrile (50 mg, 0.12 mmol) and K₂CO₃ (40 mg, 0.29 mmol). The reaction was stirred at room temperature for 16 h. The reaction was diluted with water (10 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL x 2), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by reverse phase chromatography (acetonitrile 38% - 68% / 0.225% formic acid in water) to give the title compound (4 mg, 8%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.08 (s, 1H), 8.92 (s, 1H), 8.42 (s, 1H), 8.29 - 8.22 (m, 1H), 8.13 (s, 1H), 7.97 - 7.85 (m, 3H), 7.49 - 7.41 (m, 1H), 7.26 - 7.10 (m, 1H), 6.97 - 6.87 (m, 2H), 6.56 - 6.49 (m, 1H), 5.58 - 5.53 (m, 1H), 4.11 - 4.00 (m, 1H), 3.93 (s, 3H), 3.12 - 2.97 (m, 2H), 2.76 - 2.68 (m, 1H), 2.65 - 2.60 (m, 1H), 2.53 (s, 3H), 1.70 (d, *J* = 6.0 Hz, 3H). MS: m/z 563.4 (M+Na⁺).

Example 69: (*S*)-2-(1-(2-cyano-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethoxy)-*N*-(tetrahydro-2*H*-pyran-4-yl)benzamide (Compound 439)



Step 1 – 2-hydroxy-*N*-(tetrahydro-2*H*-pyran-4-yl)benzamide:

To a mixture of 2-hydroxybenzoic acid (1 g, 7.24 mmol), tetrahydro-2*H*-pyran-4-amine (1.10g, 10.86 mmol), HATU (4.13 g, 10.86 mmol) in DMF (10 mL) was slowly added DIEA (3.78 mL, 21.72 mmol) at 0 °C. The mixture was stirred at room temperature for 16 h under N₂

atmosphere. The reaction mixture was quenched with water (60 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give crude. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (1.1 g, 69%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.60 (s, 1H), 8.62 (d, *J* = 7.6 Hz, 1H), 7.91 - 7.87 (m, 1H), 7.43 - 7.37 (m, 1H), 6.92 - 6.85 (m, 2H), 4.08 - 3.99 (m, 1H), 3.91 - 3.84 (m, 2H), 3.43 - 3.36 (m, 2H), 1.80 - 1.73 (m, 2H), 1.66 - 1.55 (m, 2H). MS: *m/z* 222.2 (M+H⁺).

Step 2 – Synthesis of 2-(1-(2-cyano-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinolin-5-yl)ethoxy)-N-(tetrahydro-2H-pyran-4-yl)benzamide:

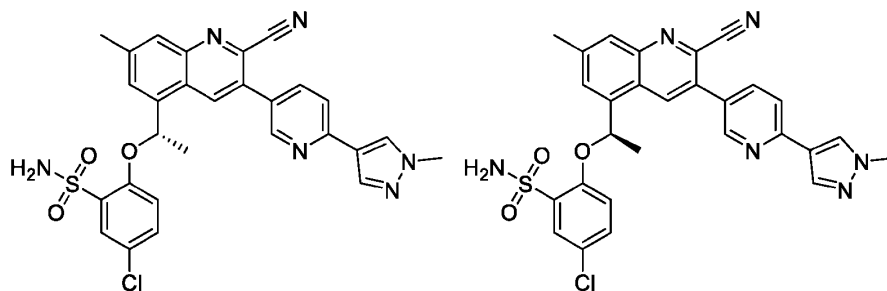
To a solution of 2-hydroxy-*N*-(tetrahydro-2H-pyran-4-yl)benzamide (175 mg, 0.79 mmol) in DMF (2 mL) was added 5-(1-bromoethyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline-2-carbonitrile (190 mg, 0.53 mmol) and K₂CO₃ (219 mg, 1.59 mmol). The mixture was stirred at 70 °C for 5 h. After cooling to room temperature, the reaction mixture was quenched with water (30 mL), extracted with EtOAc (15 mL x 2). The combined organic layers were washed with brine (15 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give crude. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to give the title compound (100 mg, 38%) as white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.72 (s, 1H), 8.15 (d, *J* = 7.6 Hz, 1H), 7.85 (s, 1H), 7.82 (s, 1H), 7.59 - 7.55 (m, 1H), 7.33 - 7.28 (m, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.00 - 6.94 (m, 1H), 6.51 - 6.44 (m, 1H), 4.03 - 4.01 (m, 3H), 3.86 - 3.79 (m, 2H), 3.57 - 3.50 (m, 2H), 3.43 - 3.37 (m, 2H), 3.30 - 3.25 (m, 1H), 2.52 (s, 3H), 1.96 - 1.92 (m, 2H), 1.84 - 1.78 (m, 4H), 1.73 (d, *J* = 6.0 Hz, 3H), 1.48 - 1.42 (m, 2H). MS: *m/z* 522.3 (M+Na⁺).

Step 3 – Synthesis of (*R*)-2-(1-(2-cyano-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinolin-5-yl)ethoxy)-N-(tetrahydro-2H-pyran-4-yl)benzamide and (*S*)-2-(1-(2-cyano-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinolin-5-yl)ethoxy)-N-(tetrahydro-2H-pyran-4-yl)benzamide:

2-(1-(2-cyano-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinolin-5-yl)ethoxy)-*N*-(tetrahydro-2H-pyran-4-yl)benzamide (100 mg, 200 μmol) was separated by using chiral SFC (DAICEL CHIRALCEL OD (250mm*30mm,10um); Supercritical CO₂ / EtOH + 0.1% NH₃·H₂O = 60/40; 80 mL/min) to afford (*R*)-2-(1-(2-cyano-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinolin-

5-yl)ethoxy)-*N*-(tetrahydro-2*H*-pyran-4-yl)benzamide (17.3 mg, first peak) and (*S*)-2-(1-(2-cyano-7-methyl-3-(tetrahydro-2*H*-pyran-4-yl)quinolin-5-yl)ethoxy)-*N*-(tetrahydro-2*H*-pyran-4-yl)benzamide (26.5 mg, second peak) both as yellow solid. Absolute configuration was arbitrarily assigned to each enantiomer. First peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.72 (s, 1H), 8.15 (d, *J* = 7.6 Hz, 1H), 7.85 (s, 1H), 7.82 (s, 1H), 7.61 - 7.56 (m, 1H), 7.33 - 7.27 (m, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 7.00 - 6.94 (m, 1H), 6.51 - 6.45 (m, 1H), 4.06 - 3.99 (m, 3H), 3.86 - 3.78 (m, 2H), 3.57 - 3.50 (m, 2H), 3.43 - 3.37 (m, 2H), 3.29 - 3.22 (m, 1H), 2.52 (s, 3H), 2.00 - 1.89 (m, 2H), 1.86 - 1.77 (m, 4H), 1.73 (d, *J* = 6.4 Hz, 3H), 1.50 - 1.41 (m, 2H). MS: *m/z* 522.3 (M+Na⁺). Second peak: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.72 (s, 1H), 8.15 (d, *J* = 7.6 Hz, 1H), 7.85 (s, 1H), 7.82 (s, 1H), 7.62 - 7.58 (m, 1H), 7.34 - 7.26 (m, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.00 - 6.93 (m, 1H), 6.52 - 6.43 (m, 1H), 4.06 - 3.97 (m, 3H), 3.86 - 3.79 (m, 2H), 3.58 - 3.50 (m, 2H), 3.43 - 3.37 (m, 2H), 3.29 - 3.22 (m, 1H), 2.52 (s, 3H), 2.00 - 1.89 (m, 2H), 1.85 - 1.78 (m, 4H), 1.73 (d, *J* = 6.0 Hz, 3H), 1.49 - 1.40 (m, 2H). MS: *m/z* 522.3 (M+Na⁺).

Example 70: Synthesis of (*S*)-5-chloro-2-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)benzenesulfonamide (Compound 668) & (*R*)-5-chloro-2-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)benzenesulfonamide (Compound 615)



Step 1 – Synthesis of 5-chloro-2-methoxybenzenesulfonamide:

To a solution of 5-chloro-2-methoxy-benzenesulfonyl chloride (3.6 g, 14.93 mmol) in THF (30 mL) was added NH₃•H₂O (5.46 g, 46.74 mmol, 30% aqueous solution). The mixture was stirred at room temperature for 1 h. The reaction was quenched with HCl (1 M) to adjust pH to 5, then the mixture was extracted with EtOAc (50 mL x 2). The combined organic layers were washed

with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give the title compound (2.3 g, 70%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.67 (d, *J* = 2.4 Hz, 1H), 7.66 - 7.60 (m, 1H), 7.30 - 7.21 (m, 3H), 3.90 (s, 3H).

Step 2 – Synthesis of 5-chloro-2-hydroxybenzenesulfonamide:

5 A solution of 5-chloro-2-methoxybenzenesulfonamide (2.3 g, 10.38 mmol) in DCM (10 mL) was evacuated and purged with N₂ for 3 times, then BBr₃ (25.94 mL, 51.88 mmol, 2 M in DCM) was added and the mixture was stirred at 0 °C for 1 h under N₂ atmosphere. The reaction was quenched with MeOH (50 mL) under N₂ atmosphere at 0 °C. The mixture was concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (1.88 g, 87%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.95 (s, 1H), 7.59 (d, *J* = 2.8 Hz, 1H), 7.48 - 7.43 (m, 1H), 7.11 (s, 2H), 7.00 (d, *J* = 8.8 Hz, 1H).

Step 3 - Synthesis of 5-(1-bromoethyl)-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinoline-2-carbonitrile:

15 To a solution of 5-(1-hydroxyethyl)-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinoline-2-carbonitrile (300 mg, 0.8 mmol) in DCM (3 mL) was added PPh₃ (639 mg, 2.44 mmol) and CBr₄ (808 mg, 2.44 mmol) at 0 °C, the resulting mixture was stirred at room temperature for 1h. The reaction mixture was used for the next step directly without further purification. MS: *m/z* 432.1 (M+H⁺).

20 **Step 4 - Synthesis of 5-chloro-2-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)benzenesulfonamide:**

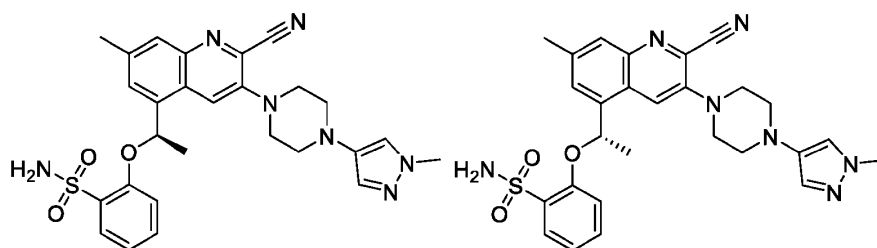
To a solution of 5-(1-bromoethyl)-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinoline-2-carbonitrile (above mentioned reaction solution, in DCM) was added DMF (3 mL), followed by 5-chloro-2-hydroxybenzenesulfonamide (488 mg, 2.35 mmol) and K₂CO₃ (434 mg, 3.14 mmol). The mixture was stirred at room temperature for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction was quenched with water (10 mL), extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude, which was purified by silica gel chromatography (solvent gradient: 50~70% EtOAc in petroleum ether) to give the title compound (298 mg, 58%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.09 (s, 1H), 8.93 (d, *J* = 2.0 Hz, 1H), 8.42 (s, 1H), 8.27 - 8.22 (m, 1H), 8.13 (s, 1H), 7.96 (s, 1H), 7.92 (s, 1H), 7.89

(d, $J = 8.4$ Hz, 1H), 7.72 (d, $J = 2.4$ Hz, 1H), 7.48 - 7.44 (m, 1H), 7.42 (s, 2H), 7.10 (d, $J = 9.2$ Hz, 1H), 6.65 - 6.55 (m, 1H), 3.93 (s, 3H), 2.51 (s, 3H), 1.76 (d, $J = 6.0$ Hz, 3H). MS: m/z 559.1 ($M+H^+$).

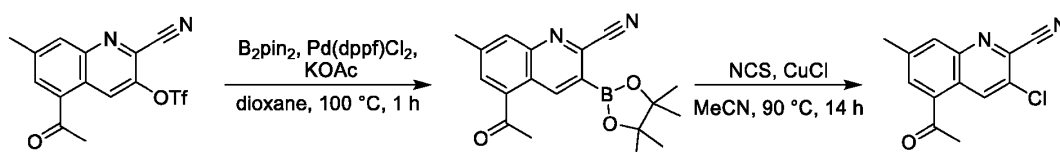
Step 5 - Synthesis of (*S*)-5-chloro-2-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)benzenesulfonamide & (*R*)-5-chloro-2-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)benzenesulfonamide:

5-chloro-2-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)benzenesulfonamide (298 mg, 533 μ mol) was separated by chiral SFC (DAICEL CHIRALCEL OD (250mm*30mm,10 μ m); Supercritical CO₂ / EtOH+0.1% NH₃•H₂O = 50/50; 80 mL/min) to afford (*S*)-5-chloro-2-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)benzenesulfonamide (77 mg, first peak) and (*R*)-5-chloro-2-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)benzenesulfonamide (62 mg, second peak) both as yellow solid. Absolute configuration was arbitrarily assigned to each enantiomer. **First Peak (Compound 668):** ¹HNMR (400 MHz, DMSO-*d*₆) δ 9.09 (s, 1H), 8.93 (d, $J = 2.0$ Hz, 1H), 8.42 (s, 1H), 8.28 - 8.22 (m, 1H), 8.13 (s, 1H), 7.96 (s, 1H), 7.92 (s, 1H), 7.89 (d, $J = 8.4$ Hz, 1H), 7.72 (d, $J = 2.8$ Hz, 1H), 7.48 - 7.44 (m, 1H), 7.42 (s, 2H), 7.10 (d, $J = 8.8$ Hz, 1H), 6.65 - 6.56 (m, 1H), 3.93 (s, 3H), 2.50 (s, 3H), 1.76 (d, $J = 6.0$ Hz, 3H). MS: m/z 559.1($M+H^+$). **Second peak (Compound 615):** ¹HNMR (400 MHz, DMSO-*d*₆) δ 9.08 (s, 1H), 8.93 (d, $J = 2.0$ Hz, 1H), 8.42 (s, 1H), 8.28 - 8.23 (m, 1H), 8.13 (s, 1H), 7.96 (s, 1H), 7.92 (s, 1H), 7.89 (d, $J = 8.4$ Hz, 1H), 7.72 (d, $J = 2.8$ Hz, 1H), 7.48 - 7.44 (m, 1H), 7.42 (s, 2H), 7.10 (d, $J = 8.8$ Hz, 1H), 6.65 - 6.57 (m, 1H), 3.93 (s, 3H), 2.50 (s, 3H), 1.76 (d, $J = 6.4$ Hz, 3H). MS: m/z 559.1($M+H^+$).

Example 71: Synthesis of (*R*)-2-(1-(2-cyano-7-methyl-3-(4-(1-methyl-1*H*-pyrazol-4-yl)piperazin-1-yl)quinolin-5-yl)ethoxy)benzenesulfonamide (Compound 621) and (*S*)-2-(1-(2-cyano-7-methyl-3-(4-(1-methyl-1*H*-pyrazol-4-yl)piperazin-1-yl)quinolin-5-yl)ethoxy)benzenesulfonamide (Compound 491)



5-Acetyl-3-chloro-7-methylquinoline-2-carbonitrile



Step 1 - Synthesis of 5-acetyl-7-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline-2-carbonitrile:

To a solution of 5-acetyl-2-cyano-7-methylquinolin-3-yl trifluoromethanesulfonate (15 g, 41.87 mmol) in dry dioxane (50 mL) was added dry B₂Pin₂ (12.23 g, 48.15 mmol), dry KOAc (12.33 g, 125.60 mmol) and Pd(dppf)Cl₂ (612.66 mg, 837.31 μmol). The mixture was evacuated and purged with N₂ for 3 times, then the mixture was stirred at 100 °C for 1 h under N₂ atmosphere. After cooling to room temperature, the reaction was concentrated in vacuo. The residue was dissolved in DCM (500 mL), filtered through silica plug (1000 mesh), the filter cake was washed with DCM (1 L). The filtrate was concentrated under reduced pressure to give a crude residue. The crude product was stirred in petroleum ether (200 mL) at room temperature for 10 min. The suspension was filtered and the filter cake was dried in vacuo to give the title compound (11.5 g, 82%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.42 (s, 1H), 8.33 (s, 1H), 8.12 (s, 1H), 2.77 (s, 3H), 2.65 (s, 3H), 1.43 (s, 12H). MS: m/z 255.1 (M-82+H⁺, boronic acid).

Step 2 - Synthesis of 5-acetyl-3-chloro-7-methylquinoline-2-carbonitrile:

To a solution of 5-acetyl-7-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline-2-carbonitrile (10 g, 29.74 mmol) in MeCN (30 mL) was added CuCl (6.48 g, 65.44 mmol) and NCS (4.37 g, 32.72 mmol). The mixture was evacuated and purged with N₂ for 3 times, then the mixture was stirred at 90 °C for 14 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The residue was dissolved in DCM (500 mL) and filtered through silica plug (1000 mesh), the filter cake was washed with DCM (5 L). The filtrate was concentrated under reduced pressure to give a crude residue which was stirred

in EtOAc (100 mL) at room temperature for 10 min. The suspension was filtered and the filter cake was dried in vacuo to give the title compound (5.5 g, 76%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.30 (s, 1H), 8.43 (s, 1H), 8.18 (s, 1H), 2.78 (s, 3H), 2.63 (s, 3H). MS: m/z 245.1 (M+H⁺).

5

Step 1 - Synthesis of *tert*-butyl 4-(1-methyl-1*H*-pyrazol-4-yl)piperazine-1-carboxylate:

To a solution of *tert*-butyl piperazine-1-carboxylate (20 g, 107.38 mmol) in *i*-PrOH (500 mL) was added 4-iodo-1-methyl-pyrazole (26.8 g, 128.86 mmol), K₃PO₄ (91.17 g, 429.53 mmol),
10 CuI (4.09 g, 21.48 mmol) and ethylene glycol (7.33 g, 118.12 mmol, 6.59 mL). The mixture was evacuated and backfilled with N₂ for 3 times, and then it was stirred at 80 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the mixture was concentrated in vacuo. The residue was purified by silica gel chromatography (solvent gradient: 30% - 50% EtOAc in hexanes) to give the title compound (11.5 g, 40%) as a yellow solid. MS: m/z 267.2 (M+H⁺).

15

Step 2 - Synthesis of 1-(1-methyl-1*H*-pyrazol-4-yl)piperazine:

A solution of *tert*-butyl 4-(1-methyl-1*H*-pyrazol-4-yl)piperazine-1-carboxylate (11.5 g, 43.18 mmol) in HCl/MeOH (40 mL, 2M) was stirred at room temperature for 16 h. The mixture was concentrated. Then was diluted with DCM (50 mL), adjusted pH to 8 with sat. aq. NaHCO₃, and extracted with DCM (50 mL x 3). The combined organic phase was washed with brine (30
20 mL x 2), dried with anhydrous Na₂SO₄, filter and concentrated in vacuum to give the title compound (5.96 g, 83%) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.30 (d, *J* = 0.4 Hz, 1H), 7.16 (d, *J* = 0.4 Hz, 1H), 3.72 (s, 3H), 3.09 - 3.04 (m, 4H), 2.98 - 2.94 (m, 4H). MS: m/z 167.1 (M+H⁺).

25

Step 3 - Synthesis of 5-acetyl-7-methyl-3-(4-(1-methyl-1*H*-pyrazol-4-yl)piperazin-1-yl)quinoline-2-carbonitrile:

A mixture of 5-acetyl-3-chloro-7-methyl-quinoline-2-carbonitrile (500 mg, 2.04 mmol), 1-(1-methyl-1*H*-pyrazol-4-yl)piperazine (679 mg, 4.1 mmol), Cs₂CO₃ (2 g, 6.13 mmol) and RuPhos Pd G₂ (159 mg, 204 μmol) in toluene (10 mL) was evacuated and backfilled with N₂ for 3 times, and then the mixture was stirred at 110 °C for 16 h under N₂ atmosphere. After cooling to room
30 temperature, the reaction mixture was diluted with EtOAc (40 mL), washed with water (20 mL x

3) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude, which was purified by silica gel chromatography (0 - 50% EtOAc in hexanes) to give the title compound (600 mg, 78%) as a yellow solid. MS: m/z 375.2 (M+H⁺).

Step 4 - Synthesis of 5-(1-hydroxyethyl)-7-methyl-3-(4-(1-methyl-1*H*-pyrazol-4-yl)piperazin-1-yl)quinoline-2-carbonitrile:

To a solution of 5-acetyl-7-methyl-3-(4-(1-methyl-1*H*-pyrazol-4-yl)piperazin-1-yl)quinoline-2-carbonitrile (600 mg, 1.6 mmol) in DCM (10 mL) was added NaBH₄ (50 mg, 1.32 mmol) and MeOH (2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched with sat. aq. NH₄Cl (10 mL) at 0 °C and extracted with DCM (20 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound (500 mg, crude) as a white solid. The crude was used for the next step directly without further purification. MS: m/z 377.2 (M+H⁺).

Step 5 - Synthesis of 5-(1-bromoethyl)-7-methyl-3-(4-(1-methyl-1*H*-pyrazol-4-yl)piperazin-1-yl)quinoline-2-carbonitrile:

To a solution of 5-(1-hydroxyethyl)-7-methyl-3-(4-(1-methyl-1*H*-pyrazol-4-yl)piperazin-1-yl)quinoline-2-carbonitrile (300 mg, 797 μmol) in DCM (5 mL) was added PPh₃ (627 mg, 2.39 mmol) and CBr₄ (793 mg, 2.39 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 0.5 h. The mixture was quenched with sat. aq. NaHCO₃ (10 mL), extracted with DCM (30 mL x 3). The combined organic layers were washed with H₂O (30 mL x 2), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound (350 mg, crude) as yellow oil. The crude was used for the next step directly without further purification.

Step 6 - Synthesis of 2-(1-(2-cyano-7-methyl-3-(4-(1-methyl-1*H*-pyrazol-4-yl)piperazin-1-yl)quinolin-5-yl)ethoxy)benzenesulfonamide:

To a mixture of 2-hydroxybenzenesulfonamide (276 mg, 1.6 mmol) and K₂CO₃ (550 mg, 3.98 mmol) in DMF (5 mL) was added 5-(1-bromoethyl)-7-methyl-3-(4-(1-methyl-1*H*-pyrazol-4-yl)piperazin-1-yl)quinoline-2-carbonitrile (350 mg, 796 μmol) at room temperature. The mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with sat. aq. NH₄Cl (20 mL) at 0 °C, extracted with DCM (50 mL x 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The crude residue was purified by

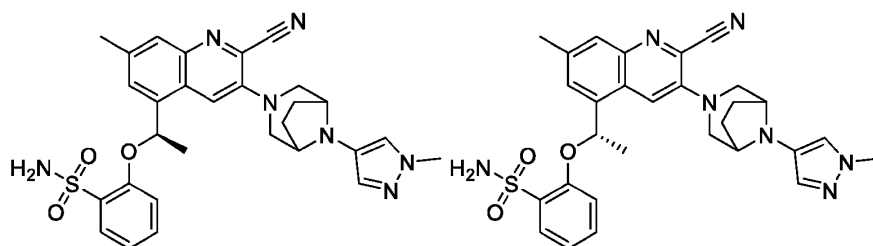
silica gel chromatography (solvent gradient: 20 - 25% (25% ethyl alcohol in EtOAc) in hexanes) to give the title compound (300 mg, 70%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.34 (s, 1H), 7.87 (d, *J* = 1.2 Hz, 1H), 7.79 - 7.73 (m, 2H), 7.42 - 7.35 (m, 2H), 7.25 (s, 1H), 7.17 (s, 2H), 7.07 - 6.97 (m, 2H), 6.50 - 6.42 (m, 1H), 3.76 (s, 3H), 3.42 - 3.38 (m, 4H), 3.14 - 3.08 (m, 4H), 2.44 (s, 3H), 1.78 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 532.2 (M+H⁺).

Step 7 - Synthesis of (*R*)-2-(1-(2-cyano-7-methyl-3-(4-(1-methyl-1*H*-pyrazol-4-yl)piperazin-1-yl)quinolin-5-yl)ethoxy)benzenesulfonamide and

(*S*)-2-(1-(2-cyano-7-methyl-3-(4-(1-methyl-1*H*-pyrazol-4-yl)piperazin-1-yl)quinolin-5-yl)ethoxy)benzenesulfonamide:

2-(1-(2-cyano-7-methyl-3-(4-(1-methyl-1*H*-pyrazol-4-yl)piperazin-1-yl)quinolin-5-yl)ethoxy)benzenesulfonamide (300 mg, 564 μmol) was separated by using chiral SFC (DAICEL CHIRALCEL OD (250mm x 30mm, 10μm); Supercritical CO₂ / EtOH + 0.1% NH₃•H₂O = 60/40; 80 mL/min) to afford (*R*)-2-(1-(2-cyano-7-methyl-3-(4-(1-methyl-1*H*-pyrazol-4-yl)piperazin-1-yl)quinolin-5-yl)ethoxy)benzenesulfonamide (135.7 mg, first peak) and (*S*)-2-(1-(2-cyano-7-methyl-3-(4-(1-methyl-1*H*-pyrazol-4-yl)piperazin-1-yl)quinolin-5-yl)ethoxy)benzenesulfonamide (124.7 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. **First peak** (Compound 621): ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.33 (s, 1H), 7.86 (s, 1H), 7.79 - 7.70 (m, 2H), 7.41 - 7.35 (m, 2H), 7.25 (s, 1H), 7.17 (s, 2H), 7.05 - 6.96 (m, 2H), 6.50 - 6.42 (m, 1H), 3.76 (s, 3H), 3.42 - 3.37 (m, 4H), 3.14 - 3.08 (m, 4H), 2.44 (s, 3H), 1.77 (d, *J* = 6.0 Hz, 3H). MS: *m/z* 532.2 (M+H⁺). **Second peak** (Compound 491): ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.33 (s, 1H), 7.86 (d, *J* = 1.2 Hz, 1H), 7.80 - 7.72 (m, 2H), 7.42 - 7.35 (m, 2H), 7.25 (s, 1H), 7.17 (s, 2H), 7.06 - 6.95 (m, 2H), 6.50 - 6.42 (m, 1H), 3.76 (s, 3H), 3.43 - 3.37 (m, 4H), 3.14 - 3.08 (m, 4H), 2.44 (s, 3H), 1.77 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 532.2 (M+H⁺).

Example 72: Synthesis of 2-((1*R*)-1-(2-cyano-7-methyl-3-(8-(1-methyl-1*H*-pyrazol-4-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)quinolin-5-yl)ethoxy)benzenesulfonamide (Compound 454) and 2-((1*S*)-1-(2-cyano-7-methyl-3-(8-(1-methyl-1*H*-pyrazol-4-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)quinolin-5-yl)ethoxy)benzenesulfonamide (Compound 490)



Step 1 - Synthesis of *tert*-butyl 8-(1-methyl-1*H*-pyrazol-4-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate:

To a solution of *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate (10 g, 47.11 mmol) in toluene (160 mL) was added 4-iodo-1-methyl-1*H*-pyrazole (12.74 g, 61.24 mmol), *t*-BuONa (6.79 g, 70.66 mmol) and RuPhos Pd G₃ (2.95 g, 3.53 mmol). The mixture was evacuated and backfilled with N₂ for 3 times, and then it was stirred at 110 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the mixture was quenched with H₂O (100 mL) and extracted with EtOAc (200 mL x 2). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 40% EtOAc in hexanes) to give the title compound (5.4 g, 40%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.26 (s, 1H), 7.10 (s, 1H), 3.73 - 3.68 (m, 5H), 3.56 - 3.47 (m, 2H), 3.17 - 3.10 (m, 1H), 3.04 - 2.97 m, 1H), 1.85 - 1.76 (m, 2H), 1.57 - 1.51 (m, 2H), 1.38 (s, 9H). MS: *m/z* 293.1 (M+H⁺).

Step 2 - Synthesis of 8-(1-methyl-1*H*-pyrazol-4-yl)-3,8-diazabicyclo[3.2.1]octane:

A solution of *tert*-butyl 8-(1-methyl-1*H*-pyrazol-4-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (5.4 g, 18.47 mmol) in HCl/dioxane (46 mL, 2M) was stirred at room temperature for 2 h. The mixture was concentrated in vacuo, the residue was dissolved in MeOH (20 mL) and added Ambersep/r 900(OH) ion exchange resin (10 g) (CAS: 9017-79-2). The mixture was stirred at room temperature for 1 h. The mixture was filtered and the filtrate was concentrated in vacuo to give the title compound (3.3 g, crude) as yellow oil that required no further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.18 (s, 1H), 7.04 (s, 1H), 3.73 - 3.64 (m, 4H), 3.55 - 3.46 (m, 2H), 2.94 - 2.85 (m, 2H), 2.43 - 2.37 (m, 2H), 1.73 (s, 3H). MS: *m/z* 193.1 (M+H⁺).

Step 3 - Synthesis of 5-acetyl-7-methyl-3-(8-(1-methyl-1*H*-pyrazol-4-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)quinoline-2-carbonitrile:

To a solution of 8-(1-methyl-1*H*-pyrazol-4-yl)-3,8-diazabicyclo[3.2.1]octane (534 mg, 2.78 mmol) in toluene (6 mL) was added 5-acetyl-3-chloro-7-methylquinoline-2-carbonitrile (340 mg, 1.39 mmol), RuPhos Pd G₂ (108 mg, 139 μ mol) and Cs₂CO₃ (1.36 g, 4.17 mmol). The mixture was evacuated and backfilled with N₂ for 3 times, and then it was stirred at 110 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the mixture was quenched with H₂O (100 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in hexanes) to give the title compound (350 mg, 63%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.70 (s, 1H), 8.27 (s, 1H), 8.01 (s, 1H), 7.33 (s, 1H), 7.18 (s, 1H), 3.95 (s, 2H), 3.73 (s, 3H), 3.30 - 3.20 (m, 4H), 2.73 (s, 3H), 2.56 (s, 3H), 1.95 - 1.89 (m, 2H), 1.73 - 1.69 (m, 2H). MS: *m/z* 401.2 (M+H⁺).

Step 4 - Synthesis of 5-(1-hydroxyethyl)-7-methyl-3-(8-(1-methyl-1*H*-pyrazol-4-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)quinoline-2-carbonitrile:

To a solution of 5-acetyl-7-methyl-3-(8-(1-methyl-1*H*-pyrazol-4-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)quinoline-2-carbonitrile (350 mg, 874 μ mol) in DCM (3 mL) was added NaBH₄ (66 mg, 1.75 mmol) at room temperature for 1 h. The mixture was quenched with aq. sat. NH₄Cl (10 mL), extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to remove DCM and give the title compound (325 mg, 92%) as a yellow solid that required no further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.12 (s, 1H), 7.68 (s, 1H), 7.61 (s, 1H), 7.33 (s, 1H), 7.18 (s, 1H), 5.47 (d, *J* = 4.0 Hz, 1H), 5.43 - 5.35 (m, 1H), 3.92 (s, 2H), 3.72 (s, 3H), 3.31 - 3.22 (m, 4H), 2.49 (s, 3H), 2.12 - 2.08 (m, 2H), 1.95 - 1.86 (m, 2H), 1.44 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 403.1 (M+H⁺).

Step 5 - Synthesis of 5-(1-bromoethyl)-7-methyl-3-(8-(1-methyl-1*H*-pyrazol-4-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)quinoline-2-carbonitrile:

To a solution of 5-(1-hydroxyethyl)-7-methyl-3-(8-(1-methyl-1*H*-pyrazol-4-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)quinoline-2-carbonitrile (325 mg, 807 μ mol) in DCM (4 mL) was added PPh₃ (635 mg, 2.42 mmol) and CBr₄ (803 mg, 2.42 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was used for the next step directly without further purification. MS: *m/z* 465.1 (M+H⁺).

Step 6 – Synthesis of 2-(1-(2-cyano-7-methyl-3-(8-(1-methyl-1*H*-pyrazol-4-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)quinolin-5-yl)ethoxy)benzenesulfonamide:

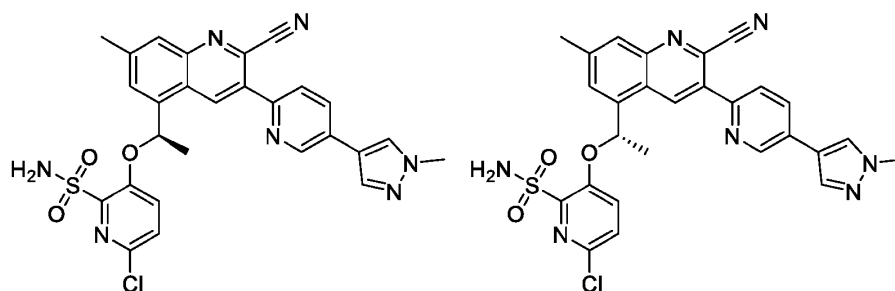
To a solution of 5-(1-bromoethyl)-7-methyl-3-(8-(1-methyl-1*H*-pyrazol-4-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)quinoline-2-carbonitrile in DCM (above mentioned reaction solution) was added DMF (5 mL), followed by 2-hydroxybenzenesulfonamide (275 mg, 1.59 mmol) and K₂CO₃ (330 mg, 2.39 mmol). The mixture was stirred at room temperature for 16 h under N₂ atmosphere. The reaction was quenched with water (15 mL), extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude, which was purified by silica gel chromatography (solvent gradient: 0 - 40% EtOAc in hexanes) to give the title compound (180 mg, 41%) as a white solid. MS: m/z 558.3 (M+H⁺).

Step 7 – Synthesis of 2-((1*R*)-1-(2-cyano-7-methyl-3-(8-(1-methyl-1*H*-pyrazol-4-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)quinolin-5-yl)ethoxy)benzenesulfonamide and 2-((1*S*)-1-(2-cyano-7-methyl-3-(8-(1-methyl-1*H*-pyrazol-4-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)quinolin-5-yl)ethoxy)benzenesulfonamide:

2-(1-(2-cyano-7-methyl-3-(8-(1-methyl-1*H*-pyrazol-4-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)quinolin-5-yl)ethoxy)benzenesulfonamide (180 mg, 179 μmol) was separated by using chiral SFC (Phenomenex-Cellulose-2 (250 mm * 30 mm, 10 μm); Supercritical CO₂/(MeOH:MeCN) + 0.1% NH₃·H₂O = 40/60; 80 mL/min) to afford 2-((1*R*)-1-(2-cyano-7-methyl-3-(8-(1-methyl-1*H*-pyrazol-4-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)quinolin-5-yl)ethoxy)benzenesulfonamide (51 mg, first peak) and 2-((1*S*)-1-(2-cyano-7-methyl-3-(8-(1-methyl-1*H*-pyrazol-4-yl)-3,8-diazabicyclo[3.2.1]octan-3-yl)quinolin-5-yl)ethoxy)benzenesulfonamide (49 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. **First peak** (Compound 454): ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.20 (s, 1H), 7.82 (s, 1H), 7.78 - 7.74 (m, 1H), 7.72 (s, 1H), 7.40 - 7.33 (m, 2H), 7.19 (s, 1H), 7.17 (s, 2H), 7.01 - 6.94 (m, 2H), 6.52 - 6.42 (m, 1H), 3.93 (s, 2H), 3.73 (s, 3H), 3.45 - 3.36 (m, 3H), 3.32 - 3.27 (m, 1H), 2.41 (s, 3H), 2.16 - 2.05 (m, 2H), 1.95 - 1.84 (m, 2H), 1.72 (d, *J* = 6.0 Hz, 3H). MS: m/z 558.3 (M+H⁺). **Second peak** (Compound 490): ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.20 (s, 1H), 7.82 (s, 1H), 7.78 - 7.74 (m, 1H), 7.72 (s, 1H), 7.40 - 7.33 (m, 2H), 7.19 (s, 1H), 7.17 (s, 2H), 7.01 - 6.95 (m, 2H), 6.52 - 6.42 (m, 1H), 3.93 (s, 2H), 3.73 (s, 3H), 3.45 - 3.37 (m, 3H), 3.32 - 3.28 (m, 1H), 2.41 (s, 3H), 2.16 - 2.05 (m, 2H), 1.95 - 1.84 (m, 2H), 1.72 (d, *J* = 6.0 Hz, 3H). MS: m/z 558.3 (M+H⁺).

Example 73: Synthesis of (*R*)-6-chloro-3-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-2-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide (Compound 531) & (*S*)-6-chloro-3-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-2-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide (Compound 654)

5



Step1 – Synthesis of 2-(benzylthio)-6-chloro-3-fluoropyridine:

To a solution of KOH (4.11 g, 73.25 mmol, 1.2 eq) in EtOH (50 mL) was added dropwise BnSH (8.49 mL, 72.30 mmol, 1.2 eq) at 0 °C. After addition, 2,6-dichloro-3-fluoro-pyridine (10 g, 60.25 mmol, 1 eq) in EtOH (50 mL) was added dropwise at 0 °C. The resulting mixture was stirred at room temperature for 16 h. Then the mixture was quenched with water (100 mL), extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The crude product was purified by silica gel chromatography (solvent gradient: 100% petroleum ether) to give the title compound (14 g, 91%) as pink oil, which was further confirmed by ¹³C-NMR (2D-NMR). ¹H NMR (400 MHz, CDCl₃) δ 7.48 - 7.44 (m, 2H), 7.37 - 7.29 (m, 2H), 7.29 - 7.24 (m, 1H), 7.22 - 7.17 (m, 1H), 7.02 - 6.98 (m, 1H), 4.44 (s, 2H).

Step 2 – Synthesis of 6-chloro-3-fluoropyridine-2-sulfonamide:

To a solution of 2-benzylsulfanyl-6-chloro-3-fluoro-pyridine (20 g, 78.83 mmol, 1 eq) in water (20 mL) and acetonitrile (200 mL) was added AcOH (36.10 mL, 630.61 mmol, 8 eq) at 0 °C. After addition, then NCS (42.10 g, 315.30 mmol, 4 eq) was added slowly at 0 °C. The resulting mixture was stirred at 0 °C for 0.5 h. The mixture was added water (50 mL), then extracted with DCM (3 x 100 mL). The combined organic layers were washed with brine (100 mL x 3) and dried over Na₂SO₄. The organic mixture was added to ammonium hydroxide (80 mL, 623.19 mmol, 29

wt%, 8 eq) in THF (80 mL) at 0 °C. After the addition, the reaction mixture was stirred at 0 °C for 10 min. Then the mixture was quenched with water (100 mL), extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The crude product was triturated with DCM (50 mL), then filtered and the filter cake was concentrated in vacuo to give the title compound (11 g, 66%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.14 - 8.09 (m, 1H), 7.97 (s, 2H), 7.92 - 7.88 (m, 1H).

Step 3 – Synthesis of 6-chloro-3-hydroxypyridine-2-sulfonamide:

To a solution of 6-chloro-3-fluoro-pyridine-2-sulfonamide (10 g, 47.48 mmol, 1 eq) in water (250 mL) was added KOH (26.64 g, 474.80 mmol, 10 eq) at room temperature. After the addition, the reaction mixture was stirred at 110 °C for 5 h. After cooling to 0 °C, the pH was adjusted to ~ 4 - 5 with concentrated HCl (12M). The mixture was extracted with DCM: *i*-PrOH = 3:1 (100 mL x 5), then the combined organic layers were washed with brine (200 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (2.9 g, 29%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.23 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.35 (s, 2H).

Step 4 - Synthesis of 2-chloro-5-(1-methyl-1H-pyrazol-4-yl)pyridine:

To a solution of 2-chloro-5-iodopyridine (10 g, 41.76 mmol) in dioxane (110 mL) and H₂O (11 mL) was added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (9.56 g, 45.94 mmol), Pd(dppf)Cl₂ (1.53 g, 2.09 mmol) and K₂CO₃ (17.32 g, 125.29 mmol). The mixture was evacuated and backfilled with N₂ for 3 times, and then it was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was quenched with H₂O (100 mL), extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (50 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% EtOAc in petroleum ether) to give the title compound (6 g, 70%) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.66 (d, *J* = 2.4 Hz, 1H), 8.28 (s, 1H), 8.05 - 8.01 (m, 1H), 7.99 (s, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 3.87 (s, 3H). MS: *m/z* 194.1 (M+H⁺).

Step 5 - Synthesis of 5-acetyl-7-methyl-3-(5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)quinoline-2-carbonitrile:

To a solution of 2-chloro-5-(1-methyl-1*H*-pyrazol-4-yl)pyridine (570 mg, 2.94 mmol) in dioxane (20 mL) and H₂O (1 mL) was added 5-acetyl-7-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline-2-carbonitrile (0.9 g, 2.68 mmol), CsF (1.22 g, 8.03 mmol), XPhos (255 mg, 535 μ mol) and Pd₂(dba)₃ (245 mg, 267 μ mol). The mixture was evacuated and backfilled with N₂ for 3 times, and then it was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction was diluted with H₂O (30 mL) and then filtered. The filter cake was washed with H₂O (30 mL x 2), dried in vacuo. The crude filter cake was purified by silica gel chromatography (solvent gradient: 0 - 1% MeOH in DCM) to give the title compound (450 mg, 45%) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.46 (s, 1H), 9.09 (d, *J* = 2.0 Hz, 1H), 8.41 (s, 1H), 8.40 - 8.38 (m, 1H), 8.25 - 8.21 (m, 1H), 8.20 (s, 1H), 8.11 (s, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 3.92 (s, 3H), 2.79 (s, 3H), 2.65 (s, 3H). MS: *m/z* 368.1 (M+H⁺).

Step 6 - Synthesis of 5-(1-hydroxyethyl)-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-2-yl)quinoline-2-carbonitrile:

To a solution of 5-acetyl-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-2-yl)quinoline-2-carbonitrile (0.45 g, 1.22 mmol) in DCM (15 mL) was added NaBH₄ (93 mg, 2.45 mmol) at 0 °C under N₂ atmosphere, MeOH (2 mL) was added until the reaction was completely clear. The resulting reaction was kept stirring at 0 °C for 1 h. The reaction was quenched with sat. aq. NH₄Cl (10 mL) at 0 °C and extracted with DCM (30 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give the title compound (420 mg, 92%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.08 (d, *J* = 2.0 Hz, 1H), 9.07 (s, 1H), 8.40 (s, 1H), 8.24 - 8.20 (m, 1H), 8.12 (s, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.87 (s, 1H), 7.76 (s, 1H), 5.59 - 5.54 (m, 2H), 3.92 (s, 3H), 2.58 (s, 3H), 1.51 (d, *J* = 6.0 Hz, 3H). MS: *m/z* 370.2 (M+H⁺).

Step 7 - Synthesis of 5-(1-bromoethyl)-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-2-yl)quinoline-2-carbonitrile:

To a solution of 5-(1-hydroxyethyl)-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-2-yl)quinoline-2-carbonitrile (0.42 g, 1.14 mmol) in DCM (10 mL) was added PPh₃ (895 mg, 3.41 mmol) and CBr₄ (1.13 g, 3.41 mmol) at 0 °C, the resulting mixture was stirred at room temperature for 1h. The reaction mixture was used for the next step directly without further purification. MS: *m/z* 432.1 (M+H⁺).

Step 8 - Synthesis of 6-chloro-3-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-2-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide:

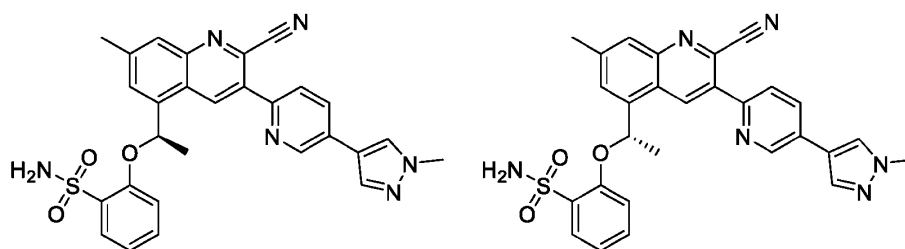
To a solution of 5-(1-bromoethyl)-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinoline-2-carbonitrile (above mentioned reaction solution, in DCM) was added DMF (9 mL), followed by 6-chloro-3-hydroxypyridine-2-sulfonamide (473 mg, 2.27 mmol) and K₂CO₃ (783 mg, 5.67 mmol). The mixture was stirred at room temperature for 16 h under N₂ atmosphere. The reaction was diluted with H₂O (20 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EE (25% EtOH in EtOAc) in hexanes) to give the title compound (250 mg, 37%) as a orange solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.17 (s, 1H), 9.10 (d, *J* = 1.6 Hz, 1H), 8.43 (s, 1H), 8.28 - 8.23 (m, 1H), 8.18 - 8.15 (m, 1H), 8.14 (s, 1H), 7.97 (s, 1H), 7.93 (s, 1H), 7.75 - 7.71 (m, 1H), 7.62 - 7.57 (m, 3H), 6.73 - 6.66 (m, 1H), 3.93 (s, 3H), 2.52 (s, 3H), 1.77 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 560.2 (M+H⁺).

Step 9 - Synthesis of (*R*)-6-chloro-3-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-2-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide & (*S*)-6-chloro-3-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-2-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide:

6-chloro-3-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-2-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide (250 mg, 446 μmol) was separated by using chiral SFC (DAICEL CHIRALPAK AD (250mm*30mm,10um); Supercritical CO₂ / *i*-PrOH+ 0.1% NH₃•H₂O = 45/55; 80 mL/min) to afford (*R*)-6-chloro-3-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-2-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide (45.53 mg, first peak) and (*S*)-6-chloro-3-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-2-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide (44.23 mg, second peak) both as yellow solid. Absolute configuration was arbitrarily assigned to each enantiomer. **First peak** (Compound 531): ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.17 (s, 1H), 9.10 (s, 1H), 8.43 (s, 1H), 8.29 - 8.22 (m, 1H), 8.19 - 8.11 (m, 2H), 8.00 - 7.91 (m, 2H), 7.76 - 7.71 (m, 1H), 7.63 - 7.55 (m, 3H), 6.73 - 6.63 (m, 1H), 3.93 (s, 3H), 2.52 (s, 3H), 1.77 (d, *J* = 6.0 Hz, 3H). MS: *m/z* 560.1 (M+H⁺). **Second peak** (Compound 654): ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.17 (s, 1H), 9.13 - 9.08 (m, 1H), 8.43 (s, 1H), 8.28 - 8.22

(m, 1H), 8.18 - 8.12 (m, 2H), 7.96 (s, 1H), 7.93 (s, 1H), 7.76 - 7.71 (m, 1H), 7.63 - 7.56 (m, 3H), 6.73 - 6.65 (m, 1H), 3.93 (s, 3H), 2.52 (s, 3H), 1.77 (d, $J = 6.4$ Hz, 3H). MS: m/z 560.1 ($M+H^+$).

Example 74: Synthesis of (*R*)-2-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-2-yl)quinolin-5-yl)ethoxy)benzenesulfonamide (Compound 532) and (*S*)-2-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-2-yl)quinolin-5-yl)ethoxy)benzenesulfonamide (Compound 641)



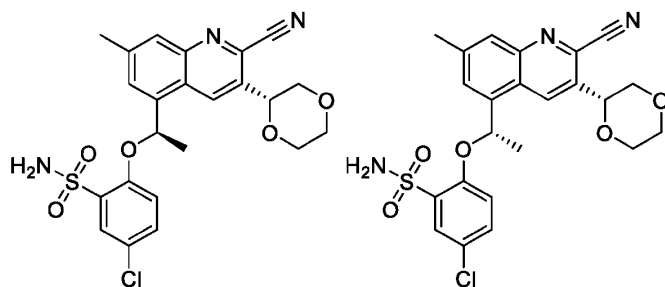
Step 1 - Synthesis of 2-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-2-yl)quinolin-5-yl)ethoxy)benzenesulfonamide:

To a solution of 5-(1-bromoethyl)-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-2-yl)quinoline-2-carbonitrile (reaction solution was used directly, 439 μ mol in 4 mL DCM) was added DMF (3 mL), followed by 2-hydroxybenzenesulfonamide (98 mg, 571.34 μ mol) and K_2CO_3 (182 mg, 1.32 mmol). The mixture was stirred at room temperature for 16 h. The reaction was quenched with H_2O (10 mL), extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give the crude, which was purified by silica gel chromatography (solvent gradient: 0 - 5% MeOH in DCM) to give the title compound (100 mg, 43%) as a white solid. 1H NMR (400 MHz, $DMSO-d_6$) δ 9.22 (s, 1H), 9.10 - 9.05 (m, 1H), 8.41 (s, 1H), 8.24 - 8.21 (m, 1H), 8.18 - 8.14 (m, 1H), 8.13 (s, 1H), 7.98 - 7.96 (m, 1H), 7.90 (s, 1H), 7.77 - 7.75 (m, 1H), 7.39 - 7.33 (m, 1H), 7.20 (s, 2H), 7.06 - 7.02 (m, 1H), 7.00 - 6.94 (m, 1H), 6.63 - 6.58 (m, 1H), 3.92 (s, 3H), 3.44 (s, 3H), 1.79 (d, $J = 6.4$ Hz, 3H). MS: m/z 525.1 ($M+H^+$).

Step 2 - Synthesis of (*R*)-2-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-2-yl)quinolin-5-yl)ethoxy)benzenesulfonamide and (*S*)-2-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-2-yl)quinolin-5-yl)ethoxy)benzenesulfonamide:

2-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-2-yl)quinolin-5-yl)ethoxy)benzenesulfonamide (100 mg, 190.62 μ mol) was separated by using chiral SFC (DAICEL CHIRALPAK IG (250mm*30mm,10 μ m); Supercritical CO₂ / *i*-PrOH + 0.1% NH₃·H₂O = 40/60; 80 mL/min) to afford (*R*)-2-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-2-yl)quinolin-5-yl)ethoxy)benzenesulfonamide (28.6 mg, first peak) and (*S*)-2-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-2-yl)quinolin-5-yl)ethoxy)benzenesulfonamide (29.1 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. **First peak** (Compound 532): ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.23 (s, 1H), 9.12 - 9.09 (m, 1H), 8.43 (s, 1H), 8.27 - 8.23 (m, 1H), 8.19 - 8.15 (m, 1H), 8.14 (s, 1H), 7.98 (s, 1H), 7.91 (s, 1H), 7.79 - 7.76 (m, 1H), 7.39 - 7.34 (m, 1H), 7.21 (s, 2H), 7.06 - 7.02 (m, 1H), 7.01 - 6.98 (m, 1H), 6.65 - 6.62 (m, 1H), 3.92 (s, 3H), 2.50 (s, 3H), 1.79 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 525.2 (M+H⁺). **Second peak** (Compound 641): ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.23 (s, 1H), 9.12 - 9.09 (m, 1H), 8.43 (s, 1H), 8.27 - 8.23 (m, 1H), 8.18 - 8.15 (m, 1H), 8.14 (s, 1H), 7.98 (s, 1H), 7.91 (s, 1H), 7.79 - 7.75 (m, 1H), 7.39 - 7.34 (m, 1H), 7.21 (s, 2H), 7.06 - 7.02 (m, 1H), 7.01 - 6.97 (m, 1H), 6.66 - 6.60 (m, 1H), 3.93 (s, 3H), 2.51 (s, 3H), 1.79 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 525.2 (M+H⁺).

Example 75: Synthesis of 5-chloro-2-((*R*)-1-(2-cyano-3-((*R*)-1,4-dioxan-2-yl)-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide (Compound 526) and 5-chloro-2-((*S*)-1-(2-cyano-3-((*R*)-1,4-dioxan-2-yl)-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide (Compound 525)



Step 1 - Synthesis of 2-(iodomethyl)-1,4-dioxane:

To a solution of 2-(allyloxy)ethan-1-ol (5 g, 48.96 mmol) in MeCN (150 mL) was added NaHCO₃ (12.34 g, 146.87 mmol) and I₂ (37.28 g, 146.87 mmol). The reaction mixture was stirred at room temperature for 20 h. The mixture was quenched with H₂O (100 mL) and extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue was purified by silica gel chromatography (solvent gradient: 0 - 40% EtOAc in hexanes) to give the title compound (7 g, 63%) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 3.96 - 3.90 (m, 1H), 3.86 - 3.81 (m, 1H), 3.80 - 3.73 (m, 1H), 3.70 - 3.59 (m, 3H), 3.37 - 3.30 (m, 1H), 3.11-3.07 (m, 2H).

Step 2 - Synthesis of 2-((1,3-dithian-2-yl)methyl)-1,4-dioxane:

A mixture of 1,3-dithiane (7.91 g, 65.78 mmol) and HMPA (11.51 mL, 65.78 mmol) in THF (30 mL) was evacuated and backfilled with N₂ for 3 times. After cooling to -78 °C, *n*-BuLi (2.5 M, 17.54 mL) was added dropwise, followed by stirring for 0.5 h under N₂ atmosphere. Then, a solution of 2-(iodomethyl)-1,4-dioxane (5 g, 21.93 mmol) in THF (100 mL) was added dropwise, the mixture was stirred at -78 °C for another 1 h. The mixture was slowly raised to room temperature, and quenched with sat. aq. NH₄Cl (20 mL) and H₂O (30 mL), then extracted with MTBE (150 mL x 3). The combined organic layers were washed with H₂O (100 mL) and brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 4% EtOAc in hexanes) to give the title compound (3 g, 62%) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 4.22 - 4.17 (m, 1H), 3.87 - 3.80 (m, 1H), 3.75 - 3.66 (m, 4H), 3.60 - 3.53 (m, 1H), 3.29 - 3.23 (m, 1H), 2.91 - 2.80 (m, 4H), 2.13 - 2.06 (m, 1H), 1.88 - 1.79 (m, 2H), 1.71 - 1.63 (m, 1H).

Step 3 - Synthesis of 2-(1,4-dioxan-2-yl)acetaldehyde:

To a solution of 2-((1,3-dithian-2-yl)methyl)-1,4-dioxane (3 g, 12.71 mmol) in MeCN (90 mL) and H₂O (30 mL) was added NaHCO₃ (5.34 g, 63.53 mmol), followed by MeI (7.91 mL, 127.07 mmol). The reaction mixture was heated to 45°C and stirred for 15 h. After cooling to room temperature, the mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give the title compound (1.5 g, crude) as yellow oil that required no further purification. ¹H NMR (400 MHz, CDCl₃) δ 9.79 - 9.77 (m, 1H), 4.13 - 4.11 (m, 1H), 3.80 - 3.73 (m, 4H), 3.65 - 3.59 (m, 1H), 3.37 - 3.30 (m, 1H), 2.62 - 2.49 (m, 1H), 2.46 - 2.36 (m, 1H).

Step 4 - Synthesis of 5-bromo-3-(1,4-dioxan-2-yl)-7-methylquinoline:

To a solution of 2-(1,4-dioxan-2-yl)acetaldehyde (1.3 g, 9.99 mmol) and 2-amino-6-bromo-4-methylbenzaldehyde (2.14 g, 9.99 mmol) in EtOH (35 mL) and H₂O (3 mL) was added NaOH (799 mg, 19.98 mmol). The reaction mixture was stirred at 90 °C for 1 h. After cooling to room temperature, the mixture was concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 15% EtOAc in hexanes) to give the title compound (1.22 g, 40%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.85 (d, *J* = 2.0 Hz, 1H), 8.44 (d, *J* = 2.0 Hz, 1H), 7.85 (s, 1H), 7.71 (d, *J* = 1.6 Hz, 1H), 4.89 - 4.85 (m, 1H), 4.07 - 4.00 (m, 2H), 3.88 - 3.84 (m, 3H), 3.60 - 3.53 (m, 1H), 2.55 (s, 3H). MS: *m/z* 308.0 (M+H⁺).

Step 5 - Synthesis of 5-bromo-3-(1,4-dioxan-2-yl)-7-methylquinoline 1-oxide:

To a solution of 5-bromo-3-(1,4-dioxan-2-yl)-7-methylquinoline (1 g, 3.24 mmol) in DCM (10 mL) was added *m*-CPBA (1.32 g, 6.49 mmol, 85% purity) at 0 °C and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched by sat. NaHCO₃ (50 mL) and extracted with DCM (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give the title compound (1 g, crude) as yellow solid that required no further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.69 (s, 1H), 8.36 (s, 1H), 7.99 (d, *J* = 1.2 Hz, 1H), 7.94 (s, 1H), 4.84 - 4.78 (m, 1H), 4.05 - 3.99 (m, 2H), 3.82 - 3.77 (m, 2H), 3.68 - 3.62 (m, 1H), 3.41 - 3.34 (m, 1H), 2.54 (s, 3H). MS: *m/z* 323.9 (M+H⁺).

Step 6 – Synthesis of 5-bromo-3-(1,4-dioxan-2-yl)-7-methylquinoline-2-carbonitrile:

To a solution of 5-bromo-3-(1,4-dioxan-2-yl)-7-methylquinoline 1-oxide (1 g, 3.08 mmol) in DCM (15 mL) was added 1-ethoxyphosphonoyloxyethane (795 μL, 6.17 mmol), TEA (624 mg, 6.17 mmol), CCl₄ (949 mg, 6.17 mmol) and TMSCN (579 μL, 4.63 mmol). The mixture was evacuated and backfilled with N₂ for 3 times, and then it was stirred at room temperature for 16 h. The reaction mixture was diluted with DCM (50 mL) and washed with NaHCO₃ (50 mL x 2), dried over Na₂SO₄, filtered and concentrated in vacuo. The reaction was filtered and the filter cake was concentrated in vacuo to give the title compound (1 g, crude) as a yellow solid that required no further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.60 (s, 1H), 8.09 (d, *J* = 1.6 Hz, 1H), 7.97 (s, 1H), 5.09 - 5.03 (m, 1H), 4.11 - 4.04 (m, 2H), 3.94 - 3.89 (m, 2H), 3.85 - 3.81 (m, 2H), 3.75 - 3.67 (m, 1H), 3.52 - 3.44 (m, 1H), 2.55 (s, 3H). MS: *m/z* 332.9 (M+H⁺).

Step 7 – Synthesis of 5-acetyl-3-(1,4-dioxan-2-yl)-7-methylquinoline-2-carbonitrile:

To a solution of 5-bromo-3-(1,4-dioxan-2-yl)-7-methylquinoline-2-carbonitrile (1 g, 3 mmol) in dioxane (15 mL) was added tributyl(1-ethoxyvinyl)stannane (2.17 g, 6 mmol), Pd(dppf)Cl₂ (110 mg, 150 μmol). The mixture was evacuated and backfilled with N₂ for 3 times, and then it was stirred at 90 °C for 16 h under N₂ atmosphere. After cooling to room temperature, HCl (2.99 mL, 1 M) was added. The mixture was stirred at room temperature for 0.5 h. The reaction mixture was added 10 % KF aqueous solution (100 mL), stirred at room temperature for 2 h. The mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% EtOAc in hexanes) to give the title compound (560 mg, 63%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.22 (s, 1H), 8.35 (d, *J* = 1.6 Hz, 1H), 8.13 (s, 1H), 5.04 - 4.99 (m, 1H), 4.08 - 4.02 (m, 2H), 3.95 - 3.82 (m, 2H), 3.73 - 3.67 (m, 1H), 3.46 - 3.39 (m, 1H), 2.77 (s, 3H), 2.62 (s, 3H). MS: *m/z* 297.1 (M+H⁺).

Step 8 – Synthesis of (*S*)-5-acetyl-3-(1,4-dioxan-2-yl)-7-methylquinoline-2-carbonitrile and (*R*)-5-acetyl-3-(1,4-dioxan-2-yl)-7-methylquinoline-2-carbonitrile:

5-acetyl-3-(1,4-dioxan-2-yl)-7-methylquinoline-2-carbonitrile (560 mg, 1.89 mmol) was separated by using chiral SFC (Daicel ChiralPak IG (250 mm * 30 mm, 10 μm); Supercritical CO₂/MeOH+0.1% NH₃•H₂O = 60/40; 80 mL/min) to afford (*S*)-5-acetyl-3-(1,4-dioxan-2-yl)-7-methylquinoline-2-carbonitrile (125 mg, first peak) and (*R*)-5-acetyl-3-(1,4-dioxan-2-yl)-7-methylquinoline-2-carbonitrile (123 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. **First peak:** ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.22 (s, 1H), 8.35 (s, 1H), 8.13 (s, 1H), 5.04 - 4.99 (m, 1H), 4.07 - 3.99 (m, 2H), 3.93 - 3.81 (m, 2H), 3.72 - 3.64 (m, 1H), 3.45 - 3.39 (m, 1H), 2.77 (s, 3H), 2.62 (s, 3H). MS: *m/z* 297.1 (M+H⁺). **Second peak:** ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.22 (s, 1H), 8.35 (s, 1H), 8.13 (s, 1H), 5.09 - 4.94 (m, 1H), 4.08 - 3.99 (m, 2H), 3.93 - 3.80 (m, 2H), 3.72 - 3.65 (m, 1H), 3.45 - 3.38 (m, 1H), 2.77 (s, 3H), 2.62 (s, 3H). MS: *m/z* 297.1 (M+H⁺).

Step 9 – Synthesis of 3-((*R*)-1,4-dioxan-2-yl)-5-(1-hydroxyethyl)-7-methylquinoline-2-carbonitrile:

To a solution of (*R*)-5-acetyl-3-(1,4-dioxan-2-yl)-7-methylquinoline-2-carbonitrile (123 mg, 415 μmol) in DCM (2 mL) was added NaBH₄ (31 mg, 830 μmol) at room temperature for 1 h. The mixture was quenched with aq. sat. NH₄Cl (10 mL), extracted with DCM (20 mL x 3). The

combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to remove DCM and give the title compound (120 mg, 97%) as a yellow solid that required no further purification. MS: m/z 299.1 (M+H⁺).

Step 10 – Synthesis of 5-(1-bromoethyl)-3-((R)-1,4-dioxan-2-yl)-7-methylquinoline-2-carbonitrile:

To a solution of 3-((R)-1,4-dioxan-2-yl)-5-(1-hydroxyethyl)-7-methylquinoline-2-carbonitrile (120 mg, 402 μmol) in DCM (2 mL) was added PPh₃ (317 mg, 1.21 mmol) and CBr₄ (400 mg, 1.21 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was used for the next step directly without further purification. MS: m/z 361.1 (M+H⁺).

Step 11 – Synthesis of 5-chloro-2-(1-(2-cyano-3-((R)-1,4-dioxan-2-yl)-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide:

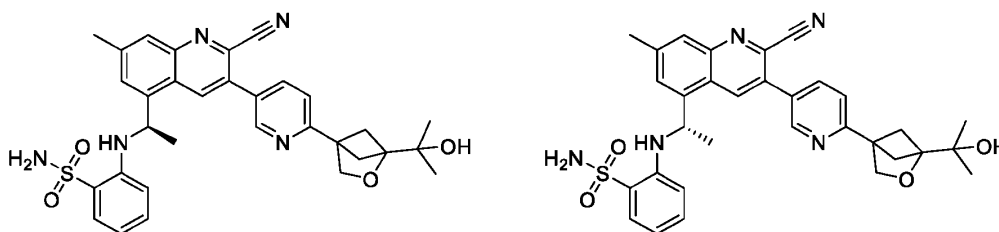
To a solution of 5-(1-bromoethyl)-3-((R)-1,4-dioxan-2-yl)-7-methylquinoline-2-carbonitrile (above mentioned reaction solution, in DCM) was added DMF (2 mL), followed by 5-chloro-2-hydroxy-benzenesulfonamide (161 mg, 775 μmol) and K₂CO₃ (161 mg, 1.16 mmol). The mixture was stirred at room temperature for 16 h under N₂ atmosphere. The reaction was quenched with water (15 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in hexanes) to give the title compound (100 mg, 55%) as a white solid. MS: m/z 488.1 (M+H⁺).

Step 12 – Synthesis of 5-chloro-2-((R)-1-(2-cyano-3-((R)-1,4-dioxan-2-yl)-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide and 5-chloro-2-((S)-1-(2-cyano-3-((R)-1,4-dioxan-2-yl)-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide:

5-chloro-2-(1-(2-cyano-3-((R)-1,4-dioxan-2-yl)-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide (100 mg, 205 μmol) was separated by using chiral SFC (DAICEL CHIRALCEL OD (250 mm * 30 mm, 10 μm); Supercritical CO₂/EtOH+0.1% NH₃•H₂O = 60/40; 80 mL/min) to afford 5-chloro-2-((R)-1-(2-cyano-3-((R)-1,4-dioxan-2-yl)-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide (14 mg, first peak) and 5-chloro-2-((S)-1-(2-cyano-3-((R)-1,4-dioxan-2-yl)-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide (21 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. **First peak**

(Compound 526): ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.92 (s, 1H), 7.93 (s, 1H), 7.87 (s, 1H), 7.72 (d, $J = 2.8$ Hz, 1H), 7.49 - 7.44 (m, 1H), 7.41 (s, 2H), 7.06 (d, $J = 9.2$ Hz, 1H), 6.48 - 6.40 (m, 1H), 5.05 - 4.99 (m, 1H), 4.03 - 3.98 (m, 2H), 3.94 - 3.80 (m, 2H), 3.79 - 3.66 (m, 2H), 2.49 (s, 3H), 1.76 (d, $J = 6.4$ Hz, 3H). MS: m/z 488.2 ($\text{M}+\text{H}^+$). **Second peak** (Compound 525): ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.89 (s, 1H), 7.91 (s, 1H), 7.87 (s, 1H), 7.73 (d, $J = 2.8$ Hz, 1H), 7.49 - 7.44 (m, 1H), 7.41 (s, 2H), 7.07 (d, $J = 9.2$ Hz, 1H), 6.57 - 6.50 (m, 1H), 5.05 - 4.99 (m, 1H), 4.03 - 3.98 (m, 2H), 3.91 - 3.81 (m, 2H), 3.78 - 3.69 (m, 2H), 2.48 (s, 3H), 1.74 (d, $J = 6.4$ Hz, 3H). MS: m/z 488.2 ($\text{M}+\text{H}^+$).

Example 76: Synthesis of (*R*)-2-((1-(2-cyano-3-(6-(1-(2-hydroxypropan-2-yl)-2-oxabicyclo[2.1.1]hexan-4-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (Compound 538) & (*S*)-2-((1-(2-cyano-3-(6-(1-(2-hydroxypropan-2-yl)-2-oxabicyclo[2.1.1]hexan-4-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (Compound 664)



Step 1 - Synthesis of 3-(benzyloxy)-5-(1-hydroxyethyl)-7-methylquinoline-2-carbonitrile:

To a solution of 5-acetyl-3-(benzyloxy)-7-methylquinoline-2-carbonitrile (5 g, 15.81 mmol) in DCM (50 mL) was added NaBH_4 (1.7 g, 47.42 mmol) at 0°C under N_2 atmosphere, MeOH (10 mL) was added until the reaction was completely clear. The resulting reaction was kept stirring at 0°C for 0.5 h. The reaction was quenched with sat. aq. NH_4Cl (80 mL) at 0°C and extracted with DCM (80 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 5% MeOH in DCM) to give the title compound (2.6 g, 51%) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.23 (s, 1H), 7.71 (s, 1H), 7.68

(s, 1H), 7.59 - 7.54 (m, 2H), 7.49 - 7.41 (m, 2H), 7.40 - 7.31 (m, 1H), 5.53 - 5.39 (m, 3H), 2.51 (s, 3H), 1.40 (d, $J = 6.4$ Hz, 3H). MS: m/z 318.9 ($M+H^+$).

Step 2 - Synthesis of 3-(benzyloxy)-5-(1-bromoethyl)-7-methylquinoline-2-carbonitrile:

5 To a solution of 3-(benzyloxy)-5-(1-hydroxyethyl)-7-methylquinoline-2-carbonitrile (8.48 g, 26.24 mmol) in DCM (80 mL) was added PBr_3 (9.37 g, 34.63 mmol) at 0 °C, and then mixture was stirred at 0 °C for 0.5 h. The reaction was quenched with sat. aq. $NaHCO_3$ (20 mL) and extracted with DCM (80 mL x 3). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated in vacuo to give the title compound (8.5 g, crude) as a white solid that required
10 no further purification. MS: m/z 381.1 ($M+H^+$).

Step 3 - Synthesis of 2-((1-(3-(benzyloxy)-2-cyano-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide:

To a solution of 3-(benzyloxy)-5-(1-bromoethyl)-7-methylquinoline-2-carbonitrile (8.5 g, 22.29 mmol) in dioxane (100 mL) was added 2-aminobenzenesulfonamide (23.03 g, 133.77
15 mmol). The mixture was heated to 90 °C and stirred for 16 h. After cooling to room temperature, the reaction was concentrated in vacuo to get crude residue. The crude product was dissolved in MeOH (100 mL) and stirred at room temperature for 30 min. The suspension was filtered and the filter cake was dried in vacuo to give the title compound (7.2 g, 68%) as a yellow solid. 1H NMR (400 MHz, $DMSO-d_6$) δ 8.40 (s, 1H), 7.74 - 7.68 (m, 2H), 7.67 - 7.64 (m, 1H), 7.62 (s, 2H), 7.60 -
20 7.55 (m, 2H), 7.48 - 7.42 (m, 2H), 7.40 - 7.34 (m, 1H), 7.14 - 7.10 (m, 1H), 6.68 - 6.61 (m, 1H), 6.44 (d, $J = 5.6$ Hz, 1H), 6.34 (d, $J = 8.4$ Hz, 1H), 5.63 - 5.39 (m, 3H), 2.40 (s, 3H), 1.53 (d, $J = 6.4$ Hz, 3H). MS: m/z 473.2 ($M+H^+$).

Step 4 - Synthesis of 2-((1-(2-cyano-3-hydroxy-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide:

25 To a solution of 2-((1-(3-(benzyloxy)-2-cyano-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (1 g, 2.12 mmol) in DCM (10 mL) was added BCl_3 (6.35 mL, 1 M) dropwise at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (20 mL), then the mixture was acidified with HCl (1 M) to adjust pH to 6, extracted with DCM (30 mL x 3). The combined organic layers were washed with brine (40 mL),

dried over Na₂SO₄, filtered and concentrated in vacuo to give the title compound (809 mg, crude) as a white solid that required no further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.66 (s, 1H), 8.09 (s, 1H), 7.71 - 7.63 (m, 2H), 7.61 (d, *J* = 1.2 Hz, 1H), 7.58 (s, 2H), 7.19 - 7.12 (m, 1H), 6.68 - 6.61 (m, 1H), 6.38 (d, *J* = 5.6 Hz, 1H), 6.34 (d, *J* = 8.4 Hz, 1H), 5.26 - 5.15 (m, 1H), 2.38 (s, 3H), 1.60 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 383.1 (M+H⁺).

Step 5 - Synthesis of 2-cyano-7-methyl-5-(1-((2-sulfamoylphenyl)amino)ethyl)quinolin-3-yl trifluoromethanesulfonate:

To a mixture of 2-cyano-7-methyl-5-(1-((2-sulfamoylphenyl)amino)ethyl)quinolin-3-yl trifluoromethanesulfonate (2.00 g, 5.23 mmol) and pyridine (2.11 mL, 26.15 mmol) in DCM (25 mL) was added Tf₂O (1.73 mL, 10.46 mmol) at 0 °C, the resulting mixture was stirred at room temperature for 16 h. The reaction was diluted with H₂O (30 mL), extracted with DCM (30 mL × 3), the combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude residue which was purified by silica gel chromatography (solvent gradient: 0~10% MeOH in DCM) to give the title compound (1.59 g, 59%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.38 (s, 1H), 8.02 - 7.86 (m, 2H), 7.71 - 7.57 (m, 3H), 7.17 - 7.08 (m, 1H), 6.69-6.62 (m, 1H), 6.47 - 6.33 (m, 2H), 5.66-5.53 (m, 1H), 1.58 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 515.0 (M+H⁺).

Step 6 - Synthesis of 2-((1-(2-cyano-7-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide:

To a solution of 2-((1-(2-cyano-7-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide (761 mg, 1.48 mmol) in dry dioxane (9 mL) was added dry B₂Pin₂ (1.13 g, 4.44 mmol), dry KOAc (0.43 g, 4.44 mmol) and Pd(dppf)Cl₂ (54.11 mg, 73.96 μmol). The mixture was evacuated and purged with N₂ for 3 times, then the mixture was stirred at 100 °C for 1 h under N₂ atmosphere. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% Methanol in DCM) to give the title compound (345 mg, 43%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.05 (s, 1H), 7.82 (s, 1H), 7.76 (s, 1H), 7.67 - 7.62 (m, 1H), 7.57 (s, 2H), 7.18 - 7.09 (m, 1H), 6.68 - 6.59 (m, 1H), 6.43 - 6.36 (m, 2H), 5.58 - 5.41 (m, 1H), 2.47 (s, 3H), 1.61 (d, *J* = 6.4 Hz, 3H), 1.38 (s, 12H). MS: *m/z* 493.2 (M+H⁺).

Step 7 - Synthesis of 2-((1-(2-cyano-3-(6-(1-(2-hydroxypropan-2-yl)-2-oxabicyclo[2.1.1]hexan-4-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide:

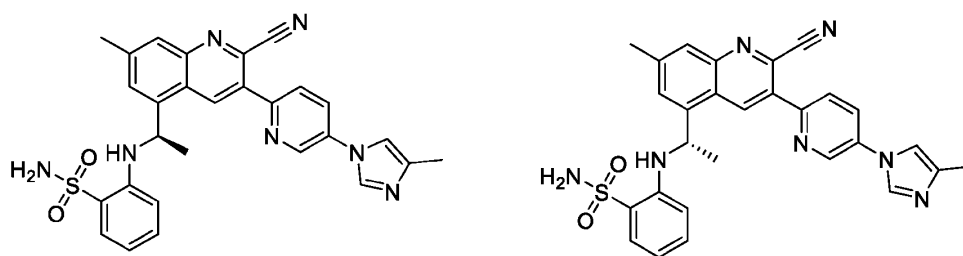
To a solution of 2-((1-(2-cyano-3-(6-(1-(2-hydroxypropan-2-yl)-2-oxabicyclo[2.1.1]hexan-4-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (100 mg, 203.09 μmol) in dioxane (2 mL) and H₂O (0.2 mL) was added 2-(4-(5-bromopyridin-2-yl)-2-oxabicyclo[2.1.1]hexan-1-yl)propan-2-ol (60 mg, 203.09 μmol), Pd₂(dba)₃ (9 mg, 10.15 μmol), CsF (123 mg, 812.35 μmol) and XPhos (19 mg, 40.62 μmol). The mixture was evacuated and backfilled with N₂ for 3 times, then the mixture was stirred at 100 °C for 2 h under N₂ atmosphere. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% MeOH in DCM) to give the title compound (66 mg, 55%) as a yellow solid. MS: m/z 584.3 (M+H⁺).

Step 8 - Synthesis of (R)-2-((1-(2-cyano-3-(6-(1-(2-hydroxypropan-2-yl)-2-oxabicyclo[2.1.1]hexan-4-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide & (S)-2-((1-(2-cyano-3-(6-(1-(2-hydroxypropan-2-yl)-2-oxabicyclo[2.1.1]hexan-4-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide:

2-((1-(2-cyano-3-(6-(1-(2-hydroxypropan-2-yl)-2-oxabicyclo[2.1.1]hexan-4-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (66 mg, 113 μmol) was separated by using chiral SFC (DAICEL CHIRALPAK IC (250mm*30mm,10 μm); Supercritical CO₂ / EtOH + 0.1% NH₃•H₂O = 55/45; 80 mL/min) to afford (R)-2-((1-(2-cyano-3-(6-(1-(2-hydroxypropan-2-yl)-2-oxabicyclo[2.1.1]hexan-4-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (19.47 mg, first peak) and (S)-2-((1-(2-cyano-3-(6-(1-(2-hydroxypropan-2-yl)-2-oxabicyclo[2.1.1]hexan-4-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (20.56 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. **First Peak** (Compound 538): ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.10 (s, 1H), 8.95 (d, *J* = 2.0 Hz, 1H), 8.30 - 8.24 (m, 1H), 7.88 (s, 1H), 7.79 (s, 1H), 7.67 - 7.63 (m, 2H), 7.62 (s, 2H), 7.16 - 7.09 (m, 1H), 6.68 - 6.58 (m, 1H), 6.45 - 6.41

(m, 2H), 5.71 - 5.60 (m, 1H), 4.51 (s, 1H), 4.04 (s, 2H), 2.49 (s, 3H), 2.23 (d, $J = 4.0$ Hz, 2H), 1.85 (d, $J = 4.0$ Hz, 2H), 1.60 (d, $J = 6.4$ Hz, 3H), 1.18 (s, 6H). MS: m/z 584.2 ($M+H^+$). **Second peak** (Compound 664): 1H NMR (400 MHz, DMSO- d_6) δ 9.10 (s, 1H), 8.95 (d, $J = 2.0$ Hz, 1H), 8.31 - 8.23 (m, 1H), 7.89 (s, 1H), 7.79 (s, 1H), 7.67 - 7.63 (m, 2H), 7.62 (s, 2H), 7.17 - 7.08 (m, 1H), 6.67 - 6.59 (m, 1H), 6.45 - 6.41 (m, 2H), 5.71 - 5.60 (m, 1H), 4.51 (s, 1H), 4.04 (s, 2H), 2.49 (s, 3H), 2.23 (d, $J = 4.4$ Hz, 2H), 1.85 (d, $J = 4.4$ Hz, 2H), 1.60 (d, $J = 6.4$ Hz, 3H), 1.18 (s, 6H). MS: m/z 584.2 ($M+H^+$).

Example 77: Synthesis of (*R*)-2-((1-(2-cyano-7-methyl-3-(5-(4-methyl-1*H*-imidazol-1-yl)pyridin-2-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide (Compound 509) & (*S*)-2-((1-(2-cyano-7-methyl-3-(5-(4-methyl-1*H*-imidazol-1-yl)pyridin-2-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide (Compound 657)



Step 1 - Synthesis of 2-chloro-5-(4-methyl-1*H*-imidazol-1-yl)pyridine:

To a solution of 2-chloro-5-iodopyridine (7 g, 29.23 mmol) in DMSO (70 mL) was added 4-methyl-1*H*-imidazole (2.88 g, 35.08 mmol), Cu₂O (209 mg, 1.46 mmol), 4,7-dimethoxy-1,10-phenanthroline (1.05 g, 4.39 mmol), Cs₂CO₃ (13.34 g, 40.93 mmol) and ethylene glycol (4.89 mL, 87.70 mmol). The mixture was evacuated and backfilled with N₂ for 3 times, then the mixture was stirred at 110 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction was quenched with H₂O (80 mL), extracted with EtOAc (80 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in hexanes) to give the title compound (3.1 g, 54%) as a yellow solid. MS: m/z 194.1 ($M+H^+$).

Step 2 - Synthesis of 2-((1-(2-cyano-7-methyl-3-(5-(4-methyl-1*H*-imidazol-1-yl)pyridin-2-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide:

To a solution of 2-((1-(2-cyano-7-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide (430 mg, 872 μmol) in dioxane (5 mL) and H_2O (0.5 mL) was added 2-chloro-5-(4-methyl-1*H*-imidazol-1-yl)pyridine (168 mg, 872 μmol), CsF (530 mg, 3.49 mmol), $\text{Pd}_2(\text{dba})_3$ (39 mg, 43 μmol) and XPhos (83 mg, 174 μmol).

The mixture was evacuated and backfilled with N_2 for 3 times, then the mixture was stirred at 100 $^\circ\text{C}$ for 2 h under N_2 atmosphere. After cooling to room temperature, the mixture was concentrated in vacuo. The residue was purified by silica gel chromatography (solvent gradient: 0 - 10% MeOH in DCM) to give the title compound (185 mg, 40%) as a yellow solid. MS: m/z 524.2 ($\text{M}+\text{H}^+$).

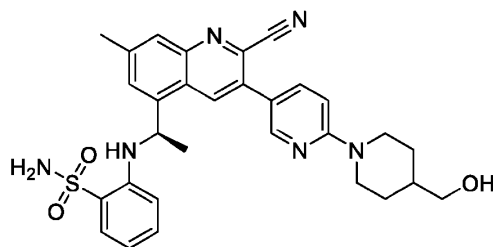
Step 3 - Synthesis of (*R*)-2-((1-(2-cyano-7-methyl-3-(5-(4-methyl-1*H*-imidazol-1-yl)pyridin-2-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide & (*S*)-2-((1-(2-cyano-7-methyl-3-(5-(4-methyl-1*H*-imidazol-1-yl)pyridin-2-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide:

2-((1-(2-cyano-7-methyl-3-(5-(4-methyl-1*H*-imidazol-1-yl)pyridin-2-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide (100 mg, 190 μmol) was separated by using chiral SFC (DAICEL CHIRALCEL OD(250mm*30mm,10 μm); Supercritical CO_2 / EtOH + 0.1% $\text{NH}_3\cdot\text{H}_2\text{O}$ = 60/40; 80 mL/min to afford (*R*)-2-((1-(2-cyano-7-methyl-3-(5-(4-methyl-1*H*-imidazol-1-yl)pyridin-2-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide (27.45 mg, first peak) and (*S*)-2-((1-(2-cyano-7-methyl-3-(5-(4-methyl-1*H*-imidazol-1-yl)pyridin-2-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide (26.18 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. **First Peak** (Compound 509): ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.26 (s, 1H), 9.20 (d, $J = 2.4$ Hz, 1H), 8.43 (d, $J = 1.2$ Hz, 1H), 8.36 (d, $J = 2.4$ Hz, 1H), 8.35 - 8.32 (m, 1H), 7.89 (s, 1H), 7.80 (s, 1H), 7.71 (s, 1H), 7.67 - 7.64 (m, 1H), 7.63 (s, 2H), 7.17 - 7.10 (m, 1H), 6.67 - 6.61 (m, 1H), 6.50 - 6.38 (m, 2H), 5.77 - 5.66 (m, 1H), 2.49 (s, 3H), 2.22 (s, 3H), 1.64 (d, $J = 6.4$ Hz, 3H). MS: m/z 524.4 ($\text{M}+\text{H}^+$). **Second peak** (Compound 657): ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.26 (s, 1H), 9.20 (d, $J = 2.4$ Hz, 1H), 8.42 (d, $J = 1.2$ Hz, 1H), 8.36 (d, $J = 2.4$ Hz, 1H), 8.35 - 8.31 (m, 1H), 7.89 (s, 1H), 7.80 (d, $J = 1.2$ Hz, 1H), 7.71 (s, 1H), 7.67 - 7.63 (m, 1H), 7.62 (s, 2H), 7.18 - 7.07 (m, 1H), 6.66 - 6.60 (m, 1H), 6.50

- 6.37 (m, 2H), 5.80 - 5.63 (m, 1H), 2.49 (s, 3H), 2.21 (s, 3H), 1.63 (d, $J = 6.4$ Hz, 3H). MS: m/z 524.4 ($M+H^+$).

Example 78: Synthesis of (*R*)-2-((1-(2-cyano-3-(6-(4-(hydroxymethyl)piperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (Compound 517)

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**Step 1 - Synthesis of (*R*)-2-((1-(2-cyano-3-(6-(4-(hydroxymethyl)piperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)-*N*,
N-bis(3,4-dimethylbenzyl)benzenesulfonamide:**

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A mixture of (*R*)-2-((1-(3-(6-chloropyridin-3-yl)-2-cyano-7-methylquinolin-5-yl)ethyl)amino)-*N,N*-bis(2,4-dimethoxybenzyl)benzenesulfonamide (0.1 g, 128.48 μ mol), 4-piperidylmethanol (74 mg, 642 μ mol) and DBU (195 mg, 1.28 mmol, 194 μ L) in NMP (1 mL) was stirred at 140 °C for 2 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was quenched with sat. aq. NH_4Cl (5 mL), extracted with EtOAc (20 mL x 3). The combined organic phases were washed with brine (10 mL x 2), dried with anhydrous Na_2SO_4 , filtered and concentrated in vacuum. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to give the title compound (90 mg, 82%) as a yellow solid. MS: m/z 857.3 ($M+H^+$).

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Step 2 - Synthesis of (*R*)-2-((1-(2-cyano-3-(6-(4-(hydroxymethyl)piperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide:

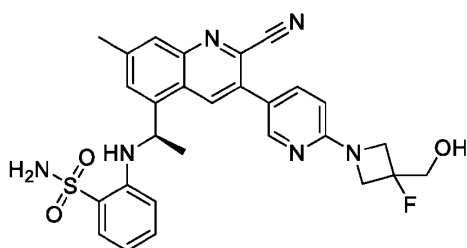
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To a mixture of (*R*)-2-((1-(2-cyano-3-(6-(4-(hydroxymethyl)piperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)-*N,N*-bis(3,4-dimethylbenzyl)benzenesulfonamide (90 mg, 105 μ mol) in DCM (3 mL) was added TFA (1.54 g, 13.46 mmol, 1 mL), and then the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with DCM (15 mL), adjusted pH to 8 with saturated $NaHCO_3$ solution, and extracted DCM (20 mL x 3). The combined organic

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phase was washed with brine (10 mL x 2), dried with anhydrous Na₂SO₄, filter and concentrated in vacuo. The residue was purified by reverse phase chromatography (acetonitrile 35% - 65% / 0.225% formic acid in water) to give the title compound (34.59 mg, 59%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.93 (s, 1H), 8.51 (d, *J* = 2.4 Hz, 1H), 8.00-7.94 (m, 1H), 7.82 (s, 1H), 7.74 (s, 1H), 7.66-7.62 (m, 1H), 7.59 (s, 2H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.03 (d, *J* = 9.2 Hz, 1H), 6.63 (t, *J* = 7.6 Hz, 1H), 6.46 - 6.40 (m, 2H), 5.68-5.61 (m, 1H), 4.52 - 4.46 (m, 2H), 4.45-4.42 (m, 1H), 3.30 - 3.27 (m, 2H), 2.94-2.86 (m, 2H), 2.46 (s, 3H), 1.80-1.73 (m, 2H), 1.72 - 1.65 (m, 1H), 1.60 (d, *J* = 6.4 Hz, 3H), 1.21 - 1.10 (m, 2H). MS: *m/z* 557.2 (M+H⁺).

Example 79: Synthesis of (*R*)-2-((1-(2-cyano-3-(6-(3-fluoro-3-(hydroxymethyl)azetidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (Compound 512)



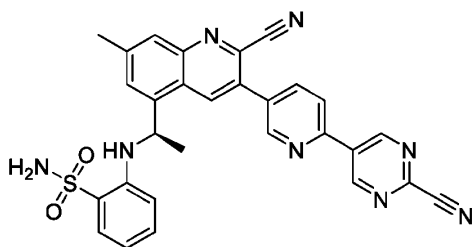
Step 1 - Synthesis of (*R*)-2-((1-(2-cyano-3-(6-(3-fluoro-3-(hydroxymethyl)azetidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)-*N,N*-bis(3,4-dimethylbenzyl)benzenesulfonamide:

A mixture of (*R*)-2-((1-(3-(6-chloropyridin-3-yl)-2-cyano-7-methylquinolin-5-yl)ethyl)amino)-*N,N*-bis(2,4-dimethoxybenzyl)benzenesulfonamide (150 mg, 193 μmol), (3-fluoroazetidin-3-yl)methanol hydrochloride (136 mg, 964 μmol) and DIPEA (498 mg, 3.85 mmol, 671 μL) in NMP (1 mL) was stirred at 140 °C for 16 h. After cooling to room temperature, the reaction mixture was quenched by H₂O (5 mL), extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL x 2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to give the title compound (100 mg, 61%) as a yellow solid. MS: *m/z* 847.3 (M+H⁺).

Step 2 - Synthesis of (*R*)-2-((1-(2-cyano-3-(6-(3-fluoro-3-(hydroxymethyl)azetidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide:

To a solution of (*R*)-2-((1-(2-cyano-3-(6-(3-fluoro-3-(hydroxymethyl)azetidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)-*N,N*-bis(3,4-dimethylbenzyl)benzenesulfonamide (100 mg, 118 μ mol) in DCM (3 mL) was added TFA (1.54 g, 13.5 mmol, 1 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with H₂O (15 mL), adjusted to pH 8 with sat. aq. NaHCO₃ and extracted DCM (20 mL x 3). The combined organic layers were washed with brine (10 mL x 2), dried with anhydrous Na₂SO₄, filter and concentrated in vacuum. The residue was purified by reverse phase chromatography (acetonitrile 35% - 65% / 0.225% formic acid in water) to afford the title compound (27.81 mg, 43%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.93 (s, 1H), 8.52 (d, *J* = 2.4 Hz, 1H), 8.05 - 8.00 (m, 1H), 7.84 (s, 1H), 7.75 (s, 1H), 7.67 - 7.62 (m, 1H), 7.59 (s, 2H), 7.17 - 7.10 (m, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.66 - 6.59 (m, 1H), 6.47 - 6.39 (m, 2H), 5.68 - 5.59 (m, 1H), 5.39 - 5.32 (m, 1H), 4.28 - 4.16 (m, 2H), 4.13 - 4.02 (m, 2H), 3.81 - 3.69 (m, 2H), 2.47 (s, 3H), 1.60 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 547.2 (M+H⁺).

Example 80: Synthesis of (*R*)-2-((1-(2-cyano-3-(6-(2-cyanopyrimidin-5-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (Compound 309)



Step 1 - Synthesis of (*R*)-2-((1-(2-cyano-7-methyl-3-(6-(trimethylstannyl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)-*N,N*-bis(2,4-dimethoxybenzyl)benzenesulfonamide:

To a solution of (*R*)-2-((1-(3-(6-chloropyridin-3-yl)-2-cyano-7-methylquinolin-5-yl)ethyl)amino)-*N,N*-bis(2,4-dimethoxybenzyl)benzenesulfonamide (200 mg, 0.26 mmol) in dioxane (6 mL) was added (SnMe₃)₂ (126 mg, 0.38 mmol) and Pd(PPh₃)₄ (30 mg, 26 μ mol).

The mixture was evacuated and backfilled with N₂ for 3 times, and then it was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the mixture was filtered and the filter cake was washed with DCM (5 mL x 2). The combined organic layers were concentrated in vacuo to give the title compound (230 mg, crude) as yellow oil that required no further purification. MS: m/z 908.4 (M+H⁺).

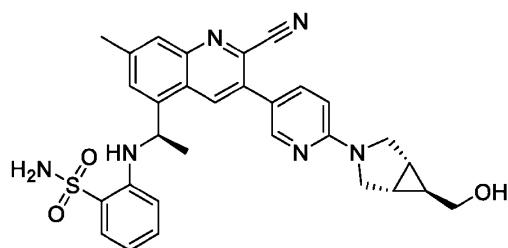
Step 2 - Synthesis of (R)-2-((1-(2-cyano-3-(6-(2-cyanopyrimidin-5-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)-N,N-bis(2,4-dimethoxybenzyl)benzenesulfonamide:

To a solution of (R)-2-((1-(2-cyano-7-methyl-3-(6-(trimethylstannyl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)-N,N-bis(2,4-dimethoxybenzyl)benzenesulfonamide (230 mg, 0.25 mmol) in DMF (5 mL) was added 5-bromopyrimidine-2-carbonitrile (93 mg, 0.51 mmol), CuI (24.16 mg, 0.13 mmol) and Pd(PPh₃)₄ (29 mg, 25 μmol). The mixture was evacuated and backfilled with N₂ for 3 times, and then it was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the mixture was filtered and the filter cake was washed with DCM (5 mL x 2). The combined organic layers were concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 100% EtOAc in petroleum ether) to give the title compound (150 mg, 70%) as a yellow solid. MS: m/z 847.4 (M+H⁺).

Step 3 - Synthesis of (R)-2-((1-(2-cyano-3-(6-(2-cyanopyrimidin-5-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide:

To a solution of (R)-2-((1-(2-cyano-3-(6-(2-cyanopyrimidin-5-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)-N,N-bis(2,4-dimethoxybenzyl)benzenesulfonamide (150 mg, 0.18 mmol) in DCM (3 mL) was added TFA (1 mL) at 0 °C. The mixture was stirred at room temperature for 1 h. The mixture was concentrated in vacuo and the residue was purified by reverse phase chromatography (acetonitrile 50% - 80% / 0.225% formic acid in water) to give the title compound (51 mg, 52%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.78 (s, 2H), 9.26 (s, 1H), 9.19 (s, 1H), 8.59 - 8.52 (m, 2H), 7.91 (s, 1H), 7.81 (s, 1H), 7.67 - 7.64 (m, 1H), 7.61 (s, 2H), 7.17 - 7.10 (m, 1H), 6.66 - 6.61 (m, 1H), 6.49 - 6.41 (m, 2H), 5.72 - 5.67 (m, 1H), 2.49 (s, 3H), 1.63 (d, *J* = 6.4 Hz, 3H). MS: m/z 547.1 (M+H⁺).

Example 81: Synthesis of 2-(((R)-1-(2-cyano-3-(6-((1*R*,5*S*,6*R*)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-3-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide (Compound 628)



Step 1 - Synthesis of 2-(((R)-1-(2-cyano-3-(6-((1R,5S,6R)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-3-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)-N,N-bis(3,4-dimethylbenzyl)benzenesulfonamide:

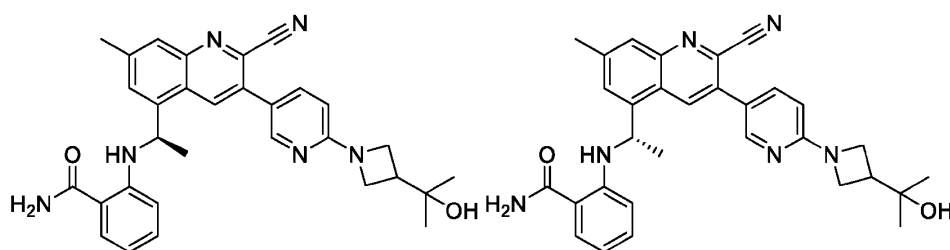
To a solution of (*R*)-2-((1-(3-(6-chloropyridin-3-yl)-2-cyano-7-methylquinolin-5-yl)ethyl)amino)-*N,N*-bis(2,4-dimethoxybenzyl)benzenesulfonamide (100 mg, 128 μ mol), ((1*R*,5*S*,6*r*)-3-azabicyclo[3.1.0]hexan-6-yl)methanol (44 mg, 385 μ mol) in NMP (1 mL) was added DIPEA (332 mg, 2.57 mmol, 448 μ L). The reaction mixture was stirred at 140 $^{\circ}$ C for 16 h. After cooling to room temperature, the reaction mixture was quenched with water (10 mL), extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (5 mL x 3), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0 - 70% EtOAc in petroleum ether) to give the title compound (105 mg, 95%) as yellow oil. MS: m/z 855.5 ($\text{M}+\text{H}^+$).

Step 2 - Synthesis of 2-(((R)-1-(2-cyano-3-(6-((1R,5S,6R)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-3-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide:

To a solution of 2-(((*R*)-1-(2-cyano-3-(6-((1*R*,5*S*,6*R*)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-3-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)-*N,N*-bis(3,4-dimethylbenzyl)benzenesulfonamide (105 mg, 122 μ mol) in DCM (3 mL) was added TFA (1.54 g, 13.46 mmol, 1 mL) at 0 $^{\circ}$ C. Then the reaction mixture was stirred at room temperature for 1 h. After that, the reaction mixture was diluted with H_2O (2 mL), basified to pH = 8 with sat. aq. NaHCO_3 and extracted with DCM (10 mL x 2). The combined organic layers were washed with brine (5 mL x 2), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (acetonitrile 23% - 53% / 0.225% formic acid in water) to give the title compound (16 mg, 23%) as a yellow solid. ^1H NMR (400

MHz, DMSO-*d*₆) δ 8.89 (s, 1H), 8.47 (d, *J* = 2.4 Hz, 1H), 7.96 - 7.93 (m, 1H), 7.82 (s, 1H), 7.73 (s, 1H), 7.65 - 7.63 (m, 1H), 7.60 (s, 2H), 7.15 - 7.11 (m, 1H), 6.68 - 6.56 (m, 2H), 6.47 - 6.35 (m, 2H), 5.67 - 5.56 (m, 1H), 4.59 (s, 1H), 3.74 (d, *J* = 10.4 Hz, 2H), 3.51 - 3.44 (m, 4H), 2.46 (s, 3H), 1.64 (s, 2H), 1.59 (d, *J* = 6.4 Hz, 3H), 0.85 - 0.81 (m, 1H). MS: *m/z* 555.1 (M+H⁺).

5 **Example 82: Synthesis of (*R*)-2-((1-(2-cyano-3-(6-(3-(2-hydroxypropan-2-yl)azetidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzamide (Compound 595) & (*S*)-2-((1-(2-cyano-3-(6-(3-(2-hydroxypropan-2-yl)azetidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzamide (Compound 599)**



10

Step 1 - Synthesis of 2-((1-(3-(6-chloropyridin-3-yl)-2-cyano-7-methylquinolin-5-yl)ethyl)amino)benzamide:

To a solution of 5-(1-bromoethyl)-3-(6-chloro-3-pyridyl)-7-methyl-quinoline-2-carbonitrile (1 g, 2.59 mmol) in dioxane (10 mL) was added 2-aminobenzamide (423 mg, 3.10 mmol). The mixture was evacuated and backfilled with N₂ for 3 times, and then it was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 40% DCM in petroleum ether) to give the title compound (1.1 g, 96%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.10 (s, 1H), 8.91 - 8.82 (m, 2H), 8.38 - 8.34 (m, 1H), 7.99 - 7.91 (m, 1H), 7.88 (s, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.66 - 7.60 (m, 2H), 7.54 - 7.50 (m, 1H), 7.30 (s, 1H), 7.16 - 7.09 (m, 1H), 7.08 - 7.00 (m, 1H), 6.70 - 6.65 (m, 1H), 6.55 (s, 1H), 6.53 - 6.44 (m, 2H), 6.37 (d, *J* = 8.4 Hz, 1H), 5.59 - 5.51 (m, 1H), 2.51 (s, 3H), 1.57 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 442.2 (M+H⁺).

20

25 **Step 2 - Synthesis of 2-((1-(2-cyano-3-(6-(3-(2-hydroxypropan-2-yl)azetidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzamide:**

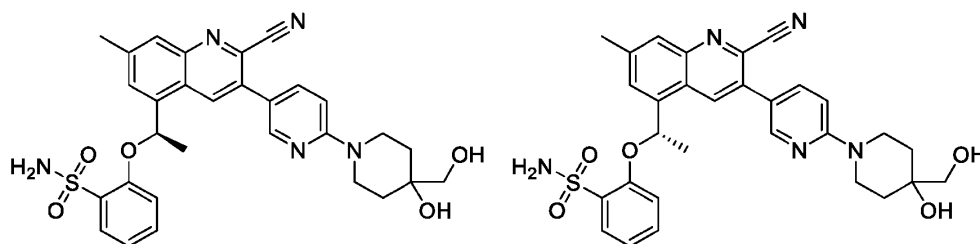
To a solution of 2-((1-(3-(6-chloropyridin-3-yl)-2-cyano-7-methylquinolin-5-yl)ethyl)amino)benzamide (100 mg, 226 μmol) in NMP (1 mL) was added 2-(azetidin-3-yl)propan-2-ol hydrochloride (137.25 mg, 905.16 μmol) and DIEA (197 μL , 1.13 mmol). The mixture was stirred at 140 $^{\circ}\text{C}$ for 2 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was quenched with H_2O (15 mL), extracted with EtOAc (20 mL x 3). The combined organic layer was washed with H_2O (20 mL x 3) and brine (20 mL), dried over Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by column chromatography (solvent gradient: 0 - 80% EtOAc in petroleum ether) to give the title compound (80 mg, 68%) as a yellow solid. MS: m/z 521.3 ($\text{M}+\text{H}^+$).

Step 3 - Synthesis of (*R*)-2-((1-(2-cyano-3-(6-(3-(2-hydroxypropan-2-yl)azetidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzamide & (*S*)-2-((1-(2-cyano-3-(6-(3-(2-hydroxypropan-2-yl)azetidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzamide:

2-((1-(2-cyano-3-(6-(3-(2-hydroxypropan-2-yl)azetidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzamide (120 mg, 230 μmol) was separated by using chiral SFC (DAICEL CHIRALPAK AD (250mm*30mm,10 μm); Supercritical CO_2 / EtOH+ 0.1% $\text{NH}_3\cdot\text{H}_2\text{O}$ = 45/55; 80 mL/min) to afford (*R*)-2-((1-(2-cyano-3-(6-(3-(2-hydroxypropan-2-yl)azetidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzamide (31.8 mg, first peak) and (*S*)-2-((1-(2-cyano-3-(6-(3-(2-hydroxypropan-2-yl)azetidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzamide (30.2 mg, second peak) both as yellow solid. Absolute configuration was arbitrarily assigned to each enantiomer. **First peak** (Compound 595): ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.87 (s, 1H), 8.82 (d, J = 6.4 Hz, 1H), 8.44 (d, J = 2.4 Hz, 1H), 7.98 - 7.87 (m, 2H), 7.81 (s, 1H), 7.65 - 7.61 (m, 1H), 7.59 - 7.57 (m, 1H), 7.32 - 7.20 (m, 1H), 7.09 - 7.02 (m, 1H), 6.57 - 6.46 (m, 2H), 6.39 (d, J = 8.0 Hz, 1H), 5.57 - 5.47 (m, 1H), 4.49 (s, 1H), 4.00 - 3.91 (m, 4H), 2.82 - 2.71 (m, 1H), 2.47 (s, 3H), 1.56 (d, J = 6.4 Hz, 3H), 1.09 (s, 6H). MS: m/z 521.3 ($\text{M}+\text{H}^+$). **Second peak** (Compound 599): ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.87 (s, 1H), 8.82 (d, J = 6.0 Hz, 1H), 8.44 (d, J = 2.4 Hz, 1H), 7.97 - 7.87 (m, 2H), 7.81 (s, 1H), 7.65 - 7.61 (m, 1H), 7.59 - 7.57 (m, 1H), 7.31 - 7.22 (m, 1H), 7.09 - 7.02 (m, 1H), 6.57 - 6.46 (m, 2H), 6.41 - 6.36 (m, 1H), 5.57 - 5.47 (m, 1H), 4.50 (s, 1H), 4.00 - 3.91 (m, 4H), 2.81 - 2.72 (m, 1H), 2.47 (s, 3H), 1.56 (d, J = 6.4 Hz, 3H), 1.09 (s, 6H). MS: m/z 521.3 ($\text{M}+\text{H}^+$).

Example 83: Synthesis of (*R*)-2-(1-(2-cyano-3-(6-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide (Compound 643) & (*S*)-2-(1-(2-cyano-3-(6-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide (Compound 639)

5



Step 1 – Synthesis of 2-(1-(3-(6-chloropyridin-3-yl)-2-cyano-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide:

To a solution of 5-(1-bromoethyl)-3-(6-chloropyridin-3-yl)-7-methylquinoline-2-carbonitrile (700 mg, 1.81 mmol) in DMF (8 mL) was added 2-hydroxybenzenesulfonamide (314 mg, 1.81 mmol) and K₂CO₃ (751 mg, 5.43 mmol). The mixture was stirred at room temperature for 2 h. The reaction was quenched with H₂O (15 mL), extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (15 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to give the title compound (867 mg, 99%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.14 (s, 1H), 8.88 (d, *J* = 2.4 Hz, 1H), 8.40 - 8.32 (m, 1H), 8.01 (s, 1H), 7.96 - 7.92 (m, 2H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.79 - 7.73 (m, 1H), 7.38 - 7.34 (m, 1H), 7.20 (s, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 7.01 - 6.97 (m, 1H), 6.60 - 6.51 (m, 1H), 1.77 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 479.1 (M+H⁺).

Step 2 – Synthesis of 2-(1-(2-cyano-3-(6-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide:

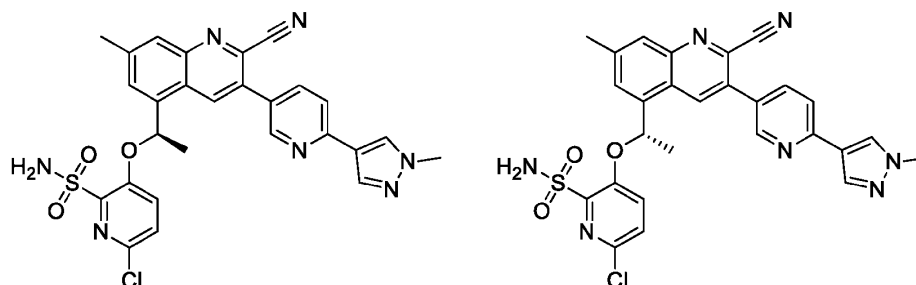
To a solution of 2-(1-(3-(6-chloropyridin-3-yl)-2-cyano-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide (200 mg, 418 μmol) in NMP (2 mL) was added DBU (252 μL, 1.67 mmol) and 4-(hydroxymethyl)piperidin-4-ol hydrochloride (210 mg, 1.25 mmol). The mixture was stirred at 140 °C for 2 h. After cooling to room temperature, the mixture was diluted with

EtOAc (30 mL), washed with H₂O (10 mL x 3) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude, which was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to give the title compound (155 mg, 65%) as a yellow solid. MS: m/z 574.2 (M+H⁺).

Step 3 – Synthesis of (*R*)-2-(1-(2-cyano-3-(6-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide & (*S*)-2-(1-(2-cyano-3-(6-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide:

2-(1-(2-cyano-3-(6-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide (155 mg, 270 μmol) was separated by using chiral SFC (DAICEL CHIRALPAK AD (250mm x 30mm,10um); Supercritical CO₂ / EtOH + 0.1% NH₃·H₂O = 50/50; 80 mL/min to afford (*R*)-2-(1-(2-cyano-3-(6-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide (46.49 mg, first peak) and (*S*)-2-(1-(2-cyano-3-(6-(4-hydroxy-4-(hydroxymethyl)piperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide (49.22 mg, second peak) both as yellow solid. Absolute configuration was arbitrarily assigned to each enantiomer. **First peak (Compound 643):** ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.95 (s, 1H), 8.51 (d, *J* = 2.4 Hz, 1H), 8.00 - 7.96 (m, 1H), 7.94 (d, *J* = 1.2 Hz, 1H), 7.85 (s, 1H), 7.78 - 7.74 (m, 1H), 7.40 - 7.33 (m, 1H), 7.19 (s, 2H), 7.06 - 7.02 (m, 2H), 7.01 - 6.97 (m, 1H), 6.65 - 6.55 (m, 1H), 4.62 (t, *J* = 5.6 Hz, 1H), 4.33 (s, 1H), 4.22 - 4.16 (m, 2H), 3.34 - 3.30 (m, 1H), 3.29 - 3.25 (m, 1H), 3.22 (d, *J* = 5.6 Hz, 2H), 2.48 (s, 3H), 1.75 (d, *J* = 6.4 Hz, 3H), 1.66 - 1.57 (m, 2H), 1.44 - 1.41 (m, 2H). MS: m/z 574.2 (M+H⁺). **Second peak (Compound 639):** ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.95 (s, 1H), 8.51 (d, *J* = 2.4 Hz, 1H), 8.00 - 7.96 (m, 1H), 7.94 (d, *J* = 1.2 Hz, 1H), 7.85 (s, 1H), 7.78 - 7.74 (m, 1H), 7.40 - 7.33 (m, 1H), 7.19 (s, 2H), 7.06 - 7.02 (m, 2H), 7.01 - 6.97 (m, 1H), 6.65 - 6.55 (m, 1H), 4.62 (t, *J* = 5.6 Hz, 1H), 4.33 (s, 1H), 4.22 - 4.16 (m, 2H), 3.34 - 3.30 (m, 1H), 3.29 - 3.25 (m, 1H), 3.22 (d, *J* = 5.6 Hz, 2H), 2.48 (s, 3H), 1.75 (d, *J* = 6.4 Hz, 3H), 1.67 - 1.56 (m, 2H), 1.44 - 1.41 (m, 2H). MS: m/z 574.2 (M+H⁺).

Example 84: Synthesis of (*R*)-6-chloro-3-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide (Compound 642) & (*S*)-6-chloro-3-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide (Compound 648)



Step 1 - Synthesis of 6-chloro-3-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide:

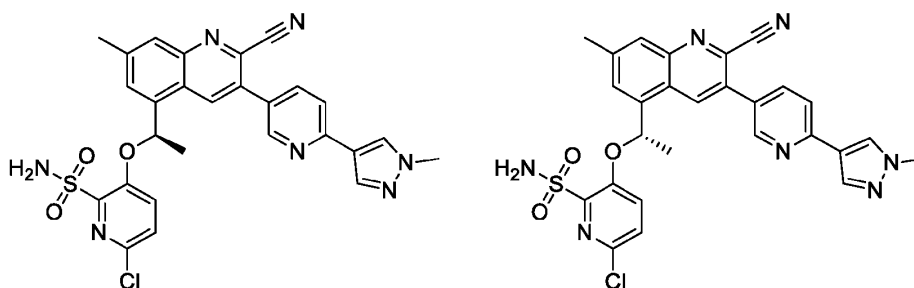
To a mixture of 5-(1-bromoethyl)-7-methyl-3-[6-(1-methylpyrazol-4-yl)-3-pyridyl]quinoline-2-carbonitrile (230 mg, 532 μmol), K_2CO_3 (220 mg, 1.6 mmol) in DMF (2 mL) was added 6-chloro-3-hydroxypyridine-2-sulfonamide (277 mg, 1.33 mmol). The reaction mixture was stirred at 80 $^\circ\text{C}$ for 2 h. After that, the mixture was concentrated, the residue was purified by silica gel chromatography (solvent gradient: 0 - 50% (25% ethyl alcohol in EtOAc) in hexanes) to give the title compound (160 mg, 54%) as a yellow solid. MS: m/z 560.1 ($\text{M}+\text{H}^+$).

Step 2 - Synthesis of (*R*)-6-chloro-3-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide & (*S*)-6-chloro-3-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide:

6-chloro-3-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide (100 mg, 179 μmol) was separated by using chiral SFC (DAICEL CHIRALCEL OD (250mm $\times$ 30mm, 10 μm); Supercritical CO_2 / EtOH + 0.1% $\text{NH}_3\cdot\text{H}_2\text{O}$ = 40/60; 150 mL/min) to afford (*R*)-6-chloro-3-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide (48.9 mg, first peak) and (*S*)-6-chloro-3-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide (54.6 mg, second peak) both as yellow solid. Absolute configuration was arbitrarily assigned to each enantiomer. **First Peak** (Compound642): ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.05 (s, 1H), 8.93 (d, J = 2.0 Hz, 1H), 8.42 (s, 1H), 8.27 - 8.22 (m, 1H), 8.13 (s, 1H), 7.99 (s, 1H), 7.94 (s, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.64 - 7.56 (m, 3H), 6.72 - 6.60 (m, 1H), 3.93 (s, 3H), 2.52 (s, 3H), 1.74 (d, J = 6.0 Hz, 3H). MS: m/z

560.1 (M+H⁺). **Second peak** (Compound 648): ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.05 (s, 1H), 8.93 (d, *J* = 2.0 Hz, 1H), 8.42 (s, 1H), 8.27 - 8.22 (m, 1H), 8.13 (s, 1H), 7.99 (s, 1H), 7.94 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.64 - 7.56 (m, 3H), 6.72 - 6.60 (m, 1H), 3.93 (s, 3H), 2.52 (s, 3H), 1.74 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 560.2 (M+H⁺).

Example 85: Synthesis of 5-chloro-2-((*R*)-1-(2-cyano-3-(5-((1*R*,5*S*,6*R*)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-3-yl)pyridin-2-yl)-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide (Compound 658) & 5-chloro-2-((*S*)-1-(2-cyano-3-(5-((1*R*,5*S*,6*S*)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-3-yl)pyridin-2-yl)-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide (Compound 619)



Step 1 - Synthesis of (1*R*,5*S*,6*r*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-azabicyclo[3.1.0]hexane:

To a solution of ((1*R*,5*S*,6*r*)-3-azabicyclo[3.1.0]hexan-6-yl)methanol (600 mg, 5.3 mmol) in DCM (10 mL) was added TBSCl (1.6 g, 10.6 mmol) and imidazole (1.08 g, 15.9 mmol). The mixture was stirred at room temperature for 16 h. The reaction was quenched with sat. aq. NaHCO₃ (20 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (40 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% MeOH in DCM) to give the title compound (1 g, 83%) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.50 - 3.46 (m, 2H), 3.17 (s, 1H), 2.84 - 2.80 (m, 2H), 2.68 - 2.64 (m, 2H), 1.24 (s, 2H), 0.96 - 0.89 (m, 1H), 0.85 (s, 9H), 0.02 (s, 6H).

Step 2 - Synthesis of (1*R*,5*S*,6*r*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(6-chloropyridin-3-yl)-3-azabicyclo[3.1.0]hexane:

To a solution of 2-chloro-5-iodopyridine (2 g, 8.35 mmol) in toluene (35 mL) was added (1*R*,5*S*,6*r*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-azabicyclo[3.1.0]hexane (2.09 g, 9.19 mmol), Pd₂(dba)₃ (764.8 mg, 0.84 mmol), Xantphos (966.6 mg, 1.67 mmol) and *t*-BuONa (2.41 g, 25.1 mmol). The mixture was evacuated and backfilled with N₂ for 3 times, and then it was stirred at 80 °C for 3 h under N₂ atmosphere. After cooling to room temperature, the reaction was diluted with H₂O (60 mL), extracted with EtOAc (60 mL x 2). The combined organic layers were washed with brine (30 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in hexanes) to give the title compound (1.46 g, 52%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.67 (d, *J* = 3.2 Hz, 1H), 7.21 (d, *J* = 8.8 Hz, 1H), 7.04 - 6.93 (m, 1H), 3.57 - 3.53 (m, 2H), 3.52 - 3.48 (m, 2H), 3.23 - 3.18 (m, 2H), 1.64 (s, 2H), 0.93 - 0.88 (m, 10H), 0.04 (s, 6H). MS: *m/z* 339.0 (M+H⁺).

Step 3 - Synthesis of 5-acetyl-3-(5-((1*R*,5*S*,6*r*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-azabicyclo[3.1.0]hexan-3-yl)pyridin-2-yl)-7-methylquinoline-2-carbonitrile:

To a solution of (1*R*,5*S*,6*r*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(6-chloropyridin-3-yl)-3-azabicyclo[3.1.0]hexane (1.3 g, 3.84 mmol) in dioxane (15 mL) and H₂O (1 mL) was added 5-acetyl-7-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline-2-carbonitrile (1.93 g, 5.75 mmol), Pd₂(dba)₃ (351.2 mg, 0.38 mmol), XPhos (366 mg, 0.36 mmol) and CsF (1.75 g, 11.5 mmol). The mixture was evacuated and backfilled with N₂ for 3 times, and then it was stirred at 100 °C for 16 h under N₂ atmosphere. After cooling to room temperature, the reaction was diluted with EtOAc (50 mL), washed with H₂O (20 mL x 3) and brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in hexanes) to give the title compound (960 mg, 73%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.36 (s, 1H), 8.34 (d, *J* = 1.2 Hz, 1H), 8.18 - 8.11 (m, 2H), 7.77 (d, *J* = 8.8 Hz, 1H), 7.15 - 7.09 (m, 1H), 3.66 - 3.62 (m, 2H), 3.61 - 3.57 (m, 2H), 3.40 - 3.36 (m, 2H), 2.77 (s, 3H), 2.63 (s, 3H), 1.70 (s, 2H), 0.89 - 0.86 (m, 10H), 0.06 (s, 6H). MS: *m/z* 513.3 (M+H⁺).

Step 4 - Synthesis of 3-(5-((1*R*,5*S*,6*r*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-azabicyclo[3.1.0]hexan-3-yl)pyridin-2-yl)-5-(1-hydroxyethyl)-7-methylquinoline-2-carbonitrile:

To a solution of 5-acetyl-3-(5-((1*R*,5*S*,6*r*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-azabicyclo[3.1.0]hexan-3-yl)pyridin-2-yl)-7-methylquinoline-2-carbonitrile (0.96 g, 1.87 mmol) in THF (10 mL) was added NaBH₄ (0.1 g, 2.6 mmol) at room temperature for 1 h. The mixture was quenched with aq. sat. NH₄Cl (10 mL), extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% MeOH in DCM) to give the title compound (0.35 g, 36 %) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.92 (s, 1H), 8.15 (d, *J* = 2.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.81 (s, 1H), 7.71 (d, *J* = 1.2 Hz, 1H), 7.15 - 7.09 (m, 1H), 5.60 - 5.45 (m, 2H), 3.66 - 3.62 (m, 2H), 3.61 - 3.57 (m, 2H), 3.39 - 3.35 (m, 2H), 2.56 (s, 3H), 1.76 - 1.65 (m, 2H), 1.50 (d, *J* = 6.4 Hz, 3H), 0.94 - 0.86 (m, 10 H), 0.06 (s, 6H). MS: *m/z* 515.3 (M+H⁺).

Step 5 - Synthesis of 5-(1-bromoethyl)-3-(5-((1*R*,5*S*,6*r*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-azabicyclo[3.1.0]hexan-3-yl)pyridin-2-yl)-7-methylquinoline-2-carbonitrile:

To a solution of 3-(5-((1*R*,5*S*,6*r*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-azabicyclo[3.1.0]hexan-3-yl)pyridin-2-yl)-5-(1-hydroxyethyl)-7-methylquinoline-2-carbonitrile (350 mg, 0.68 mmol) in DCM (5 mL) was added PPh₃ (535 mg, 2.04 mmol) and CBr₄ (676 mg, 2.04 mmol) at 0 °C, the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was used for the next step directly without further purification. MS: *m/z* 577.3 (M+H⁺).

Step 6 - Synthesis of 2-(1-(3-(5-((1*R*,5*S*,6*r*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-azabicyclo[3.1.0]hexan-3-yl)pyridin-2-yl)-2-cyano-7-methylquinolin-5-yl)ethoxy)-5-chlorobenzenesulfonamide:

To a solution of 5-(1-bromoethyl)-3-(5-((1*R*,5*S*,6*r*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-azabicyclo[3.1.0]hexan-3-yl)pyridin-2-yl)-7-methylquinoline-2-carbonitrile (above mentioned reaction solution, in DCM) was added DMF (5 mL), followed by 5-chloro-2-hydroxybenzenesulfonamide (150 mg, 0.72 mmol) and K₂CO₃ (200 mg, 1.45 mmol). The mixture was stirred at room temperature for 16 h. The reaction was quenched with H₂O (10 mL), extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (solvent gradient: 10% - 30% EtOAc in hexanes) to give the title compound (160 mg, 47%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.02 (s, 1H), 8.15

(d, $J = 3.2$ Hz, 1H), 7.95 (d, $J = 8.8$ Hz, 1H), 7.89 - 7.85 (m, 2H), 7.72 (d, $J = 2.4$ Hz, 1H), 7.47 - 7.40 (m, 3H), 7.18 - 7.11 (m, 1H), 7.05 (d, $J = 9.2$ Hz, 1H), 6.64 - 6.56 (m, 1H), 3.68 - 3.64 (m, 2H), 3.62 - 3.58 (m, 2H), 3.40 - 3.36 (m, 2H), 2.48 (s, 3H), 1.76 (d, $J = 6.4$ Hz, 3H), 1.71 (s, 2H), 0.95 - 0.89 (m, 10H), 0.07 (s, 6H). MS: m/z 704.4 ($M+H^+$).

5 **Step 7 - Synthesis of 5-chloro-2-(1-(2-cyano-3-(5-((1*R*,5*S*,6*r*)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-3-yl)pyridin-2-yl)-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide:**

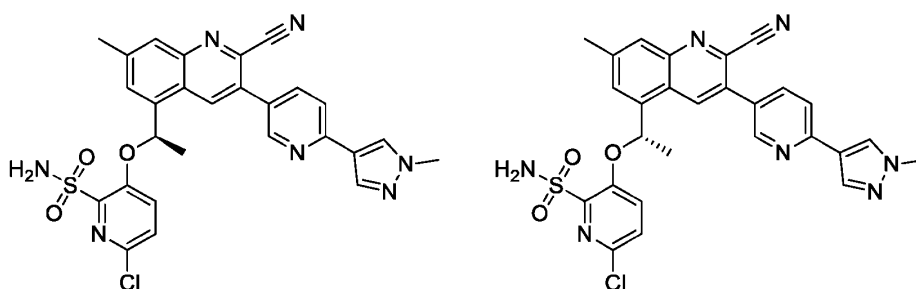
To a solution of 2-(1-(3-(5-((1*R*,5*S*,6*r*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-azabicyclo[3.1.0]hexan-3-yl)pyridin-2-yl)-2-cyano-7-methylquinolin-5-yl)ethoxy)-5-chlorobenzenesulfonamide (0.16 g, 227.16 μ mol) in THF (1 mL) was added TBAF (1 M, 227 μ L). The mixture was stirred at room temperature for 16 h. The reaction was quenched with H₂O (10 mL), extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude, which was purified by silica gel chromatography (solvent gradient: 10% - 30% EtOAc in hexanes) to give the title compound (100 mg, 75%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.02 (s, 1H), 8.16 (d, $J = 2.8$ Hz, 1H), 7.95 (d, $J = 8.8$ Hz, 1H), 7.88 (s, 1H), 7.85 (s, 1H), 7.72 (d, $J = 2.8$ Hz, 1H), 7.47 - 7.41 (m, 3H), 7.16 - 7.10 (m, 1H), 7.05 (d, $J = 8.8$ Hz, 1H), 6.60 (q, $J = 6.4$ Hz, 1H), 4.60 (t, $J = 5.6$ Hz, 1H), 3.67 - 3.63 (m, 2H), 3.34 - 3.22 (m, 4H), 2.47 (s, 2H), 1.76 (d, $J = 6.4$ Hz, 3H), 1.68 (s, 2H), 0.92 - 0.86 (m, 1H). MS: m/z 590.2 ($M+H^+$).

20 **Step 8 - Synthesis of 5-chloro-2-((*R*)-1-(2-cyano-3-(5-((1*R*,5*S*,6*R*)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-3-yl)pyridin-2-yl)-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide & 5-chloro-2-((*S*)-1-(2-cyano-3-(5-((1*R*,5*S*,6*S*)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-3-yl)pyridin-2-yl)-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide:**

25 5-chloro-2-(1-(2-cyano-3-(5-((1*R*,5*S*,6*r*)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-3-yl)pyridin-2-yl)-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide (100 mg, 169 μ mol) was separated by chiral SFC (DAICEL CHIRALCEL OJ (250mm*30mm,10 μ m); Supercritical CO₂ / EtOH+0.1% NH₃•H₂O = 60/40; 80 mL/min) to afford 5-chloro-2-((*R*)-1-(2-cyano-3-(5-((1*R*,5*S*,6*R*)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-3-yl)pyridin-2-yl)-7-methylquinolin-5-yl)ethoxy)benzenesulfonamide (43.86 mg, first peak) and 5-chloro-2-((*S*)-1-(2-cyano-3-(5-((1*R*,5*S*,6*S*)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-3-yl)pyridin-2-yl)-7-methylquinolin-5-

yl)ethoxy)benzenesulfonamide (41.25 mg, second peak) both as yellow solid. Absolute configuration was arbitrarily assigned to each enantiomer. **First Peak** (Compound 658): ¹HNMR (400 MHz, DMSO-*d*₆) δ 9.03 (s, 1H), 8.16 (d, *J* = 2.8 Hz, 1H), 7.95 (d, *J* = 8.8 Hz, 1H), 7.88 (s, 1H), 7.85 (s, 1H), 7.72 (d, *J* = 2.8 Hz, 1H), 7.47 - 7.41 (m, 3H), 7.16 - 7.11 (m, 1H), 7.05 (d, *J* = 9.2 Hz, 1H), 6.64 - 6.56 (m, 1H), 4.59 (t, *J* = 5.6 Hz, 1H), 3.68 - 3.64 (m, 2H), 3.39 - 3.35 (m, 4H), 2.48 (s, 3H), 1.76 (d, *J* = 6.4 Hz, 3H), 1.68 (s, 2H), 0.93 - 0.86 (m, 1H). MS: *m/z* 590.2(M+H⁺).
Second peak (Compound 619): ¹HNMR (400 MHz, DMSO-*d*₆) δ 9.03 (s, 1H), 8.16 (d, *J* = 2.8 Hz, 1H), 7.95 (d, *J* = 8.8 Hz, 1H), 7.88 (s, 1H), 7.85 (s, 1H), 7.72 (d, *J* = 2.8 Hz, 1H), 7.49 - 7.38 (m, 3H), 7.16 - 7.14 (m, 1H), 7.05 (d, *J* = 9.2 Hz, 1H), 6.65 - 6.54 (m, 1H), 4.58 (t, *J* = 5.6 Hz, 1H), 3.67 - 3.63 (m, 2H), 3.39 - 3.35 (m, 4H), 2.48 (s, 3H), 1.76 (d, *J* = 6.4 Hz, 3H), 1.68 (s, 2H), 0.93 - 0.86 (m, 1H). MS: *m/z* 590.2(M+H⁺).

Example 86: Synthesis of (*R*)-6-chloro-3-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyrazin-2-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide (Compound 547) & (*S*)-6-chloro-3-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyrazin-2-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide (Compound 655)



Step 1 - Synthesis of 2-bromo-5-(1-methyl-1*H*-pyrazol-4-yl)pyrazine:

To a solution of 2-bromo-5-iodo-pyrazine (10 g, 35.1 mmol) in dioxane (50 mL) and H₂O (5 mL) was added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (7.30 g, 35.1 mmol), Pd(dppf)Cl₂•DCM (2.87 g, 3.51 mmol) and K₂CO₃ (14.55 g, 105.3 mmol). The mixture was evacuated and backfilled with N₂ for 3 times, and then it was stirred at 80 °C for 3 h under N₂ atmosphere. After cooling to room temperature, the residue was diluted with H₂O (60 mL), extracted with EtOAc (100 mL x 2). The combined organic layers were washed with brine (100 mL x 2), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was

purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in hexanes) to give the title compound (2.8 g, 33%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.82 (d, *J* = 1.6 Hz, 1H), 8.74 (d, *J* = 1.2 Hz, 1H), 8.42 (s, 1H), 8.10 (s, 1H), 3.90 (s, 3H).

Step 2 - Synthesis of 5-acetyl-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyrazin-2-yl)quinoline-2-carbonitrile:

To a solution of 2-bromo-5-(1-methylpyrazol-4-yl)pyrazine (0.5 g, 2.09 mmol) in dioxane (5 mL) and H₂O (1 mL) was added 5-acetyl-7-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline-2-carbonitrile (0.7 g, 2.09 mmol), Pd(PPh₃)₄ (241 mg, 209 μmol) and K₂CO₃ (867 mg, 6.27 mmol). The mixture was evacuated and backfilled with N₂ for 3 times, and then it was stirred at 100 °C for 2 h under N₂ atmosphere. After cooling to room temperature, the residue was filtered and the filtrate was concentrated in vacuo. The crude product was stirred in MeOH (10 mL) at room temperature for 10 min. The suspension was filtered and the filter cake was dried in vacuo to give the title compound (300 mg, 39%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.52 (s, 1H), 9.22 (d, *J* = 1.2 Hz, 1H), 9.14 (d, *J* = 1.2 Hz, 1H), 8.55 (s, 1H), 8.41 (s, 1H), 8.27 - 8.18 (m, 2H), 3.95 (s, 3H), 2.80 (s, 3H), 2.66 (s, 3H). MS: *m/z* 369.1 (M+H⁺).

Step 3 - Synthesis of 5-(1-hydroxyethyl)-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyrazin-2-yl)quinoline-2-carbonitrile:

To a solution of 5-acetyl-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyrazin-2-yl)quinoline-2-carbonitrile (0.3 g, 0.81 mmol) in THF (3 mL) was added NaBH₄ (0.037 g, 0.81 mmol) at room temperature for 1 h. The mixture was quenched with aq. sat. NH₄Cl (10 mL), extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% MeOH in DCM) to give the title compound (0.16 g, 53 %) as a yellow solid. MS: *m/z* 371.1 (M+H⁺).

Step 4 - Synthesis of 5-(1-bromoethyl)-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyrazin-2-yl)quinoline-2-carbonitrile:

To a solution of 5-(1-hydroxyethyl)-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyrazin-2-yl)quinoline-2-carbonitrile (160 mg, 0.43 mmol) in DCM (2 mL) was added PPh₃ (339.8 mg, 1.3 mmol) and CBr₄ (429.7 mg, 1.3 mmol) at 0 °C, the resulting mixture was stirred at room temperature for 1h. The reaction mixture was used for the next step directly without further purification. MS: *m/z* 433.1 (M+H⁺).

Step 5 - Synthesis of 6-chloro-3-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyrazin-2-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide:

To a solution of 5-(1-bromoethyl)-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyrazin-2-yl)quinoline-2-carbonitrile (above mentioned reaction solution, in DCM) was added DMF (3 mL), followed by 6-chloro-3-hydroxy-pyridine-2-sulfonamide (216 mg, 1.04 mmol) and K₂CO₃ (143 mg, 1.04 mmol). The mixture was stirred at room temperature for 16 h. The reaction was quenched with H₂O (10 mL), extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (solvent gradient: 10% - 30% EtOAc in hexanes) to give the title compound (100 mg, 51%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.35 - 9.27 (m, 2H), 9.23 (s, 1H), 8.56 (s, 1H), 8.25 (s, 1H), 8.00 (s, 1H), 7.96 (s, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.63 - 7.57 (m, 3H), 6.71 - 6.62 (m, 1H), 3.96 (s, 3H), 2.54 (s, 3H), 1.78 (d, *J* = 6.4 Hz, 3H). *m/z* 561.1 (M+H⁺).

Step 6 - Synthesis of (*R*)-6-chloro-3-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyrazin-2-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide & (*S*)-6-chloro-3-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyrazin-2-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide:

6-chloro-3-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyrazin-2-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide (100 mg, 178 μmol) was separated by chiral SFC (DAICEL CHIRALCEL OD (250mm*30mm,10um); Supercritical CO₂ / MeOH+0.1% NH₃•H₂O = 60/40; 80 mL/min) to afford (*R*)-6-chloro-3-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyrazin-2-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide (26.53 mg, first peak) and (*S*)-6-chloro-3-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1*H*-pyrazol-4-yl)pyrazin-2-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide (27.92 mg, second peak) both as white solid. Absolute configuration was arbitrarily assigned to each enantiomer. **First Peak (Compound 547):** ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.33 - 9.26 (m, 2H), 9.23 (d, *J* = 0.8 Hz, 1H), 8.56 (s, 1H), 8.25 (s, 1H), 8.00 (s, 1H), 7.96 (s, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 3H), 6.70 - 6.60 (m, 1H), 3.96 (s, 3H), 2.54 (s, 3H), 1.78 (d, *J* = 6.4 Hz, 3H). MS: *m/z* 561.1(M+H⁺). **Second peak (Compound 655):** ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.33 - 9.27 (m, 2H), 9.23 (d, *J* = 1.2 Hz, 1H), 8.56 (s, 1H), 8.25 (s, 1H), 8.00 (s, 1H), 7.96 (s, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.60 (d, *J* = 8.8 Hz,

3H), 6.73 - 6.60 (m, 1H), 3.96 (s, 3H), 2.54 (s, 3H), 1.78 (d, $J = 6.4$ Hz, 3H). MS: m/z 561.1($M+H^+$).

Analytical data of compound is shown in Table 2 below. The compounds in Table 2 were prepared using procedures analogous to those disclosed above with appropriate modifications.

Table 2. Additional Compounds of Formula (I) and Formula (II).

Cmpd. No.	IUPAC name	LCMS $[M+H]^+$	1H NMR (ppm)
8A	2-(((<i>R</i>)-1-(2,7-dimethyl-3-((<i>R</i>)-tetrahydro-2 <i>H</i> -pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid	405.0	1H NMR (400 MHz, DMSO- d_6) δ 12.76 (s, 1H), 8.67 - 8.27 (m, 2H), 7.80 (d, $J = 7.2$ Hz, 1H), 7.57 (s, 1H), 7.34 (s, 1H), 7.23 - 7.12 (m, 1H), 6.58 - 6.41 (m, 2H), 5.44 - 5.40 (m, 1H), 3.89 - 3.87 (m, 1H), 3.45 - 3.40 (m, 2H), 3.09 - 3.05 (m, 1H), 2.68 (s, 3H), 2.41 (s, 3H), 1.96 - 1.91 (m, 1H), 1.85 - 1.78 (m, 1H), 1.74 - 1.66 (m, 2H), 1.60 (d, $J = 6.0$ Hz, 3H), 1.58 - 1.57 (m, 1H).
8B	2-(((<i>R</i>)-1-(2,7-dimethyl-3-((<i>S</i>)-tetrahydro-2 <i>H</i> -pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid	405.0	1H NMR (400 MHz, DMSO- d_6) δ 8.46 (s, 1H), 8.33 (s, 1H), 7.87 - 7.76 (m, 1H), 7.57 (s, 1H), 7.32 (s, 1H), 7.25 - 7.11 (m, 1H), 6.58 - 6.42 (m, 2H), 5.51 - 5.36 (m, 1H), 3.95 - 3.84 (m, 2H), 3.48 - 3.42 (m, 2H), 3.12 - 3.02 (m, 1H), 2.68 (s, 3H), 2.41 (s, 3H), 1.97 - 1.89 (m, 1H), 1.89 - 1.79 (m, 1H), 1.75 - 1.65 (m, 2H), 1.60 (d, $J = 6.4$ Hz, 3H).
8C	2-(((<i>S</i>)-1-(2,7-dimethyl-3-((<i>R</i>)-tetrahydro-2 <i>H</i> -pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid	405.0	1H NMR (400 MHz, DMSO- d_6) δ 8.46 (s, 1H), 8.34 (s, 1H), 7.88 - 7.74 (m, 1H), 7.56 (s, 1H), 7.34 (s, 1H), 7.24 - 7.09 (m, 1H), 6.61 - 6.41 (m, 2H), 5.47 - 5.32 (m, 1H), 3.96 - 3.79 (m, 2H), 3.47 - 3.40 (m, 2H), 3.13 - 3.00 (m, 1H), 2.68 (s, 3H), 2.41 (s, 3H), 2.00 - 1.89 (m, 1H), 1.87 - 1.77 (m, 1H), 1.77 - 1.64 (m, 2H), 1.60 (d, $J = 6.4$ Hz, 3H).
8D	2-(((<i>S</i>)-1-(2,7-dimethyl-3-((<i>S</i>)-tetrahydro-2 <i>H</i> -pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid	405.0	1H NMR (400 MHz, DMSO- d_6) δ 8.53 (s, 1H), 8.33 (s, 1H), 7.91 - 7.72 (m, 1H), 7.56 (s, 1H), 7.32 (s, 1H), 7.23 - 7.09 (m, 1H), 6.62 - 6.38 (m, 2H), 5.44 (s, 1H), 3.96 - 3.84 (m, 2H), 3.47 - 3.43 (m, 2H), 3.11 - 3.04 (m, 1H), 2.68 (s, 3H), 2.40 (s, 3H), 1.98 - 1.89 (m, 1H), 1.89 - 1.79 (m, 1H), 1.75 - 1.66 (m, 2H), 1.60 (d, $J = 6.4$ Hz, 3H).
10	2-((1-(3-(3-fluorophenyl)-2,7-dimethylquinolin-5-	414.9	1H NMR (400 MHz, DMSO- d_6) δ 8.58 - 8.41 (m, 2H), 7.85 - 7.77 (m, 1H), 7.66 (s, 1H), 7.60 - 7.51 (m, 1H), 7.48 - 7.42 (m, 1H), 7.41 - 7.34 (m, 2H), 7.33 - 7.24 (m, 1H), 7.18 - 7.08 (m, 1H), 6.55 -

	yl)ethyl)amino)benzoic acid		6.46 (m, 1H), 6.40 (d, $J = 8.0$ Hz, 1H), 5.56 - 5.39 (m, 1H), 2.59 (s, 3H), 2.43 (s, 3H), 1.57 (d, $J = 6.8$ Hz, 3H).
10A	(<i>R</i>)-2-((1-(3-(3-fluorophenyl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid	415.0	^1H NMR (400 MHz, DMSO- d_6) δ 8.63 - 8.51 (m, 1H), 8.46 (s, 1H), 7.84 - 7.77 (m, 1H), 7.66 (s, 1H), 7.60 - 7.50 (m, 1H), 7.45 (d, $J = 9.6$ Hz, 1H), 7.41 - 7.34 (m, 2H), 7.33 - 7.25 (m, 1H), 7.17 - 7.07 (m, 1H), 6.55 - 6.45 (m, 1H), 6.40 (d, $J = 8.4$ Hz, 1H), 5.49 - 5.43 (m, 1H), 2.59 (s, 3H), 2.43 (s, 3H), 1.57 (d, $J = 6.8$ Hz, 3H).
10B	(<i>S</i>)-2-((1-(3-(3-fluorophenyl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid	415.0	^1H NMR (400 MHz, DMSO- d_6) δ 8.62 - 8.50 (m, 1H), 8.46 (s, 1H), 7.83 - 7.77 (m, 1H), 7.66 (s, 1H), 7.61 - 7.50 (m, 1H), 7.45 (d, $J = 9.6$ Hz, 1H), 7.41 - 7.34 (m, 2H), 7.33 - 7.24 (m, 1H), 7.18 - 7.07 (m, 1H), 6.56 - 6.44 (m, 1H), 6.40 (d, $J = 8.4$ Hz, 1H), 5.50 - 5.44 (m, 1H), 2.59 (s, 3H), 2.43 (s, 3H), 1.57 (d, $J = 6.4$ Hz, 3H).
11	2-((1-(3-(2-cyclopropylpyridin-4-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid	438.1	^1H NMR (400 MHz, DMSO- d_6) δ 8.61 - 8.47 (m, 3H), 7.86 - 7.77 (m, 1H), 7.67 (s, 1H), 7.48 (s, 1H), 7.37 (s, 1H), 7.34 - 7.28 (m, 1H), 7.18 - 7.08 (m, 1H), 6.55 - 6.46 (m, 1H), 6.40 (d, $J = 8.4$ Hz, 1H), 5.57 - 5.38 (m, 1H), 2.60 (s, 3H), 2.44 (s, 3H), 2.23 - 2.13 (m, 1H), 1.57 (d, $J = 6.8$ Hz, 3H), 1.02 - 0.97 (m, 4H).
11A	(<i>R</i>)-2-((1-(3-(2-cyclopropylpyridin-4-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid	438.1	^1H NMR (400 MHz, DMSO- d_6) δ 8.70 - 8.46 (m, 3H), 7.83 - 7.77 (m, 1H), 7.67 (s, 1H), 7.48 (s, 1H), 7.37 (s, 1H), 7.34 - 7.27 (m, 1H), 7.19 - 7.04 (m, 1H), 6.55 - 6.46 (m, 1H), 6.40 (d, $J = 8.4$ Hz, 1H), 5.60 - 5.34 (m, 1H), 2.60 (s, 3H), 2.44 (s, 3H), 2.23 - 2.14 (m, 1H), 1.57 (d, $J = 6.8$ Hz, 3H), 1.04 - 0.96 (m, 4H).
11B	(<i>S</i>)-2-((1-(3-(2-cyclopropylpyridin-4-yl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid	438.1	^1H NMR (400 MHz, DMSO- d_6) δ 8.66 - 8.47 (m, 3H), 7.83 - 7.77 (m, 1H), 7.67 (s, 1H), 7.48 (s, 1H), 7.37 (s, 1H), 7.34 - 7.28 (m, 1H), 7.18 - 7.06 (m, 1H), 6.59 - 6.45 (m, 1H), 6.39 (d, $J = 8.4$ Hz, 1H), 5.57 - 5.41 (m, 1H), 2.60 (s, 3H), 2.44 (s, 3H), 2.23 - 2.14 (m, 1H), 1.57 (d, $J = 6.4$ Hz, 3H), 1.02 - 0.96 (m, 4H).
29	2-((1-(3-(3-(difluoromethyl)phenyl)-2,7-dimethylquinolin-5-yl)ethyl)amino)benzoic acid	447.0	^1H NMR (400 MHz, DMSO- d_6) δ 8.52 - 8.38 (m, 2H), 7.84 - 7.78 (m, 1H), 7.77 - 7.70 (m, 2H), 7.69 - 7.65 (m, 3H), 7.36 (s, 1H), 7.27 - 6.96 (m, 2H), 6.60 - 6.47 (m, 1H), 6.41 (d, $J = 8.0$ Hz, 1H), 5.55 - 5.43 (m, 1H), 2.58 (s, 3H), 2.43 (s, 3H), 1.57 (d, $J = 6.8$ Hz, 3H).
30	2-((1-(2-cyano-7-methyl-3-(tetrahydro-	416.3	^1H NMR (400 MHz, DMSO- d_6) δ 12.78 (s, 1H), 8.76 (s, 1H), 8.62 - 8.40 (m, 1H), 7.91 - 7.71 (m,

	2 <i>H</i> -pyran-3-yl)quinolin-5-yl)ethylamino)benzoic acid		2H), 7.60 - 7.57 (m, 1H), 7.26 - 7.10 (m, 1H), 6.57 - 6.53 (m, 1H), 6.50 - 6.41 (m, 1H), 5.68 - 5.46 (m, 1H), 4.02 - 3.85 (m, 2H), 3.57 - 3.43 (m, 3H), 2.48 - 2.45 (m, 3H), 2.13 - 1.91 (m, 2H), 1.78 - 1.67 (m, 2H), 1.61 (d, <i>J</i> = 5.6 Hz, 3H).
31	2-((1-(2-carbamoyl-7-methyl-3-(tetrahydro-2 <i>H</i> -pyran-3-yl)quinolin-5-yl)ethylamino)benzoic acid	434.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.77 (s, 1H), 8.57 (d, <i>J</i> = 5.6 Hz, 1H), 8.05 (s, 1H), 7.85 - 7.79 (m, 1H), 7.72 - 7.65 (m, 2H), 7.45 (d, <i>J</i> = 8.0 Hz, 1H), 7.25 - 7.12 (m, 1H), 6.56 - 6.44 (m, 2H), 5.58 - 5.44 (m, 1H), 3.98 - 3.84 (m, 2H), 3.40 - 3.88 (m, 3H), 2.46 - 2.44 (m, 3H), 2.06 - 1.78 (m, 2H), 1.69 - 1.59 (m, 5H).
32	2-((1-(3-(cyclopropylmethoxy)-2,7-dimethylquinolin-5-yl)ethylamino)benzoic acid	391.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.54 - 8.34 (m, 1H), 7.82 - 7.74 (m, 2H), 7.53 (s, 1H), 7.28 (d, <i>J</i> = 1.2 Hz, 1H), 7.19 - 7.11 (m, 1H), 6.54 - 6.47 (m, 1H), 6.42 (d, <i>J</i> = 8.4 Hz, 1H), 5.50 - 5.29 (m, 1H), 3.99 (d, <i>J</i> = 6.8 Hz, 2H), 2.54 (s, 3H), 2.37 (s, 3H), 1.57 (d, <i>J</i> = 6.4 Hz, 3H), 1.34 - 1.22 (m, 1H), 0.65 - 0.55 (m, 2H), 0.45 - 0.34 (m, 2H).
33	2-((1-(3-(benzyloxy)-2,7-dimethylquinolin-5-yl)ethylamino)benzoic acid	427.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.80 (s, 1H), 8.55 - 8.41 (m, 1H), 7.91 (s, 1H), 7.83 - 7.78 (m, 1H), 7.57 - 7.51 (m, 3H), 7.45 - 7.38 (m, 2H), 7.37 - 7.30 (m, 1H), 7.27 (d, <i>J</i> = 1.2 Hz, 1H), 7.17 - 7.09 (m, 1H), 6.55 - 6.48 (m, 1H), 6.37 (d, <i>J</i> = 8.4 Hz, 1H), 5.40 - 5.29 (m, 3H), 2.58 (s, 3H), 2.36 (s, 3H), 1.51 (d, <i>J</i> = 6.8 Hz, 3H).
34	2-((1-(3-(1-(2,2-difluoroethyl)piperidin-3-yl)-2,7-dimethylquinolin-5-yl)ethylamino)benzoic acid	468.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.75 (s, 1H), 8.47 - 8.38 (m, 1H), 8.34 (s, 1H), 7.85 - 7.77 (m, 1H), 7.57 (s, 1H), 7.36 - 7.29 (m, 1H), 7.26 - 7.15 (m, 1H), 6.58 - 6.46 (m, 2H), 6.34 - 6.00 (m, 1H), 5.48 - 5.35 (m, 1H), 3.10 - 3.00 (m, 1H), 2.95 - 2.88 (m, 2H), 2.80 - 2.70 (m, 2H), 2.67 (s, 3H), 2.41 (s, 3H), 2.32 - 2.20 (m, 2H), 1.83 - 1.79 (m, 1H), 1.76 - 1.63 (m, 2H), 1.61 (d, <i>J</i> = 6.8 Hz, 3H), 1.57 - 1.47 (m, 1H).
35	2-((1-(2,7-dimethyl-3-(tetrahydro-2 <i>H</i> -pyran-3-yl)quinolin-5-yl)ethylamino)-5-fluorobenzoic acid	423.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.07 (s, 1H), 8.33 (s, 1H), 8.23 (s, 1H), 7.57 (s, 1H), 7.54 - 7.49 (m, 1H), 7.33 - 7.29 (m, 1H), 7.17 - 7.10 (m, 1H), 6.52 - 6.44 (m, 1H), 5.48 - 5.37 (m, 1H), 3.95 - 3.85 (m, 2H), 3.45 - 3.37 (m, 2H), 3.12 - 3.03 (m, 1H), 2.68 (s, 3H), 2.42 - 2.39 (m, 3H), 1.99 - 1.90 (m, 1H), 1.88 - 1.78 (m, 1H), 1.75 - 1.66 (m, 2H), 1.60 (d, <i>J</i> = 6.4 Hz, 3H).
36	2-((1-(3-(2-cyclopropylpyridin-4-yl)-2,7-	456.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.52 - 8.49 (m, 2H), 7.67 (s, 1H), 7.55 - 7.50 (m, 1H), 7.50 - 7.48 (m, 1H), 7.36 (d, <i>J</i> = 1.2 Hz, 1H), 7.34 - 7.31 (m,

	dimethylquinolin-5-yl)ethylamino)-5-fluorobenzoic acid		¹ H, 7.08 - 7.01 (m, 1H), 6.41 - 6.36 (m, 1H), 5.48 - 5.44 (m, 1H), 2.60 (s, 3H), 2.43 (s, 3H), 2.23 - 2.17 (m, 1H), 1.56 (d, <i>J</i> = 6.4 Hz, 3H), 1.01 - 0.97 (m, 4H).
37	2-((1-(2,7-dimethyl-3-((tetrahydro-2H-pyran-4-yl)oxy)quinolin-5-yl)ethylamino)benzoic acid	421.1	¹ H NMR (400MHz, DMSO- <i>d</i> ₆) δ 12.73 (s, 1H), 8.39 (s, 1H), 7.82 (s, 1H), 7.82 - 7.78 (m, 1H), 7.55 (s, 1H), 7.32 (d, <i>J</i> = 1.2 Hz, 1H), 7.23 - 7.17 (m, 1H), 6.55 - 6.49 (m, 2H), 5.43 - 5.39 (m, 1H), 4.84 - 4.76 (m, 1H), 3.88 - 3.79 (m, 2H), 3.56 - 3.43 (m, 2H), 2.53 (s, 3H), 2.39 (s, 3H), 2.03 - 1.92 (m, 2H), 1.70 - 1.62 (m, 2H), 1.58 (d, <i>J</i> = 6.4 Hz, 3H).
38	(<i>R</i>)-2-((1-(2-(difluoromethyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinolin-5-yl)ethylamino)benzoic acid	441.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.79 (s, 1H), 8.75 (s, 1H), 8.52 (s, 1H), 7.85 - 7.78 (m, 1H), 7.77 - 7.73 (m, 1H), 7.52 - 7.47 (m, 1H), 7.40 - 7.09 (m, 2H), 6.57 - 6.43 (m, 2H), 5.71 - 5.51 (m, 1H), 4.12 - 3.88 (m, 2H), 3.57 - 3.45 (m, 2H), 3.42 - 3.36 (m, 1H), 2.45 (s, 3H), 2.06 - 1.88 (m, 2H), 1.77 - 1.65 (m, 2H), 1.60 (d, <i>J</i> = 6.4 Hz, 3H).
39	2-(((<i>R</i>)-1-(2-(difluoromethyl)-7-methyl-3-((<i>S</i>)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethylamino)benzoic acid	441.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.76 (s, 1H), 8.73 (s, 1H), 8.45(s, 1H), 7.87 - 7.78 (m, 1H), 7.75 (s, 1H), 7.56 - 7.49 (m, 1H), 7.36 - 7.04 (m, 2H), 6.63 - 6.44 (m, 2H), 5.69 - 5.43 (m, 1H), 3.97 - 3.87 (m, 1H), 3.86 - 3.78 (m, 1H), 3.57 - 3.43 (m, 3H), 2.46 (s, 3H), 1.98 - 1.87 (m, 2H), 1.72 - 1.65 (m, 2H), 1.62 (d, <i>J</i> = 6.4 Hz, 3H).
40	2-(((<i>S</i>)-1-(2-(difluoromethyl)-7-methyl-3-((<i>S</i>)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethylamino)benzoic acid	441.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.77 (m, 1H), 8.73 (s, 1H), 8.55 - 8.37 (m, 1H), 7.87 - 7.79 (m, 1H), 7.75 (s, 1H), 7.51 (s, 1H), 7.35 - 7.07 (m, 2H), 6.64 - 6.33 (m, 2H), 5.67 - 5.47 (m, 1H), 3.99 - 3.87 (m, 1H), 3.86 - 3.74 (m, 1H), 3.56 - 3.40 (m, 3H), 2.46 (s, 3H), 1.99 - 1.89 (m, 2H), 1.70 (s, 2H), 1.62 (d, <i>J</i> = 6.4 Hz, 3H).
41	(<i>R</i>)-2-((1-(2-cyano-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinolin-5-yl)ethylamino)benzoic acid	416.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.82 (s, 1H), 8.76 (s, 1H), 8.45 (d, <i>J</i> = 5.2 Hz, 1H), 7.87 - 7.77 (m, 2H), 7.58 (d, <i>J</i> = 1.2 Hz, 1H), 7.25 - 7.14 (m, 1H), 6.56 - 6.52 (m, 1H), 6.50 (d, <i>J</i> = 8.4 Hz, 1H), 5.68 - 5.58 (m, 1H), 4.09 - 4.00 (m, 2H), 3.60 - 3.50 (m, 2H), 3.30 - 3.23 (m, 1H), 2.48 (s, 3H), 2.07 - 1.90 (m, 2H), 1.87 - 1.79 (m, 2H), 1.61 (d, <i>J</i> = 6.4 Hz, 3H).
42	(<i>S</i>)-2-((1-(2-cyano-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinolin-5-	416.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.79 (s, 1H), 8.76 (s, 1H), 8.46 (d, <i>J</i> = 5.2 Hz, 1H), 7.86 - 7.76 (m, 2H), 7.58 (d, <i>J</i> = 1.2 Hz, 1H), 7.24 - 7.13 (m, 1H), 6.58 - 6.51 (m, 1H), 6.50 (d, <i>J</i> = 8.4 Hz,

	yl)ethyl)amino)benzoic acid		¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.17 (s, 1H), 8.72 (s, 1H), 8.43 (d, <i>J</i> = 6.4 Hz, 1H), 7.81 (s, 1H), 7.55 (s, 1H), 7.34 (d, <i>J</i> = 8.8 Hz, 1H), 7.01 (d, <i>J</i> = 8.8 Hz, 1H), 5.73 - 5.68 (m, 1H), 4.10 - 3.98 (m, 2H), 3.57 - 3.53 (m, 2H), 3.30 - 3.24 (m, 1H), 2.49 (s, 3H), 2.11 - 1.91 (m, 2H), 1.87 - 1.80 (m, 2H), 1.62 (d, <i>J</i> = 6.4 Hz, 3H).
43	(<i>R</i>)-6-chloro-3-((1-(2-cyano-7-methyl-3-(tetrahydro-2 <i>H</i> -pyran-4-yl)quinolin-5-yl)ethyl)amino)picolinic acid	451.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.17 (s, 1H), 8.72 (s, 1H), 8.43 (d, <i>J</i> = 6.4 Hz, 1H), 7.81 (s, 1H), 7.55 (s, 1H), 7.34 (d, <i>J</i> = 8.8 Hz, 1H), 7.01 (d, <i>J</i> = 8.8 Hz, 1H), 5.73 - 5.68 (m, 1H), 4.10 - 3.98 (m, 2H), 3.57 - 3.53 (m, 2H), 3.30 - 3.24 (m, 1H), 2.49 (s, 3H), 2.11 - 1.91 (m, 2H), 1.87 - 1.80 (m, 2H), 1.62 (d, <i>J</i> = 6.8 Hz, 3H).
44	6-chloro-3-((1-(2-cyano-7-methyl-3-(tetrahydro-2 <i>H</i> -pyran-4-yl)quinolin-5-yl)ethyl)amino)picolinic acid	451.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.16 (s, 1H), 8.72 (s, 1H), 8.44 (d, <i>J</i> = 6.4 Hz, 1H), 7.81 (s, 1H), 7.55 (s, 1H), 7.33 (d, <i>J</i> = 8.8 Hz, 1H), 7.01 (d, <i>J</i> = 8.8 Hz, 1H), 5.78 - 5.63 (m, 1H), 4.13 - 3.98 (m, 2H), 3.62 - 3.50 (m, 2H), 3.28 - 3.22 (m, 1H), 2.47 (s, 3H), 2.10 - 1.91 (m, 2H), 1.88 - 1.79 (m, 2H), 1.62 (d, <i>J</i> = 6.4 Hz, 3H).
45	2-((1-(2,7-dimethyl-3-(tetrahydro-2 <i>H</i> -pyran-3-yl)quinolin-5-yl)ethyl)amino)	440.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.92 (s, 1H), 7.81 - 7.64 (m, 3H), 7.62 - 7.55 (m, 2H), 7.22 - 7.13 (m, 1H), 6.66 (m, 1H), 6.54 - 6.39 (m, 2H), 5.73 - 5.60 (m, 1H), 3.98 - 3.88 (m, 2H), 3.64 - 3.45 (m, 2H), 3.25 - 3.12 (m, 1H), 2.91 (s, 3H), 2.50 (s, 3H), 2.07 - 1.95 (m, 2H), 1.81 - 1.67 (m, 2H), 1.66 - 1.57 (m, 3H).
46	2-(((<i>R</i>)-1-(2,7-dimethyl-3-((<i>R</i>)-tetrahydro-2 <i>H</i> -pyran-3-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide	440.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.55 (s, 1H), 7.70 - 7.60 (m, 2H), 7.59 - 7.51 (m, 3H), 7.24 - 6.97 (m, 1H), 6.67 - 6.60 (m, 1H), 6.50 - 6.40 (m, 2H), 5.59 - 5.47 (m, 1H), 3.94 - 3.90 (m, 2H), 3.58 - 3.42 (m, 2H), 3.19 - 3.08 (m, 1H), 2.77 (s, 3H), 2.43 (s, 3H), 2.05 - 1.88 (m, 2H), 1.80 - 1.66 (m, 2H), 1.62 (d, <i>J</i> = 6.4 Hz, 3H).
47	2-(((<i>R</i>)-1-(2,7-dimethyl-3-((<i>S</i>)-tetrahydro-2 <i>H</i> -pyran-3-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide	440.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.37 (s, 1H), 7.69 - 7.64 (m, 1H), 7.60 - 7.40 (m, 4H), 7.18 - 7.14 (m, 1H), 6.64 - 6.60 (m, 1H), 6.45 - 6.40 (m, 2H), 5.53 - 5.48 (m, 1H), 3.92 (m, 2H), 3.48 (m, 2H), 3.17 - 3.04 (m, 1H), 2.70 (s, 3H), 2.39 (s, 3H), 2.02 - 1.90 (m, 2H), 1.78 - 1.67 (m, 2H), 1.60 (d, <i>J</i> = 6.4 Hz, 3H).
48	2-(((<i>S</i>)-1-(2,7-dimethyl-3-((<i>R</i>)-tetrahydro-2 <i>H</i> -pyran-3-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide	440.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.38 (s, 1H), 7.65 (d, <i>J</i> = 8.0 Hz, 1H), 7.60 - 7.53 (m, 3H), 7.45 (s, 1H), 7.18 - 7.14 (m, 1H), 6.65 - 6.61 (m, 1H), 6.48 - 6.39 (m, 2H), 5.53 - 5.48 (m, 1H), 3.94 - 3.90 (m, 2H), 3.51 - 3.46 (m, 2H), 3.16 - 3.06 (m, 1H), 2.71 (s, 3H), 2.39 (s, 3H), 2.02 - 1.89 (m,

			2H), 1.79 - 1.67 (m, 2H), 1.60 (d, $J = 6.4$ Hz, 3H).
49	2-(((<i>S</i>)-1-(2,7-dimethyl-3-((<i>R</i>)-tetrahydro-2 <i>H</i> -pyran-3-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide	440.3	$^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 8.38 (s, 1H), 7.65 (d, $J = 7.6$ Hz, 1H), 7.60 - 7.51 (m, 3H), 7.49 - 7.43 (m, 1H), 7.22 - 7.12 (m, 1H), 6.64 - 6.60 (m, 1H), 6.49 - 6.40 (m, 2H), 5.49 - 5.43 (m, 1H), 3.97 - 3.86 (m, 2H), 3.54 - 3.43 (m, 2H), 3.16 - 3.04 (m, 1H), 2.70 (s, 3H), 2.40 (s, 3H), 2.04 - 1.87 (m, 2H), 1.80 - 1.66 (m, 2H), 1.60 (d, $J = 6.4$ Hz, 3H).
50	(<i>R</i>)-2-((1-(2,7-dimethyl-3-((tetrahydro-2 <i>H</i> -pyran-4-yl)oxy)quinolin-5-yl)ethyl)amino)benzenesulfonamide	456.1	$^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 7.86 (s, 1H), 7.64 (d, $J = 8.0$ Hz, 1H), 7.54 (s, 3H), 7.44 (s, 1H), 7.19 - 7.15 (m, 1H), 6.65 - 6.60 (m, 1H), 6.48 (d, $J = 8.4$ Hz, 1H), 6.38 (d, $J = 5.6$ Hz, 1H), 5.50 - 5.40 (m, 1H), 4.95 - 4.86 (m, 1H), 3.91 - 3.80 (m, 2H), 3.58 - 3.45 (m, 2H), 2.55 (s, 3H), 2.38 (s, 3H), 2.07 - 1.96 (m, 2H), 1.75 - 1.63 (m, 2H), 1.58 (d, $J = 6.4$ Hz, 3H).
51	(<i>S</i>)-2-((1-(2,7-dimethyl-3-((tetrahydro-2 <i>H</i> -pyran-4-yl)oxy)quinolin-5-yl)ethyl)amino)benzenesulfonamide	456.1	$^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 7.85 (s, 1H), 7.64 (d, $J = 7.8$ Hz, 1H), 7.54 (s, 3H), 7.44 (s, 1H), 7.19 - 7.14 (m, 1H), 6.66 - 6.61 (m, 1H), 6.48 (d, $J = 8.4$ Hz, 1H), 6.38 (d, $J = 5.6$ Hz, 1H), 5.50 - 5.39 (m, 1H), 4.93 - 4.88 (m, 1H), 3.87 - 3.81 (m, 2H), 3.57 - 3.46 (m, 2H), 2.55 (s, 3H), 2.38 (s, 3H), 2.07 - 1.97 (m, 2H), 1.75 - 1.63 (m, 2H), 1.58 (d, $J = 6.4$ Hz, 3H).
52	2-((1-(7-methyl-2-(oxetan-3-yl)-3-(tetrahydro-2 <i>H</i> -pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid	447.2	$^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 8.47 (s, 1H), 8.43 (d, $J = 2.4$ Hz, 1H), 7.84 - 7.78 (m, 1H), 7.69 (s, 1H), 7.41 - 7.35 (m, 1H), 7.23 - 7.15 (m, 1H), 6.57 - 6.46 (m, 2H), 5.53 - 5.42 (m, 1H), 5.08 - 4.91 (m, 4H), 4.88 - 4.80 (m, 1H), 3.92 - 3.85 (m, 1H), 3.78 - 3.71 (m, 1H), 3.55 - 3.48 (m, 2H), 2.74 - 2.68 (m, 1H), 2.46 - 2.42 (m, 3H), 1.87 - 1.63 (m, 4H), 1.61 (d, $J = 6.4$ Hz, 3H).
53	2-((1-(7-methyl-2-(3-methyloxetan-3-yl)-3-(tetrahydro-2 <i>H</i> -pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid	461.2	$^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 8.75 - 8.39 (m, 2H), 7.83 - 7.80 (m, 1H), 7.59 (s, 1H), 7.36 (s, 1H), 7.24 - 7.14 (m, 1H), 6.57 - 6.44 (m, 2H), 5.53 - 5.50 (m, 1H), 5.17 - 5.10 (m, 2H), 4.65 - 4.55 (m, 2H), 3.91 - 3.88 (m, 1H), 3.78 - 3.75 (m, 1H), 3.51 - 3.45 (m, 2H), 2.41 (s, 3H), 2.29 - 2.19 (m, 1H), 1.97 - 1.78 (m, 2H), 1.73 (s, 3H), 1.70 - 1.62 (m, 2H), 1.58 (d, $J = 6.8$ Hz, 3H).
54	2-((1-(3-(6,6-dimethyltetrahydro-2 <i>H</i> -pyran-3-yl)-2,7-dimethylquinolin-5-	433.2	$^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 12.70 (s, 1H), 8.36 (s, 2H), 7.82 - 7.79 (m, 1H), 7.58 (s, 1H), 7.33 (d, $J = 8.0$ Hz, 1H), 7.23 - 7.20 (m, 1H), 6.60 - 6.49 (m, 2H), 5.58 - 5.43 (m, 1H), 3.70 - 3.67

	yl)ethylamino)benzoic acid		(m, 1H), 3.62 - 3.47 (m, 1H), 3.03 - 2.94 (m, 1H), 2.68 (s, 3H), 2.44 - 2.40 (m, 3H), 2.06 - 1.85 (m, 1H), 1.80 - 1.77 (m, 1H), 1.67 - 1.55 (m, 5H), 1.25 - 1.20 (m, 6H).
55	2-((1-(2-chloro-7-methyl-3-(tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethylamino)benzoic acid	425.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.77 (s, 1H), 8.56 (s, 1H), 8.48 - 8.38 (m, 1H), 7.83 - 7.78 (m, 1H), 7.61 (s, 1H), 7.48 - 7.43 (m, 1H), 7.23 - 7.17 (m, 1H), 6.56 - 6.46 (m, 2H), 5.53 - 5.44 (m, 1H), 3.95 - 3.86 (m, 2H), 3.47 - 3.40 (m, 2H), 3.26 - 3.23 (m, 1H), 2.45 - 2.42 (m, 3H), 2.00 - 1.83 (m, 2H), 1.73 - 1.66 (m, 2H), 1.63 - 1.58 (m, 3H).
56	(<i>R</i>)-2-((1-(3-(2-cyclopropylpyrimidin-5-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethylamino)benzoic acid	475.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.89 (s, 1H), 8.81 (s, 2H), 8.21 (s, 1H), 7.86 (s, 1H), 7.84 - 7.80 (m, 1H), 7.55 (s, 1H), 7.30 - 6.93 (m, 2H), 6.51 - 6.46 (m, 1H), 6.36 - 6.32 (m, 1H), 5.58 - 5.47 (m, 1H), 2.48 (s, 3H), 2.33 - 2.29 (m, 1H), 1.57 (d, <i>J</i> = 6.4 Hz, 3H), 1.15 - 1.08 (m, 4H).
57	6-chloro-3-(((<i>R</i>)-1-(2,7-dimethyl-3-((<i>S</i>)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethylamino)picolinic acid	440.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.55 (s, 1H), 8.29 (s, 1H), 7.58 (s, 1H), 7.33 - 7.28 (m, 2H), 7.03 (d, <i>J</i> = 9.2 Hz, 1H), 5.53 - 5.45 (m, 1H), 3.93 - 3.87 (m, 2H), 3.55 - 3.53 (m, 2H), 3.10 - 3.05 (m, 1H), 2.68 (s, 3H), 2.41 (s, 3H), 1.96 - 1.93 (m, 1H), 1.84 - 1.79 (m, 1H), 1.69 - 1.67 (m, 2H), 1.61 (d, <i>J</i> = 6.4 Hz, 3H).
58	6-chloro-3-(((<i>S</i>)-1-(2,7-dimethyl-3-((<i>S</i>)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethylamino)picolinic acid	440.5	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.41 (d, <i>J</i> = 6.4 Hz, 1H), 8.30 (s, 1H), 7.58 (s, 1H), 7.33 (d, <i>J</i> = 9.2 Hz, 1H), 7.28 (s, 1H), 7.01 (d, <i>J</i> = 9.2 Hz, 1H), 5.58 - 5.48 (m, 1H), 3.95 - 3.88 (m, 2H), 3.52 - 3.44 (m, 2H), 3.12 - 3.05 (m, 1H), 2.69 (s, 3H), 2.40 (s, 3H), 1.99 - 1.91 (m, 1H), 1.90 - 1.80 (m, 1H), 1.76 - 1.67 (m, 2H), 1.61 (d, <i>J</i> = 6.4 Hz, 3H).
59	(<i>S</i>)-2-((1-(3-(6-(difluoromethyl)pyridin-3-yl)-2,7-dimethylquinolin-5-yl)ethylamino)benzoic acid	448.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.91 (s, 1H), 8.61 (s, 1H), 8.55 - 8.44 (m, 1H), 8.26 - 8.23 (m, 1H), 7.85 (d, <i>J</i> = 8.0 Hz, 1H), 7.82 - 7.79 (m, 1H), 7.68 (s, 1H), 7.37 (s, 1H), 7.21 - 6.94 (m, 2H), 6.53 - 6.49 (m, 1H), 6.41 - 6.38 (m, 1H), 5.53 - 5.50 (m, 1H), 2.61 (s, 3H), 2.44 (s, 3H), 1.57 (d, <i>J</i> = 6.0 Hz, 3H).
60	5-(2-(((<i>R</i>)-1-(2,7-dimethyl-3-((<i>R</i>)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethylamino)phenyl)isoxazol-3-ol	444.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.37 (s, 1H), 7.56 (s, 1H), 7.51 - 7.47 (m, 1H), 7.42 (s, 1H), 7.12 - 7.05 (m, 1H), 6.68 - 6.62 (m, 1H), 6.49 (d, <i>J</i> = 8.4 Hz, 1H), 6.40 (s, 1H), 5.89 (d, <i>J</i> = 5.6 Hz, 1H), 5.42 - 5.37 (m, 1H), 3.94 - 3.82 (m, 2H), 3.47 - 3.39 (m, 2H), 3.12 - 3.02 (m, 1H), 2.68 (s,

			3H), 2.41 (s, 3H), 1.99 - 1.77 (m, 2H), 1.76 - 1.65 (m, 2H), 1.62 (d, $J = 6.8$ Hz, 3H).
61	5-(2-(((<i>R</i>)-1-(2,7-dimethyl-3-((<i>S</i>)-tetrahydro-2 <i>H</i> -pyran-3-yl)quinolin-5-yl)ethyl)amino)phenyl)isoxazol-3-ol	444.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.35 (s, 1H), 7.56 (s, 1H), 7.51 - 7.46 (m, 1H), 7.41 (d, $J = 1.2$ Hz, 1H), 7.12 - 7.04 (m, 1H), 6.68 - 6.61 (m, 1H), 6.48 (d, $J = 8.4$ Hz, 1H), 6.41 (s, 1H), 5.89 (d, $J = 5.6$ Hz, 1H), 5.44 - 5.36 (m, 1H), 3.94 - 3.83 (m, 2H), 3.49 - 3.40 (m, 2H), 3.13 - 2.99 (m, 1H), 2.68 (s, 3H), 2.40 (s, 3H), 1.95 - 1.78 (m, 2H), 1.75 - 1.66 (m, 2H), 1.62 (d, $J = 6.8$ Hz, 3H).
62	5-(2-(((<i>S</i>)-1-(2,7-dimethyl-3-((<i>S</i>)-tetrahydro-2 <i>H</i> -pyran-3-yl)quinolin-5-yl)ethyl)amino)phenyl)isoxazol-3-ol	444.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.39 (s, 1H), 8.37 (s, 1H), 7.56 (s, 1H), 7.50 - 7.46 (m, 1H), 7.42 (s, 1H), 7.11 - 7.05 (m, 1H), 6.67 - 6.62 (m, 1H), 6.49 (d, $J = 8.4$ Hz, 1H), 6.41 (s, 1H), 5.89 (d, $J = 6.0$ Hz, 1H), 5.43 - 5.35 (m, 1H), 3.94 - 3.84 (m, 2H), 3.45 - 3.36 (m, 2H), 3.12 - 3.02 (m, 1H), 2.68 (s, 3H), 2.41 (s, 3H), 2.00 - 1.75 (m, 2H), 1.75 - 1.64 (m, 2H), 1.62 (d, $J = 6.4$ Hz, 3H).
63	5-(2-(((<i>S</i>)-1-(2,7-dimethyl-3-((<i>R</i>)-tetrahydro-2 <i>H</i> -pyran-3-yl)quinolin-5-yl)ethyl)amino)phenyl)isoxazol-3-ol	444.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.37 (s, 1H), 8.36 (s, 1H), 7.56 (s, 1H), 7.51 - 7.46 (m, 1H), 7.41 (d, $J = 1.2$ Hz, 1H), 7.12 - 7.04 (m, 1H), 6.68 - 6.62 (m, 1H), 6.48 (d, $J = 8.4$ Hz, 1H), 6.42 (s, 1H), 5.90 (d, $J = 5.6$ Hz, 1H), 5.45 - 5.36 (m, 1H), 3.98 - 3.81 (m, 2H), 3.47 - 3.36 (m, 2H), 3.12 - 3.02 (m, 1H), 2.68 (s, 3H), 2.40 (s, 3H), 1.95 - 1.77 (m, 2H), 1.75 - 1.66 (m, 2H), 1.62 (d, $J = 6.8$ Hz, 3H).
64	(<i>R</i>)-2-((1-(3-(6-cyclopropylpyridin-2-yl)-2-(difluoromethyl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid	474.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.78 (s, 1H), 8.91 (s, 1H), 8.45 (d, $J = 5.6$ Hz, 1H), 7.88 - 7.85 (m, 2H), 7.85 - 7.80 (m, 1H), 7.68 (d, $J = 7.6$ Hz, 1H), 7.53 (s, 1H), 7.50 - 7.21 (m, 2H), 7.19 - 7.12 (m, 1H), 6.56 - 6.48 (m, 1H), 6.45 (d, $J = 8.4$ Hz, 1H), 5.71 - 5.52 (m, 1H), 2.48 (s, 3H), 2.26 - 2.17 (m, 1H), 1.62 (d, $J = 6.8$ Hz, 3H), 1.04 - 0.96 (m, 4H).
65	(<i>S</i>)-2-((1-(2-(difluoromethyl)-3-(2-(difluoromethyl)pyridin-4-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid	484.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.87 - 8.81 (m, 2H), 7.87 (s, 2H), 7.83 - 7.73 (m, 2H), 7.54 (s, 1H), 7.27 - 6.89 (m, 3H), 6.57 - 6.49 (m, 1H), 6.40 (d, $J = 8.8$ Hz, 1H), 5.59 - 5.52 (m, 1H), 2.48 (s, 3H), 1.58 (d, $J = 6.4$ Hz, 3H).
66	(<i>R</i>)-2-((1-(2-(difluoromethyl)-7-	457.4	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.99 - 12.54 (m, 1H), 8.43 (s, 1H), 8.16 (s, 1H), 7.83 - 7.79

	methyl-3- ((tetrahydro-2 <i>H</i> - pyran-4- yl)oxy)quinolin-5- yl)ethyl)amino)benzo ic acid		(m, 1H), 7.72 (s, 1H), 7.48 (s, 1H), 7.36 - 7.06 (m, 2H), 6.56 - 6.46 (m, 2H), 5.53 - 5.46 (m, 1H), 5.01 - 4.94 (m, 1H), 3.88 - 3.81 (m, 2H), 3.56 - 3.46 (m, 2H), 2.42 (s, 3H), 2.04 - 1.94 (m, 2H), 1.74 - 1.63 (m, 2H), 1.63 - 1.57 (m, 3H).
67	2-(((<i>R</i>)-1-(2-cyano-7- methyl-3-((<i>R</i>)- tetrahydro-2 <i>H</i> -pyran- 3-yl)quinolin-5- yl)ethyl)amino)benzo ic acid	416.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.76 (s, 1H), 8.76 (s, 1H), 8.45 (d, <i>J</i> = 4.0 Hz, 1H), 7.85 - 7.76 (m, 2H), 7.60 (d, <i>J</i> = 1.2 Hz, 1H), 7.24 - 7.14 (m, 1H), 6.56 - 6.51 (m, 1H), 6.47 (d, <i>J</i> = 8.4 Hz, 1H), 5.62 - 5.47 (m, 1H), 3.99 - 3.88 (m, 2H), 3.57 - 3.46 (m, 2H), 3.27 - 3.22 (m, 1H), 2.47 (s, 3H), 2.10 - 1.89 (m, 2H), 1.76 - 1.67 (m, 2H), 1.61 (d, <i>J</i> = 6.8 Hz, 3H).
68	2-(((<i>R</i>)-1-(2-cyano-7- methyl-3-((<i>S</i>)- tetrahydro-2 <i>H</i> -pyran- 3-yl)quinolin-5- yl)ethyl)amino)benzo ic acid	416.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.77 (s, 1H), 8.56 - 8.41 (m, 1H), 7.92 - 7.75 (m, 2H), 7.58 (d, <i>J</i> = 1.2 Hz, 1H), 7.28 - 7.11 (m, 1H), 6.58 - 6.51 (m, 1H), 6.44 (d, <i>J</i> = 8.4 Hz, 1H), 5.64 - 5.52 (m, 1H), 4.04 - 3.87 (m, 2H), 3.57 - 3.47 (m, 2H), 3.28 - 3.22 (m, 1H), 2.47 (s, 3H), 2.08 - 1.94 (m, 2H), 1.79 - 1.68 (m, 2H), 1.61 (d, <i>J</i> = 6.8 Hz, 3H).
69	2-(((<i>S</i>)-1-(2-cyano-7- methyl-3-((<i>S</i>)- tetrahydro-2 <i>H</i> -pyran- 3-yl)quinolin-5- yl)ethyl)amino)benzo ic acid	416.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.20 - 12.28 (m, 1H), 8.76 (s, 1H), 8.44 (d, <i>J</i> = 5.2 Hz, 1H), 7.85 - 7.76 (m, 2H), 7.60 (d, <i>J</i> = 1.2 Hz, 1H), 7.24 - 7.16 (m, 1H), 6.57 - 6.51 (m, 1H), 6.50 - 6.45 (m, 1H), 5.61 - 5.51 (m, 1H), 4.00 - 3.87 (m, 2H), 3.57 - 3.50 (m, 1H), 3.50 - 3.42 (m, 1H), 3.26 - 3.21 (m, 1H), 2.48 - 2.46 (m, 3H), 2.08 - 1.89 (m, 2H), 1.75 - 1.67 (m, 2H), 1.61 (d, <i>J</i> = 6.8 Hz, 3H).
70	2-(((<i>S</i>)-1-(2-cyano-7- methyl-3-((<i>R</i>)- tetrahydro-2 <i>H</i> -pyran- 3-yl)quinolin-5- yl)ethyl)amino)benzo ic acid	416.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.76 (s, 1H), 8.76 (s, 1H), 8.45 (d, <i>J</i> = 5.2 Hz, 1H), 7.85 - 7.76 (m, 2H), 7.57 (d, <i>J</i> = 1.2 Hz, 1H), 7.22 - 7.15 (m, 1H), 6.58 - 6.50 (m, 1H), 6.44 (d, <i>J</i> = 8.4 Hz, 1H), 5.68 - 5.48 (m, 1H), 4.04 - 3.86 (m, 2H), 3.55 - 3.46 (m, 2H), 3.28 - 3.22 (m, 1H), 2.46 (s, 3H), 2.08 - 1.92 (m, 2H), 1.77 - 1.68 (m, 2H), 1.61 (d, <i>J</i> = 6.8 Hz, 3H).
71	(<i>R</i>)-2-((1-(7-methyl- 3-(tetrahydro-2 <i>H</i> - pyran-4-yl)-2- (trifluoromethyl)quin olin-5- yl)ethyl)amino)benzo ic acid	459.1	¹ H NMR (400MHz, DMSO- <i>d</i> ₆) δ 8.90 (s, 1H), 8.80 - 8.65 (s, 1H), 7.83 - 7.79 (m, 2H), 7.56 (s, 1H), 7.15 - 7.11 (m, 1H), 6.52 - 6.48 (m, 1H), 6.45 (d, <i>J</i> = 8.4 Hz, 1H), 5.64 (d, <i>J</i> = 5.2 Hz, 1H), 4.04 - 3.98 (m, 2H), 3.51 - 3.46 (m, 2H), 3.20 - 3.15 (m, 1H), 2.46 (s, 3H), 2.08 - 1.98 (m, 2H), 1.72 - 1.66 (m, 2H), 1.60 (d, <i>J</i> = 6.4 Hz, 3H).

72	2-(((R)-1-(2-cyclopropyl-7-methyl-3-((R)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid	431.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.72 (s, 1H), 8.40 (d, <i>J</i> = 5.6 Hz, 1H), 8.30 (s, 1H), 7.82 - 7.78 (m, 1H), 7.49 (s, 1H), 7.30 (s, 1H), 7.23 - 7.17 (m, 1H), 6.55 - 6.49 (m, 2H), 5.43 - 5.36 (m, 1H), 4.00 - 3.95 (m, 1H), 3.94 - 3.89 (m, 1H), 3.46 - 3.39 (m, 3H), 2.46 - 2.42 (m, 1H), 2.39 (s, 3H), 2.04 - 1.99 (m, 1H), 1.89 - 1.81 (m, 1H), 1.77 - 1.66 (m, 2H), 1.61 (d, <i>J</i> = 6.8 Hz, 3H), 1.16 - 1.11 (m, 1H), 1.10 - 1.05 (m, 1H), 1.02 - 0.99 (m, 2H).
73	2-(((R)-1-(2-cyclopropyl-7-methyl-3-((S)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid	431.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.71 (s, 1H), 8.40 (d, <i>J</i> = 5.6 Hz, 1H), 8.28 (s, 1H), 7.81 - 7.79 (m, 1H), 7.48 (s, 1H), 7.28 (s, 1H), 7.22 - 7.17 (m, 1H), 6.55 - 6.48 (m, 2H), 5.45 - 5.39 (m, 1H), 3.99 - 3.93 (m, 1H), 3.92 - 3.89 (m, 1H), 3.46 - 3.40 (m, 3H), 2.46 - 2.42 (m, 1H), 2.39 (s, 3H), 2.03 - 1.97 (m, 1H), 1.92 - 1.83 (m, 1H), 1.77 - 1.68 (m, 2H), 1.60 (d, <i>J</i> = 6.4 Hz, 3H), 1.13 - 1.08 (m, 1H), 1.07 - 1.05 (m, 1H), 1.04 - 0.99 (m, 2H).
74	2-(((R)-1-(7-chloro-2-cyclopropyl-3-((R)-tetrahydro-2H-pyran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid	451.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.81 (s, 1H), 8.44 - 8.37 (m, 2H), 7.84 - 7.81 (m, 1H), 7.72 (d, <i>J</i> = 1.6 Hz, 1H), 7.36 (d, <i>J</i> = 2.0 Hz, 1H), 7.23 - 7.17 (m, 1H), 6.58 - 6.54 (m, 1H), 6.43 (d, <i>J</i> = 8.4 Hz, 1H), 5.56 - 5.47 (m, 1H), 4.04 - 3.90 (m, 2H), 3.51 - 3.47 (m, 2H), 3.45 - 3.40 (m, 2H), 2.06 - 1.89 (m, 2H), 1.80 - 1.69 (m, 2H), 1.61 (d, <i>J</i> = 6.4 Hz, 3H), 1.29 - 1.20 (m, 1H), 1.20 - 1.03 (m, 4H).
75	(R)-6-chloro-3-((1-(2-cyano-3-(2-cyclopropylpyrimidin-5-yl)-7-methylquinolin-5-yl)ethyl)amino)picolinic acid	485.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.14 (s, 1H), 9.11 (s, 2H), 9.09 (s, 1H), 8.45 (d, <i>J</i> = 6.4 Hz, 1H), 7.90 (s, 1H), 7.60 (s, 1H), 7.29 (d, <i>J</i> = 9.2 Hz, 1H), 6.94 (d, <i>J</i> = 8.8 Hz, 1H), 5.71 - 5.63 (m, 1H), 2.50 (s, 3H), 2.37 - 2.31 (m, 1H), 1.61 (d, <i>J</i> = 6.4 Hz, 3H), 1.20 - 1.09 (m, 4H).
141	2-(((1-(3-(2-oxabicyclo[2.1.1]hexan-4-yl)-7-chloro-2-cyanoquinolin-5-yl)ethyl)amino)benzoic acid	434.0	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.86 (s, 1H), 8.74 (s, 1H), 8.15 (d, <i>J</i> = 1.6 Hz, 1H), 7.83 (d, <i>J</i> = 7.6 Hz, 1H), 7.69 (d, <i>J</i> = 1.6 Hz, 1H), 7.21 - 7.10 (m, 1H), 6.58 - 6.54 (m, 1H), 6.45 - 6.38 (m, 1H), 5.67 - 5.54 (m, 1H), 4.71 (s, 1H), 3.93 (s, 2H), 2.32 - 2.22 (m, 4H), 1.63 (d, <i>J</i> = 6.8 Hz, 3H).
205	2-(((R)-1-(2-cyano-3-(6-((3 <i>S</i> ,4 <i>S</i>)-3,4-dihydroxypyrrolidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide	545.4	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.90 (s, 1H), 8.48 (d, <i>J</i> = 2.0 Hz, 1H), 7.99 - 7.93 (m, 1H), 7.82 (s, 1H), 7.74 (s, 1H), 7.67 - 7.62 (m, 1H), 7.60 (s, 2H), 7.18 - 7.10 (m, 1H), 6.66 - 6.58 (m, 2H), 6.47 - 6.39 (m, 2H), 5.69 - 5.58 (m, 1H), 5.20 - 5.15 (m, 2H), 4.10 - 4.06 (m, 2H), 3.66 - 3.58 (m,

			2H), 3.48 - 3.38 (m, 2H), 2.46 (s, 3H), 1.60 (d, $J = 6.4$ Hz, 3H).
270	(<i>R</i>)-2-((1-(2-cyano-3-(6-(4-hydroxypiperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide	543.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.94 (s, 1H), 8.51 (d, $J = 2.4$ Hz, 1H), 8.01 - 7.95 (m, 1H), 7.82 (s, 1H), 7.74 (s, 1H), 7.64 (d, $J = 8.0$ Hz, 1H), 7.60 (s, 2H), 7.17 - 7.09 (m, 1H), 7.05 (d, $J = 9.2$ Hz, 1H), 6.67 - 6.58 (m, 1H), 6.46 - 6.39 (m, 2H), 5.70 - 5.60 (m, 1H), 4.74 (d, $J = 4.0$ Hz, 1H), 4.25 - 4.00 (m, 2H), 3.82 - 3.70 (m, 1H), 3.27 - 3.17 (m, 2H), 2.46 (s, 3H), 1.87 - 1.74 (m, 2H), 1.60 (d, $J = 6.4$ Hz, 3H), 1.46 - 1.33 (m, 2H).
280	<i>cis</i> -3-(5-(2-cyano-7-methyl-5-(1-((2-sulfamoylphenyl)amino)ethyl)quinolin-3-yl)pyridin-2-yl)cyclobutanecarboxamide	541.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.07 (s, 1H), 8.93 (d, $J = 2.0$ Hz, 1H), 8.21 - 8.17 (m, 1H), 7.88 (s, 1H), 7.78 (s, 1H), 7.66 - 7.63 (m, 1H), 7.61 (s, 2H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.30 - 7.21 (m, 1H), 7.18 - 7.09 (m, 1H), 6.77 - 6.76 (m, 1H), 6.65 - 6.61 (m, 1H), 6.47 - 6.39 (m, 2H), 5.71 - 5.59 (m, 1H), 3.66 - 3.61 (m, 1H), 3.05 - 2.99 (m, 1H), 2.49 (s, 3H), 2.48 - 2.41 (m, 4H), 1.60 (d, $J = 6.8$ Hz, 3H).
289	(<i>S</i>)-7-methyl-3-(6-(1-methyl-1 <i>H</i> -pyrazol-4-yl)pyridin-3-yl)-5-(1-((2-(methylsulfonyl)phenyl)amino)ethyl)quinoline-2-carbonitrile	523.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.08 (s, 1H), 8.93 (d, $J = 2.0$ Hz, 1H), 8.42 (s, 1H), 8.29 - 8.20 (m, 1H), 8.13 (s, 1H), 7.92 - 7.83 (m, 2H), 7.72 - 7.59 (m, 2H), 7.33 - 7.23 (m, 1H), 6.79 - 6.63 (m, 2H), 6.53 (d, $J = 8.4$ Hz, 1H), 5.74 - 5.62 (m, 1H), 3.93 (s, 3H), 3.28 (s, 3H), 2.50 (s, 3H), 1.63 (d, $J = 6.4$ Hz, 3H).
290	2-(((<i>S</i>)-1-(2-cyano-3-(6-(((<i>S</i>)-3-hydroxypiperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide	543.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.93 (s, 1H), 8.50 (d, $J = 2.4$ Hz, 1H), 8.00 - 7.94 (m, 1H), 7.82 (s, 1H), 7.74 (d, $J = 1.2$ Hz, 1H), 7.67 - 7.62 (m, 1H), 7.61 (s, 2H), 7.20 - 7.09 (m, 1H), 7.01 (d, $J = 8.8$ Hz, 1H), 6.65 - 6.61 (m, 1H), 6.46 - 6.39 (m, 2H), 5.70 - 5.60 (m, 1H), 4.91 (d, $J = 4.4$ Hz, 1H), 4.33 - 4.24 (m, 1H), 4.12 - 4.03 (m, 1H), 3.59 - 3.47 (m, 1H), 3.13 - 3.03 (m, 1H), 2.93 - 2.80 (m, 1H), 2.46 (s, 3H), 1.98 - 1.89 (m, 1H), 1.81 - 1.71 (m, 1H), 1.60 (d, $J = 6.4$ Hz, 3H), 1.50 - 1.37 (m, 2H).
291	2-(((<i>S</i>)-1-(2-cyano-3-(6-(((<i>R</i>)-3-hydroxypiperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide	543.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.93 (s, 1H), 8.50 (d, $J = 2.4$ Hz, 1H), 8.00 - 7.93 (m, 1H), 7.82 (s, 1H), 7.74 (d, $J = 1.2$ Hz, 1H), 7.68 - 7.63 (m, 1H), 7.61 (s, 2H), 7.18 - 7.08 (m, 1H), 7.01 (d, $J = 9.2$ Hz, 1H), 6.68 - 6.58 (m, 1H), 6.49 - 6.36 (m, 2H), 5.71 - 5.64 (m, 1H), 4.91 (d, $J = 4.4$ Hz, 1H), 4.33 - 4.24 (m, 1H), 4.13 - 4.03 (m, 1H), 3.58 - 3.47 (m, 1H), 3.12 - 3.02 (m, 1H), 2.94 -

			2.80 (m, 1H), 2.46 (s, 3H), 1.99 - 1.89 (m, 1H), 1.83 - 1.71 (m, 1H), 1.60 (d, $J = 6.4$ Hz, 3H), 1.52 - 1.33 (m, 2H).
317	(<i>S</i>)-2-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1 <i>H</i> -pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)-6-fluorobenzenesulfonamide	543.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.10 (s, 1H), 8.93 (d, $J = 2.4$ Hz, 1H), 8.42 (s, 1H), 8.28 - 8.22 (m, 1H), 8.13 (s, 1H), 7.99 (d, $J = 1.2$ Hz, 1H), 7.93 (s, 1H), 7.89 (d, $J = 8.4$ Hz, 1H), 7.52 (s, 2H), 7.41 - 7.32 (m, 1H), 6.91 - 6.81 (m, 2H), 6.61 - 6.54 (m, 1H), 3.93 (s, 3H), 2.53 (s, 3H), 1.76 (d, $J = 6.0$ Hz, 3H).
320	2-((1-(3-(6-(1-acetylpyrrolidin-3-yl)pyridin-3-yl)-2-cyano-7-methylquinolin-5-yl)ethyl)amino)benzenesulfonamide	555.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.09 (s, 1H), 8.96 (s, 1H), 8.28 - 8.22 (m, 1H), 7.88 (s, 1H), 7.79 (s, 1H), 7.67 - 7.62 (m, 2H), 7.60 (s, 2H), 7.16 - 7.10 (m, 1H), 6.66 - 6.60 (m, 1H), 6.46 - 6.41 (m, 2H), 5.71 - 5.62 (m, 1H), 3.98 - 3.84 (m, 1H), 3.80 - 3.45 (m, 4H), 2.50 - 2.49 (m, 3H), 2.44 - 2.34 (m, 1H), 2.28 - 2.06 (m, 1H), 2.01 - 1.98 (m, 3H), 1.60 (d, $J = 6.4$ Hz, 3H).
323	7-methyl-5-((<i>R</i>)-1-((1-oxo-1,2,3,4-tetrahydroisoquinolin-8-yl)amino)ethyl)-3-((<i>R</i>)-tetrahydrofuran-3-yl)quinoline-2-carbonitrile	427.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.31 (d, $J = 6.4$ Hz, 1H), 8.74 (s, 1H), 7.87 - 7.83 (m, 1H), 7.78 (s, 1H), 7.59 (d, $J = 1.2$ Hz, 1H), 7.03 - 6.97 (m, 1H), 6.36 (d, $J = 7.2$ Hz, 1H), 6.27 (d, $J = 8.4$ Hz, 1H), 5.48 - 5.39 (m, 1H), 4.17 - 4.10 (m, 1H), 4.02 - 3.95 (m, 1H), 3.93 - 3.87 (m, 1H), 3.87 - 3.79 (m, 2H), 3.30 - 3.27 (m, 2H), 2.77 (t, $J = 6.4$ Hz, 2H), 2.47 (s, 3H), 2.46 - 2.42 (m, 1H), 2.20 - 2.13 (m, 1H), 1.57 (d, $J = 6.8$ Hz, 3H).
328	2-(((<i>R</i>)-1-(2-cyano-3-((<i>S</i>)-3-fluorotetrahydro-2 <i>H</i> -pyran-3-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid	434.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.82 (s, 1H), 7.85 - 7.78 (m, 2H), 7.66 (s, 1H), 7.16 - 7.03 (m, 1H), 6.53 - 6.45 (m, 1H), 6.39 (d, $J = 8.8$ Hz, 1H), 5.55 - 5.44 (m, 1H), 4.11 - 4.03 (m, 1H), 4.01 - 3.88 (m, 2H), 3.61 - 3.53 (m, 2H), 2.44 (s, 3H), 2.31 - 2.22 (m, 1H), 2.03 - 1.92 (m, 1H), 1.69 - 1.64 (m, 1H), 1.61 (d, $J = 6.0$ Hz, 3H).
340	5-(1-(2-(1-cyano-3-hydroxycyclobutyl)phenoxy)ethyl)-7-methyl-3-(6-(1-methyl-1 <i>H</i> -pyrazol-4-yl)pyridin-3-yl)quinoline-2-carbonitrile	541.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.95 - 8.89 (m, 1H), 8.42 (s, 1H), 8.29 - 8.22 (m, 1H), 8.13 (s, 1H), 7.97 - 7.85 (m, 3H), 7.49 - 7.41 (m, 1H), 7.26 - 7.10 (m, 1H), 6.97 - 6.87 (m, 2H), 6.56 - 6.49 (m, 1H), 5.58 - 5.53 (m, 1H), 4.11 - 4.00 (m, 1H), 3.93 (s, 3H), 3.12 - 2.97 (m, 2H), 2.76 - 2.62 (m, 2H), 2.53 (s, 3H), 1.71 (d, $J = 6.0$ Hz, 3H).
344	(<i>S</i>)-2-((1-(3-(2-oxabicyclo[2.1.1]hexan-4-yl)-2-cyano-7-	449.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.63 (s, 1H), 7.81 (s, 1H), 7.73 (s, 1H), 7.68 - 7.61 (m, 1H), 7.58 (s, 2H), 7.21 - 7.11 (m, 1H), 6.70 - 6.60 (m,

	methylquinolin-5-yl)ethylamino)benzenesulfonamide		¹ H, 6.46 (d, <i>J</i> = 8.4 Hz, 1H), 6.39 (d, <i>J</i> = 6.0 Hz, 1H), 5.60 - 5.54 (m, 1H), 4.69 (s, 1H), 3.92 (s, 2H), 2.46 (s, 3H), 2.30 - 2.20 (m, 4H), 1.61 (d, <i>J</i> = 6.8 Hz, 3H).
353	2-((1-(2-cyano-3-(3-fluorotetrahydro-2H-pyran-3-yl)-7-methylquinolin-5-yl)ethylamino)benzoic acid	434.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.85 (s, 1H), 8.83 (d, <i>J</i> = 8.4 Hz, 1H), 8.47 (s, 1H), 7.89 - 7.79 (m, 2H), 7.68 - 7.58 (m, 1H), 7.24 - 7.13 (m, 1H), 6.62 - 6.51 (m, 1H), 6.49 - 6.37 (m, 1H), 5.69 - 5.48 (m, 1H), 4.19 - 4.05 (m, 1H), 4.04 - 3.81 (m, 2H), 3.66 - 3.50 (m, 1H), 2.65 - 2.53 (m, 1H), 2.50 - 2.42 (m, 3H), 2.32 - 2.18 (m, 1H), 2.05 - 1.91 (m, 1H), 1.71 - 1.56 (m, 4H).
355	(<i>S</i>)-2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1 <i>H</i> -pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethylamino)benzamide	488.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.07 (s, 1H), 8.92 (d, <i>J</i> = 1.6 Hz, 1H), 8.86 (d, <i>J</i> = 6.4 Hz, 1H), 8.42 (s, 1H), 8.26 - 8.21 (m, 1H), 8.12 (s, 1H), 7.98 - 7.92 (m, 1H), 7.91 - 7.85 (m, 2H), 7.64 - 7.60 (m, 2H), 7.33 - 7.26 (m, 1H), 7.09 - 7.02 (m, 1H), 6.49 (m, 1H), 6.38 (d, <i>J</i> = 8.4 Hz, 1H), 5.60 - 5.54 (m, 1H), 3.93 (s, 3H), 2.53 (s, 3H), 1.57 (d, <i>J</i> = 6.4 Hz, 3H).
356	(<i>S</i>)-5-(1-(2-(4-cyanotetrahydro-2H-pyran-4-yl)phenoxy)ethyl)-7-methyl-3-(tetrahydro-2H-pyran-4-yl)quinoline-2-carbonitrile	482.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.79 (s, 1H), 7.92 (s, 1H), 7.85 (s, 1H), 7.36 (d, <i>J</i> = 7.6 Hz, 1H), 7.27 - 7.19 (m, 1H), 7.02 - 6.88 (m, 2H), 6.62 - 6.53 (m, 1H), 4.10 - 3.98 (m, 4H), 3.87 - 3.72 (m, 2H), 3.65 - 3.50 (m, 2H), 3.31 - 3.24 (m, 1H), 2.48 (s, 3H), 2.46 - 2.39 (m, 2H), 2.13 - 1.99 (m, 4H), 1.88 - 1.79 (m, 2H), 1.70 (d, <i>J</i> = 6.4 Hz, 3H).
357	(<i>R</i>)-7-methyl-5-(1-((2-(oxetan-3-yl)-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3- <i>a</i>]pyridin-5-yl)amino)ethyl)-3-(tetrahydro-2H-pyran-4-yl)quinoline-2-carbonitrile	485.0	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.71 (s, 1H), 8.38 (d, <i>J</i> = 6.8 Hz, 1H), 7.82 (s, 1H), 7.68 (s, 1H), 6.93 - 6.86 (m, 1H), 6.32 (d, <i>J</i> = 9.2 Hz, 1H), 5.62 - 5.52 (m, 1H), 5.51 - 5.41 (m, 1H), 5.02 (d, <i>J</i> = 7.2 Hz, 1H), 4.93 - 4.82 (m, 4H), 4.06 - 3.98 (m, 2H), 3.60 - 3.48 (m, 2H), 3.32 - 3.22 (m, 1H), 2.50 (s, 3H), 2.05 - 1.90 (m, 2H), 1.87 - 1.75 (m, 2H), 1.59 (d, <i>J</i> = 6.4 Hz, 3H).
360	(<i>S</i>)-2-(1-(2-cyano-7-methyl-3-(6-(1-methyl-1 <i>H</i> -pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethoxy)benzenesulfonamide	525.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.12 (s, 1H), 8.93 (d, <i>J</i> = 2.4 Hz, 1H), 8.43 (s, 1H), 8.25 (dd, <i>J</i> ₁ = 8.0, <i>J</i> ₂ = 2.4 Hz, 1H), 8.13 (s, 1H), 7.99 (s, 1H), 7.91 (s, 1H), 7.89 (d, <i>J</i> = 8.4 Hz, 1H), 7.77 (dd, <i>J</i> ₁ = 7.6, <i>J</i> ₂ = 1.6 Hz, 1H), 7.40 - 7.34 (m, 1H), 7.20 (s, 2H), 7.05 (d, <i>J</i> = 8.0 Hz, 1H), 7.01 - 6.98 (m, 1H), 6.62 - 6.58 (m, 1H), 3.93 (s, 3H), 2.52 (s, 3H), 1.77 (d, <i>J</i> = 6.0 Hz, 3H).

365	5-((<i>S</i>)-1-(2-(3-hydroxy-1,1-dioxidothietan-3-yl)phenoxy)ethyl)-7-methyl-3-((<i>S</i>)-tetrahydrofuran-3-yl)quinoline-2-carbonitrile	479.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.71 (s, 1H), 7.85 (s, 1H), 7.77 (d, <i>J</i> = 1.6 Hz, 1H), 7.51 - 7.44 (m, 1H), 7.18 - 7.09 (m, 1H), 6.94 - 6.91 (m, 1H), 6.74 (d, <i>J</i> = 8.4 Hz, 1H), 6.56 (s, 1H), 6.42 - 6.34 (m, 1H), 5.05 - 4.86 (m, 2H), 4.35 - 4.28 (m, 1H), 4.25 - 4.18 (m, 1H), 4.16 - 4.10 (m, 1H), 4.05 - 3.95 (m, 1H), 3.95 - 3.82 (m, 3H), 2.49 (s, 3H), 2.48 - 2.44 (m, 1H), 2.25 - 2.16 (m, 1H), 1.75 (d, <i>J</i> = 6.4 Hz, 3H).
366	(<i>S</i>)-2-((1-(2-cyano-8-fluoro-7-methyl-3-(tetrahydro-2 <i>H</i> -pyran-4-yl)quinolin-5-yl)ethyl)amino)benzoic acid	434.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.81 (s, 1H), 8.81 (s, 1H), 8.42 (d, <i>J</i> = 5.2 Hz, 1H), 7.87 - 7.75 (m, 1H), 7.62 (d, <i>J</i> = 6.8 Hz, 1H), 7.24 - 7.13 (m, 1H), 6.62 - 6.51 (m, 1H), 6.48 - 6.40 (m, 1H), 5.67 - 5.52 (m, 1H), 4.12 - 3.90 (m, 2H), 3.61 - 3.47 (m, 2H), 3.31 - 3.23 (m, 1H), 2.40 (s, 3H), 2.06 - 1.89 (m, 2H), 1.87 - 1.78 (m, 2H), 1.59 (d, <i>J</i> = 6.4 Hz, 3H).
367	(<i>S</i>)-2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1 <i>H</i> -pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid	489.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.84 (s, 1H), 9.08 (s, 1H), 8.92 (d, <i>J</i> = 2.0 Hz, 1H), 8.50 (s, 1H), 8.42 (s, 1H), 8.25 - 8.22 (m, 1H), 8.12 (s, 1H), 7.91 - 7.86 (m, 2H), 7.83 - 7.81 (m, 1H), 7.61 (s, 1H), 7.19 - 7.12 (m, 1H), 6.57 - 6.50 (m, 1H), 6.41 (d, <i>J</i> = 8.4 Hz, 1H), 5.72 - 5.60 (m, 1H), 3.93 (s, 3H), 2.47 (s, 3H), 1.61 (d, <i>J</i> = 6.4 Hz, 3H).
389	(<i>S</i>)-2-((1-(2-cyano-3-(2-cyclopropylpyridin-4-yl)-7-methylquinolin-5-yl)ethyl)amino)benzoic acid	449.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.03 (s, 1H), 8.75 - 8.62 (m, 1H), 8.60 (d, <i>J</i> = 5.2 Hz, 1H), 7.89 (s, 1H), 7.85 - 7.79 (m, 1H), 7.70 (s, 1H), 7.63 (s, 1H), 7.59 - 7.54 (m, 1H), 7.17 - 7.07 (m, 1H), 6.56 - 6.47 (m, 1H), 6.39 (d, <i>J</i> = 8.4 Hz, 1H), 5.69 - 5.55 (m, 1H), 2.27 - 2.18 (m, 1H), 1.60 (d, <i>J</i> = 6.4 Hz, 3H), 1.08 - 0.98 (m, 4H).
405	(<i>R</i>)-2-((1-(2-cyano-7-methyl-3-(6-(1-methyl-1 <i>H</i> -pyrazol-4-yl)pyridin-3-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide	524.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.08 (s, 1H), 8.96 - 8.90 (m, 1H), 8.41 (s, 1H), 8.27 - 8.21 (m, 1H), 8.15 - 8.11 (m, 1H), 7.91 - 7.87 (m, 2H), 7.79 - 7.73 (m, 1H), 7.66 - 7.62 (m, 1H), 7.18 - 7.10 (m, 1H), 6.68 - 6.57 (m, 1H), 6.49 - 6.42 (m, 1H), 5.65 (q, <i>J</i> = 6.8 Hz, 1H), 3.92 (s, 3H), 2.52 (s, 3H), 1.61 (d, <i>J</i> = 6.8 Hz, 3H).
425	2-(((<i>R</i>)-1-(7-chloro-2-cyano-3-((<i>R</i>)-tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzoic acid	422.0	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.91 (s, 1H), 8.83 (s, 1H), 8.56 - 8.43 (m, 1H), 8.13 (d, <i>J</i> = 1.6 Hz, 1H), 7.85 - 7.80 (m, 1H), 7.65 (d, <i>J</i> = 2.0 Hz, 1H), 7.23 - 7.14 (m, 1H), 6.60 - 6.54 (m, 1H), 6.40 (d, <i>J</i> = 8.0 Hz, 1H), 5.68 - 5.55 (m, 1H), 4.18 - 4.12 (m, 1H), 4.05 - 3.97 (m, 1H), 3.97 - 3.85

			(m, 3H), 2.47 - 2.45 (m, 1H), 2.25 - 2.15 (m, 1H), 1.61 (d, $J = 6.8$ Hz, 3H).
430	2-(((<i>S</i>)-1-(2-cyano-7-methyl-3-(((<i>S</i>)-tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzamide	401.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.84 (d, $J = 6.0$ Hz, 1H), 8.75 (s, 1H), 7.92 (s, 1H), 7.78 (s, 1H), 7.65 - 7.59 (m, 2H), 7.27 (s, 1H), 7.09 - 7.05 (m, 1H), 6.52 - 6.48 (m, 1H), 6.40 (d, $J = 8.4$ Hz, 1H), 5.51 - 5.38 (m, 1H), 4.17 - 4.10 (m, 1H), 4.05 - 3.97 (m, 1H), 3.94 - 3.81 (m, 3H), 2.46 (s, 3H), 2.48 - 2.41 (m, 1H), 2.24 - 2.11 (m, 1H), 1.56 (d, $J = 6.4$ Hz, 3H).
431	2-(((<i>S</i>)-1-(2-cyano-7-methyl-3-(((<i>R</i>)-tetrahydrofuran-3-yl)quinolin-5-yl)ethyl)amino)benzamide	401.0	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.82 (d, $J = 6.4$ Hz, 1H), 8.72 (s, 1H), 7.92 (s, 1H), 7.78 (s, 1H), 7.65 - 7.59 (m, 2H), 7.25 (s, 1H), 7.11-7.07 (m, 1H), 6.52 - 6.48 (m, 1H), 6.41 (d, $J = 8.4$ Hz, 1H), 5.47 - 5.43 (m, 1H), 4.16 - 4.12 (m, 1H), 4.02 - 3.95 (m, 1H), 3.92 - 3.76 (m, 3H), 2.46 (s, 3H), 2.48 - 2.41 (m, 1H), 2.25 - 2.14 (m, 1H), 1.57 (d, $J = 6.8$ Hz, 3H).
458	3-(((<i>R</i>)-1-(3-(((1 <i>S</i> ,4 <i>R</i>)-2-oxabicyclo[2.2.1]heptan-4-yl)-2-cyano-7-methylquinolin-5-yl)ethoxy)-6-chloropyridine-2-sulfonamide	499.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.65 (s, 1H), 7.92 (d, $J = 1.2$ Hz, 1H), 7.87 (s, 1H), 7.76 (d, $J = 9.2$ Hz, 1H), 7.63 (d, $J = 8.8$ Hz, 1H), 7.57 (s, 2H), 6.56 (q, $J = 6.4$ Hz, 1H), 4.51 (s, 1H), 4.24 (d, $J = 6.4$ Hz, 1H), 3.87 - 3.80 (m, 1H), 2.49 - 2.47 (m, 3H), 2.40 - 2.32 (m, 2H), 2.31 - 2.27 (m, 1H), 2.06 - 1.94 (m, 1H), 1.92 - 1.79 (m, 2H), 1.76 (d, $J = 6.4$ Hz, 3H).
491	(<i>S</i>)-2-(1-(2-cyano-7-methyl-3-(4-(1-methyl-1 <i>H</i> -pyrazol-4-yl)piperazin-1-yl)quinolin-5-yl)ethoxy)benzenesulfonamide	532.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.33 (s, 1H), 7.86 (d, $J = 1.2$ Hz, 1H), 7.80 - 7.72 (m, 2H), 7.42 - 7.35 (m, 2H), 7.25 (s, 1H), 7.17 (s, 2H), 7.06 - 6.95 (m, 2H), 6.50 - 6.42 (m, 1H), 3.76 (s, 3H), 3.43 - 3.37 (m, 4H), 3.14 - 3.08 (m, 4H), 2.44 (s, 3H), 1.77 (d, $J = 6.4$ Hz, 3H).
508	(<i>R</i>)-3-(((1-(2-cyano-7-methyl-3-(5-(4-methyl-1 <i>H</i> -imidazol-1-yl)pyridin-2-yl)quinolin-5-yl)ethyl)amino)picolinamide	489.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.22 (s, 1H), 9.21 - 9.16 (m, 2H), 8.42 - 8.41 (m, 1H), 8.39 - 8.34 (m, 1H), 8.34 - 8.29 (m, 1H), 8.16 (d, $J = 2.8$ Hz, 1H), 7.89 (s, 1H), 7.77 (d, $J = 3.6$ Hz, 1H), 7.71 (s, 1H), 7.62 (s, 1H), 7.58 (d, $J = 2.8$ Hz, 1H), 7.18 - (m, 1H), 6.86 (d, $J = 8.4$ Hz, 1H), 5.71 - 5.61 (m, 1H), 2.49 - 2.48 (m, 3H), 2.21 (s, 3H), 1.62 (d, $J = 6.4$ Hz, 3H).

531	(<i>R</i>)-6-chloro-3-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1 <i>H</i> -pyrazol-4-yl)pyridin-2-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide	560.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.17 (s, 1H), 9.10 (s, 1H), 8.43 (s, 1H), 8.29 - 8.22 (m, 1H), 8.19 - 8.11 (m, 2H), 8.00 - 7.91 (m, 2H), 7.76 - 7.71 (m, 1H), 7.63 - 7.55 (m, 3H), 6.73 - 6.63 (m, 1H), 3.93 (s, 3H), 2.52 (s, 3H), 1.77 (d, <i>J</i> = 6.0 Hz, 3H).
576	(<i>R</i>)-2-(1-(2-cyano-7-methyl-3-(5-(4-methyl-1 <i>H</i> -imidazol-1-yl)pyrazin-2-yl)quinolin-5-yl)ethoxy)benzenesulfonamide	526.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.40 (s, 2H), 9.30 (s, 1H), 8.66 (s, 1H), 8.03 (s, 1H), 7.95 (s, 1H), 7.86 (s, 1H), 7.79 - 7.73 (m, 1H), 7.40 - 7.34 (m, 1H), 7.21 (s, 2H), 7.08 - 7.04 (m, 1H), 7.01 - 6.98 (m, 1H), 6.62 - 6.58 (m, 1H), 2.53 (s, 3H), 2.24 (s, 3H), 1.81 (d, <i>J</i> = 6.4 Hz, 3H).
579	(<i>R</i>)-2-((1-(2-cyano-7-methyl-3-(4-(4-methyl-1 <i>H</i> -imidazol-1-yl)piperidin-1-yl)quinolin-5-yl)ethyl)amino)benzenesulfonamide	530.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.26 (s, 1H), 7.71 (s, 1H), 7.67 - 7.62 (m, 3H), 7.59 (s, 2H), 7.20 - 7.12 (m, 1H), 7.04 (s, 1H), 6.65 - 6.62 (m, 1H), 6.43 (d, <i>J</i> = 8.4 Hz, 1H), 6.39 (d, <i>J</i> = 6.0 Hz, 1H), 5.53 - 5.50 (m, 1H), 4.29 - 4.13 (m, 1H), 3.75 - 3.62 (m, 2H), 3.12 - 3.05 (m, 2H), 2.41 (s, 3H), 2.21 - 2.07 (m, 7H), 1.60 (d, <i>J</i> = 6.8 Hz, 3H).
610	(<i>S</i>)-3-chloro-6-(1-(2-cyano-7-methyl-3-(tetrahydro-2 <i>H</i> -pyran-4-yl)quinolin-5-yl)ethoxy)-2-fluorobenzenesulfonamide	504.0	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.75 (s, 1H), 7.91 (s, 1H), 7.83 (s, 1H), 7.71 (s, 2H), 7.61 (t, <i>J</i> = 8.4 Hz, 1H), 6.94 (d, <i>J</i> = 9.2 Hz, 1H), 6.66 - 6.54 (m, 1H), 4.10 - 4.01 (m, 2H), 3.60 - 3.49 (m, 2H), 3.30 - 3.22 (m, 1H), 2.48 (s, 3H), 2.14 - 1.99 (m, 2H), 1.90 - 1.79 (m, 2H), 1.72 (d, <i>J</i> = 6.4 Hz, 3H).
614	2-((<i>R</i>)-1-(3-((1 <i>S</i> ,5 <i>R</i>)-3-oxabicyclo[3.1.0]hexan-1-yl)-2-cyano-7-methylquinolin-5-yl)ethoxy)-5-chlorobenzenesulfonamide	484.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.95 (s, 1H), 7.89 (s, 1H), 7.85 (s, 1H), 7.72 (d, <i>J</i> = 2.4 Hz, 1H), 7.49 - 7.44 (m, 1H), 7.40 (s, 2H), 7.07 (d, <i>J</i> = 8.8 Hz, 1H), 6.53 - 6.44 (m, 1H), 4.13 - 4.07 (m, 1H), 4.04 (d, <i>J</i> = 8.0 Hz, 1H), 3.95 (d, <i>J</i> = 8.4 Hz, 1H), 3.83 (d, <i>J</i> = 8.4 Hz, 1H), 2.48 (s, 3H), 2.23 - 2.14 (m, 1H), 1.76 (d, <i>J</i> = 6.4 Hz, 3H), 1.36 - 1.28 (m, 1H), 1.06 - 1.02 (m, 1H).
620	(<i>S</i>)-5-chloro-2-(1-(2-cyano-7-methyl-3-(4-(1-methyl-1 <i>H</i> -pyrazol-4-yl)piperazin-1-yl)quinolin-5-yl)ethoxy)benzenesulfonamide	566.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.30 (s, 1H), 7.83 (d, <i>J</i> = 1.2 Hz, 1H), 7.76 (s, 1H), 7.72 (d, <i>J</i> = 2.8 Hz, 1H), 7.49 - 7.45 (m, 1H), 7.38 (s, 2H), 7.37 (s, 1H), 7.25 (s, 1H), 7.06 (d, <i>J</i> = 9.2 Hz, 1H), 6.51 - 6.43 (m, 1H), 3.76 (s, 3H), 3.43 - 3.37 (m, 4H), 3.16 - 3.08 (m, 4H), 2.44 (s, 3H), 1.76 (d, <i>J</i> = 6.4 Hz, 3H).

622	(<i>S</i>)-2-(1-(2-cyano-7-methyl-3-(4-(1-methyl-1 <i>H</i> -pyrazol-4-yl)piperazin-1-yl)quinolin-5-yl)ethoxy)-5-fluorobenzenesulfonamide	550.3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.31 (s, 1H), 7.84 (d, <i>J</i> = 1.2 Hz, 1H), 7.75 (s, 1H), 7.54 - 7.50 (m, 1H), 7.37 (s, 3H), 7.31 - 7.24 (m, 2H), 7.06 - 7.01 (m, 1H), 6.47 - 6.39 (m, 1H), 3.76 (s, 3H), 3.41 - 3.38 (m, 4H), 3.13 - 3.09 (m, 4H), 2.44 (s, 3H), 1.75 (d, <i>J</i> = 6.4 Hz, 3H).
644	3-((<i>S</i>)-1-(3-((1 <i>S</i> ,5 <i>R</i>)-3-oxabicyclo[3.1.0]hexan-1-yl)-2-cyano-7-methylquinolin-5-yl)ethoxy)-6-chloropyridine-2-sulfonamide	485.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.95 (s, 1H), 7.91 (s, 1H), 7.86 (s, 1H), 7.76 - 7.72 (m, 1H), 7.66 - 7.55 (m, 3H), 6.57 - 6.50 (m, 1H), 4.12 - 4.03 (m, 2H), 3.96 (d, <i>J</i> = 8.0 Hz, 1H), 3.83 (d, <i>J</i> = 8.0 Hz, 1H), 2.51 (s, 3H), 2.23 - 2.16 (m, 1H), 1.74 (d, <i>J</i> = 6.0 Hz, 3H), 1.34 - 1.30 (m, 1H), 1.06 - 1.04 (m, 1H).
646	(<i>S</i>)-6-chloro-3-(1-(2-cyano-7-methyl-3-(4-methyltetrahydro-2 <i>H</i> -pyran-4-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide	501.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.56 (s, 1H), 7.90 (s, 1H), 7.86 (s, 1H), 7.76 (d, <i>J</i> = 8.8 Hz, 1H), 7.62 (d, <i>J</i> = 8.8 Hz, 1H), 7.57 (s, 2H), 6.64 - 6.56 (m, 1H), 3.81 - 3.74 (m, 2H), 3.72 - 3.66 (m, 2H), 2.39 - 2.32 (m, 1H), 2.30 - 2.23 (m, 1H), 2.12 - 2.08 (m, 2H), 1.76 (d, <i>J</i> = 6.4 Hz, 3H), 1.61 (s, 3H).
649	(<i>S</i>)-6-chloro-3-(1-(2-cyano-3-(6-(3-(difluoromethyl)azetidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethoxy)pyridine-2-sulfonamide	585.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.89 (s, 1H), 8.51 (d, <i>J</i> = 2.4 Hz, 1H), 8.04 - 7.99 (m, 1H), 7.94 (s, 1H), 7.89 (s, 1H), 7.73 (d, <i>J</i> = 8.8 Hz, 1H), 7.62 - 7.55 (m, 3H), 6.68 - 6.61 (m, 2H), 6.57 - 6.26 (m, 1H), 4.20 - 4.13 (m, 2H), 4.03 - 3.97 (m, 2H), 3.46 - 3.40 (m, 1H), 2.50 (s, 3H), 1.72 (d, <i>J</i> = 6.4 Hz, 3H).
653	(<i>S</i>)-6-chloro-3-(1-(2-cyano-3-(6-(4-hydroxypiperidin-1-yl)pyridin-3-yl)-7-methylquinolin-5-yl)ethoxy)pyridine-2-sulfonamide	579.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.89 (s, 1H), 8.52 (d, <i>J</i> = 2.8 Hz, 1H), 8.03 - 7.97 (m, 1H), 7.94 (s, 1H), 7.88 (s, 1H), 7.73 (d, <i>J</i> = 8.8 Hz, 1H), 7.68 - 7.48 (m, 3H), 7.06 (d, <i>J</i> = 8.8 Hz, 1H), 6.70 - 6.62 (m, 1H), 4.75 (d, <i>J</i> = 4.4 Hz, 1H), 4.19 - 4.09 (m, 2H), 3.82 - 3.73 (m, 1H), 3.28 - 3.19 (m, 2H), 2.49 (s, 3H), 1.87 - 1.79 (m, 2H), 1.72 (d, <i>J</i> = 6.4 Hz, 3H), 1.46 - 1.34 (m, 2H).
655	(<i>S</i>)-6-chloro-3-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1 <i>H</i> -pyrazol-4-yl)pyrazin-2-yl)quinolin-5-yl)ethoxy)pyridine-2-sulfonamide	561.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.30 (s, 1H), 9.29 (d, <i>J</i> = 1.2 Hz, 1H), 9.23 (d, <i>J</i> = 1.2 Hz, 1H), 8.56 (s, 1H), 8.25 (s, 1H), 8.00 (s, 1H), 7.96 (s, 1H), 7.76 (d, <i>J</i> = 8.8 Hz, 1H), 7.63 - 7.55 (m, 3H), 6.71 - 6.61 (m, 1H), 3.96 (s, 3H), 2.54 (s, 3H), 1.78 (d, <i>J</i> = 6.4 Hz, 3H).

656	6-chloro-3-((<i>S</i>)-1-(2-cyano-3-(5-((1 <i>R</i> ,5 <i>S</i> ,6 <i>S</i>)-6-(difluoromethyl)-3-azabicyclo[3.1.0]hexan-3-yl)pyridin-2-yl)-7-methylquinolin-5-yl)ethoxy)pyridine-2-sulfonamide	611.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.01 (s, 1H), 8.19 (d, <i>J</i> = 2.8 Hz, 1H), 7.96 (d, <i>J</i> = 8.8 Hz, 1H), 7.91 (s, 1H), 7.87 (s, 1H), 7.71 (d, <i>J</i> = 8.8 Hz, 1H), 7.61 - 7.56 (m, 3H), 7.20 - 7.16 (m, 1H), 6.69 - 6.62 (m, 1H), 6.11 - 5.72 (m, 1H), 3.75 (d, <i>J</i> = 9.6 Hz, 2H), 3.39 (d, <i>J</i> = 9.6 Hz, 2H), 2.54 (s, 3H), 2.09 (s, 2H), 1.74 (d, <i>J</i> = 6.4 Hz, 3H), 1.43 - 1.32 (m, 1H).
667	(<i>R</i>)-5-chloro-2-(1-(2-cyano-7-methyl-3-(5-(1-methyl-1 <i>H</i> -pyrazol-4-yl)pyridin-2-yl)quinolin-5-yl)ethoxy)benzenesulfonamide	559.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.20 (s, 1H), 9.10 (d, <i>J</i> = 2.0 Hz, 1H), 8.43 (s, 1H), 8.28 - 8.22 (m, 1H), 8.19 - 8.12 (m, 2H), 7.94 - 7.91 (m, 2H), 7.72 (d, <i>J</i> = 2.4 Hz, 1H), 7.49 - 7.37 (m, 3H), 7.08 (d, <i>J</i> = 8.8 Hz, 1H), 6.67 - 6.62 (m, 1H), 3.92 (s, 3H), 2.49 (m, 3H), 1.78 (d, <i>J</i> = 6.0 Hz, 3H).

Biochemical Assays

PI3Ka cellular assay experimental procedure:

SKBR3 or T47D cells are seeded in DMEM containing 10% FBS at 25k cells/well into 96-well cell culture format. Cells are incubated overnight at 37°C in a 5% CO₂ incubator and the following day cell media is aspirated, adherent cells are washed 1X with room temperature PBS prior to serum-free media application. Cells are returned to 37°C 5% CO₂ incubator and incubated a further 16hrs. Compounds are added to serum starved adherent cells with a top dose of 10,000nM and 3x multiple dose reductions for a minimum dose of 0.5nM diluted in DMSO. Cell/compound incubation continues for 1hr in a 37°C, 5% CO₂ incubator prior to 10 minute PIK3CA stimulation with 20ng/ml EGF. Cells treated with 0.1% DMSO and 20ng/mL EGF are employed as negative control, cells treated with 10uM Alpelisib and 20ng/mL EGF are employed as a positive control. After 10 mins, plates are removed from incubator and cells are lysed with buffer and shaking 45 minutes. 20uL of lysate is transferred to an opti-384 plate and 2.5 μl of Phospho-AKT d2 antibody with 2.5 μl of Phospho-AKT Eu Cryptate solution in the detection buffer are added to each well. 384 well plate is left overnight at room temperature before reading HTRF on an Envision plate reader. The MCF7 pAKT (E545K) and NCI-H1341 pAKT (E542K) cellular assays were performed analogously to the T47D assay described herein.

The biological activity of certain compounds using the assays described above is shown in Table 2. The ranges are as follows:

for T47D pAKT IC₅₀ (nM): A denotes < 750 nM; B denotes 750 nM ≤ IC₅₀ < 2,000 nM; C denotes ≥ 2,000 nM;;

for T47D (H1047R) selectivity over SKBR3 (WT): A denotes > 20-fold; B denotes 20-fold ≥ value > 5-fold; C denotes ≤ 5-fold. ND denotes value not determined with that assay for the specified compound;;

for MCF7 pAKT IC₅₀ (nM): A denotes < 750 nM; B denotes 750 nM ≤ IC₅₀ < 2,000 nM; C denotes ≥ 2,000 nM;

for MCF7 (E545K) selectivity over SKBR3 (WT): A denotes > 20-fold; B denotes 20-fold ≥ value > 5-fold; C denotes ≤ 5-fold;;

for NCI-H1341 pAKT (E542K) IC₅₀ (nM): A denotes < 750 nM; B denotes 750 nM ≤ IC₅₀ < 2,000 nM; C denotes ≥ 2,000 nM.; and

for NCI-H1341 pAKT (E542K) selectivity over SKBR3 (WT): A denotes > 20-fold; B denotes 20-fold ≥ value > 5-fold; C denotes ≤ 5-fold.

Table 2. Biological Activity of Selected Compounds

Cmpd No.	T47D pAKT (H1047R): Avg IC₅₀ (nM)	T47D (H1047R) selectivity over SKBR3 (WT)	MCF7 pAKT (E545K): Avg IC₅₀ (nM)	MCF7 (E545K) selectivity over SKBR3 (WT)	NCI-H1341 pAKT (E542K): Avg IC₅₀ (nM)	NCI-H1341 (E542K) selectivity over SKBR3 (WT)
1	A	A			A	
2	A	A			A	
3	A	A			A	
4	C	C			A	
5	A	A			A	
6	A	A			A	
7	A	A			A	
8A	C	C				
8B	C	C				
8C	A	A	B	B		
8D	A	A	C	C		
10	A	A			A	
10A	C	C				
10B	A	A	B	B		
11	A	A			A	

11A	C	C				
11B	A	A	B	B		
12	A	A	C	C	A	
29	A	A			A	
30	A	A	C	C	A	
31	C	C	C	C	A	
32	A	A			A	
33	A	A			A	
34	B	B	C	C	A	
35	A	A	C	C	A	
36	A	A			A	
37	A	A			A	
38	A	A	A	A	A	
39	A	A	C	C	A	
40	A	A	B	B	A	
41	C	C			A	
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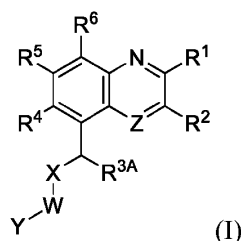
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663	A	A	A	A	A	B
665	A	A	A	B	C	C
666	A	A	A	B	C	C

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

- 5 Z is N or CH;

R¹ is hydrogen, halogen, cyano, C3-C6 cycloalkyl, C1-C6 thioalkyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 alkoxyalkyl, 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl; or C1-C6 alkyl optionally substituted with (i) C3-C6 cycloalkyl or (ii) 4-10 membered heterocyclyl;

- 10 R² is C6-C10 aryl optionally substituted with 1-4 independently selected R^{2A}, 5-10 membered heteroaryl optionally substituted with 1-4 independently selected R^{2A}, 4-10 membered heterocyclyl optionally substituted with 1-4 independently selected R^{2A}, C4-C10 cycloalkyl optionally substituted with 1-4 independently selected R^{2A}, 4-10 membered heterocycloxy optionally substituted with 1-4 independently selected R^{2A}, 5-10 heteroaryloxy optionally substituted with 1-4 independently selected R^{2A}, C1-C6 alkoxyalkyl optionally substituted with –C(=O)NR^{AR^C}, or C1-C6 alkoxy optionally substituted with –C(=O)NR^{AR^C}, C4-C10 cycloalkyl, 4-10 membered heterocyclyl, 5-10 membered heteroaryl, or phenyl;

each R^{2A} is independently selected from:

- 20 (i) halogen;
 (ii) cyano;
 (iii) hydroxyl;
 (iv) -NR^{AR^B};
 (v) -C(=O)NR^{AR^B};

- 25 (vi) ;

- (vii) -NHC(=O)R^C;
- (viii) -C(=O)OR^D;
- (ix) -SO₂R^D;
- (x) -NHSO₂R^D;
- 5 (xi) -SO₂NR^DR^E;
- (xii) -NHC(=O)C1-C6 alkyl optionally substituted with NR^AR^B;
- (xiii) C1-C6 haloalkyl;
- (xiv) C1-C6 hydroxyalkyl;
- (xv) 5-10 membered heteroaryl optionally substituted with 1-3 substituents independently
 10 selected from hydroxyl, cyano, halogen, -C(=O)NR^AR^B, -NR^AR^B, C1-C6 alkyl optionally substituted with hydroxyl; and 4-10 membered heterocyclyl optionally substituted with hydroxyl or C1-C6 alkyl;
- (xvi) 4-10 membered heterocyclyl optionally substituted with 1-3 substituents independently selected from hydroxyl, cyano, halogen, C1-C6 haloalkyl, -C(=O)C1-C6 alkyl, -
 15 SO₂(C1-C6 alkyl), -SO₂NR^DR^E, C1-C6 alkoxy, -C(=O)NR^AR^B, -NR^AR^B, -NHC(=O)C1-C6 alkyl optionally substituted with -NR^AR^B, and C1-C6 alkyl optionally substituted with C1-C6 alkoxy or hydroxyl;
- (xvii) C1-C6 alkyl optionally substituted with 1-3 substituents independently selected from hydroxyl, oxo, -NR^AR^B, -C(=O)NR^AR^B, C1-C6 alkoxy, and 4-10 membered heterocyclyl
 20 optionally substituted with hydroxyl, C1-C6 alkyl, aralkyl, heteroaralkyl, -C(=O)NR^AR^B, or -C(=O)C3-C6 cycloalkyl;
- (xviii) C1-C6 alkoxy optionally substituted with -NR^AR^B or 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl, aralkyl, heteroaralkyl, or -C(=O)C3-C6 cycloalkyl;
- (xix) C3-C6 cycloalkyl optionally substituted with hydroxyl, -C(=O)NR^AR^B,
 25 -C(=NH)OR^D, or 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl; and
- (xx) 4-10 membered heterocycloxy optionally substituted with hydroxyl, cyano, halogen, or C1-C6 alkyl optionally substituted with hydroxyl;
- each R^A and R^B is independently selected from hydrogen, hydroxyl, C1-C6 alkoxy, C3-C6 cycloalkyl, C2-C6 alkenyl, and C1-C6 alkyl optionally substituted with hydroxyl or C1-C6 alkoxy,
 30 or R^A and R^B together with the nitrogen atom to which they are attached form a 4-10 membered

heterocyclyl optionally substituted with 1-2 substituents independently selected from halogen, C1-C6 alkyl, and $-C(=O)C1-C6$ alkyl;

each R^C is independently selected from C3-C6 cycloalkyl, $-C(=O)NHR^{Y1}$, and a C1-C6 alkyl optionally substituted with $-NR^A R^B$ or with 4-10 membered heterocyclyl optionally substituted with C1-C6 alkyl or with C1-C6 hydroxylalkyl;

each R^D and R^E is independently selected from hydrogen, hydroxyl, phenyl, C1-C6 alkoxy, and C1-C6 alkyl optionally substituted with oxo or $-NR^A R^B$;

each R^{3A} and R^{3B} is independently selected from hydrogen, C1-C6 alkyl, C1-C6 alkoxy, and C1-C6 haloalkyl, or R^{3A} and R^{3B} , together with the carbon and nitrogen atoms, respectively, to which they are attached together form a 4-8 membered heterocyclyl group;

R^4 is hydrogen, halogen, C1-C6 alkyl, or acrylamido;

R^5 is hydrogen, halogen, C1-C6 alkyl, cyano, $-NR^{5A} R^{5B}$, $-NR^{5A} C(=O)R^{5B}$, or $-C(=O)NR^{5A} R^{5B}$;

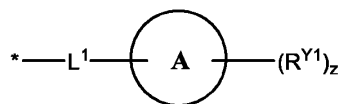
R^{5A} and R^{5B} are independently selected from hydrogen, C1-C6 alkyl, C2-C6 alkenyl, and C1-C6 hydroxyalkyl;

R^6 is hydrogen, halogen, or C1-C6 alkyl;

X is a bond, CH_2 , $CH(CH_3)$, $C(CH_3)_2$, or ;

W is NR^{3B} or O;

Y is phenyl, naphthyl, or 5-10 membered heteroaryl, wherein the phenyl, naphthyl, and 5-10 membered heteroaryl are optionally and independently substituted with 1-3 independently



selected R^Y or , wherein * represents the connection of L^1 to the remainder of the compound of Formula (I);

each R^Y is independently selected from: halogen, cyano, hydroxyl, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkoxy, C1-C6 hydroxyalkyl, $-(CH_2)_n-C(=O)R^F$, $-(CH_2)_n-NHC(=O)R^F$, $-(CH_2)_n-NHC(=O)OR^F$, $-C(=O)C(=O)NHR^F$, $-CO_2R^G$, $-(CH_2)_n-SO_2NR^H R^I$, $-(CH_2)_n-NHSO_2R^J$, $-(CH_2)_n-S(=O)(=NR^H)R^J$, $-(CH_2)_n-SO_2R^J$, $-(CH_2)_n-C(=O)NR^H R^I$, $-(CH_2)_n-C(=O)NR^H OR^I$, and C1-C6 haloalkyl optionally substituted with hydroxyl;

each R^F is independently selected from: C3-C6 cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocyclyl optionally substituted with C1-C6 alkyl; and C1-C6 alkyl optionally substituted with hydroxyl or $-\text{SO}_2(\text{C1-C6 alkyl})$;

each R^G is independently selected from: hydrogen, C3-C6 cycloalkyl, 5-6 membered heteroaryl, 4-6 membered heterocyclyl, and C1-C6 alkyl optionally substituted with hydroxyl or $-\text{SO}_2(\text{C1-C6 alkyl})$;

each R^H and R^I is independently selected from: hydrogen, C1-C6 alkoxy, C3-C6 cycloalkyl, C2-C6 alkenyl, $-(\text{CH}_2)_n-\text{C}(=\text{O})\text{NH}_2$, $-(\text{CH}_2)_n-\text{SO}_2\text{NH}_2$, $-(\text{CH}_2)_n-\text{SO}_2(\text{C1-C6 alkyl})$, C1-C6 alkyl optionally substituted with 1-2 substituents independently selected from hydroxyl, $-\text{SO}_2(\text{C1-C6 alkyl})$, C1-C6 alkoxy, 5-6 membered heteroaryl, C3-C6 cycloalkyl, and $-\text{C}(=\text{O})\text{NR}^{K1}\text{R}^{K2}$; or R^H and R^I together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclyl optionally substituted with 1-2 substituents independently selected from halogen, C1-C6 alkyl, and $-\text{C}(=\text{O})\text{C1-C6 alkyl}$;

R^J is C1-C6 alkyl, C3-C6 cycloalkyl, or C1-C6 alkoxy;

each R^{K1} and R^{K2} is independently hydrogen or C1-C6 alkyl;

Ring A is phenyl, 4-10 membered heteroaryl, 4-10 membered heterocyclyl, or C4-C10 cycloalkyl;

L^1 is a bond, C1-C6 alkoxy, $-(\text{CH}_2)_n-\text{NHC}(=\text{O})-$, $-\text{C}(=\text{O})\text{NH}-(\text{CH}_2)_n-$, $-\text{CO}_2-$, $-\text{SO}_2-$, $-\text{NHSO}_2-$, $-\text{SO}_2\text{NH}-$, $-\text{S}(=\text{O})(=\text{NR}^G)-$, $-\text{SO}_2(\text{C1-C6 alkylene})-$, $-\text{C}(=\text{O})\text{C}(=\text{O})\text{NH}-$, or C1-C6 alkylene optionally substituted with oxo;

each R^{Y1} is independently selected from: cyano, hydroxyl, halogen, $-\text{C}(=\text{O})\text{R}^F$, $-\text{NHC}(=\text{O})\text{R}^F$, $-\text{CO}_2\text{R}^G$, $-\text{SO}_2\text{NR}^H\text{R}^I$, $-\text{NHSO}_2\text{R}^J$, $-\text{S}(=\text{O})(=\text{NR}^H)\text{R}^J$, $-\text{SO}_2(\text{C1-C6 alkyl})$, $-\text{C}(=\text{O})\text{NR}^H\text{R}^I$, 4-6 membered heteroaryl, C1-C6 alkoxy optionally substituted with R^{Y2} , C1-C6 haloalkyl, C1-C6 alkyl optionally substituted with R^{Y2} , and 4-6 membered heterocyclyl optionally substituted with hydroxyl or C1-C6 alkyl;

R^{Y2} is hydroxyl, $-\text{NR}^H\text{R}^I$, $-\text{C}(=\text{O})\text{NR}^H\text{R}^I$, or $-\text{SO}_2\text{NR}^H\text{R}^I$;

n is 0, 1, or 2; and

z is 0, 1, 2, or 3.

2. The compound of Claim 1, wherein Z is CH.

3. The compound of Claim 1, wherein Z is N.

4. The compound of any one of Claims 1-3, wherein R^I is hydrogen.

5. The compound of any one of Claims 1-3, wherein R^1 is halogen.
6. The compound of any one of Claims 1-3, wherein R^1 cyano.
7. The compound of any one of Claims 1-3, wherein R^1 is C3-C6 cycloalkyl.
8. The compound of any one of Claims 1-3, wherein R^1 is C1-C6 alkyl optionally
5 substituted with C3-C6 cycloalkyl, or 4-10 membered heterocyclyl.
9. The compound of any one of Claims 1-3 or 8, wherein R^1 is C1-C6 alkyl
10. The compound of any one of Claims 1-3, 8, or 9, wherein R^1 is methyl.
11. The compound of any one of Claims 1-3, wherein R^1 is 4-10 membered
heterocyclyl optionally substituted with C1-C6 alkyl.
12. The compound of any one of Claims 1-3, wherein R^1 is C1-C6 thioalkyl.
13. The compound of any one of Claims 1-3, wherein R^1 is C1-C6 haloalkyl.
14. The compound of any one of Claims 1-3, wherein R^1 is C1-C6 alkoxy.
15. The compound of any one of Claims 1-3, wherein R^1 is C1-C6 alkoxyalkyl.
16. The compound of any one of Claims 1-15, wherein R^2 is C6-C10 aryl optionally
15 substituted with 1-4 independently selected R^{2A} .
17. The compound of any one of Claims 1-15, wherein R^2 is phenyl optionally
substituted with 1-4 independently selected R^{2A} .
18. The compound of any one of Claims 1-15, wherein R^2 is 5-10 membered heteroaryl
optionally substituted with 1-4 independently selected R^{2A} .
19. The compound of any one of Claims 1-15, wherein R^2 is 4-10 membered
20 heterocyclyl optionally substituted with 1-3 independently selected R^{2A} .
20. The compound of any one of Claims 1-15, wherein R^2 is 4-10 membered
heterocyclyl substituted with 1-3 independently selected R^{2A} .
21. The compound of any one of Claims 1-15, wherein R^2 is 4-10 membered
25 heterocyclyl.
22. The compound of any one of Claims 1-15, wherein R^2 is C4-C10 cycloalkyl
optionally substituted with 1-3 independently selected R^{2A} .
23. The compound of any one of Claims 1-15, wherein R^2 is 4-10 membered
heterocycloxy optionally substituted with 1-4 independently selected R^{2A} .
24. The compound of any one of Claims 1-15, wherein R^2 is 5-10 heteroaryloxy
30 optionally substituted with 1-4 independently selected R^{2A} .

25. The compound of any one of Claims 1-15, wherein R^2 is C1-C6 alkoxy optionally substituted with $-C(=O)NR^A R^C$, C4-C10 cycloalkyl, 4-10 membered heterocyclyl, 5-10 membered heteroaryl, or phenyl.

26. The compound of any one of Claims 1-15, wherein R^2 is C1-C6 alkoxyalkyl optionally substituted with $-C(=O)NR^A R^C$.

27. The compound of any one of Claims 1-26, wherein each R^{2A} is independently selected from:

(i) halogen;

(ii) C3-C6 cycloalkyl optionally substituted with hydroxyl, $-C(=O)NR^A R^B$, or $-C(=N)OR^D$;

(iii) methyl;

(iv) C1-C2 haloalkyl;

(v) 4-6 membered heterocyclyl optionally substituted with 1-3 substituents independently selected from halogen, hydroxyl, $-C(=O)NR^A R^B$, $-C(=O)C1-C6$ alkyl, $-NR^A R^B$, and C1-C6 alkyl optionally substituted with hydroxyl; and

(vi) 5-6 membered heteroaryl optionally substituted with halogen, cyano, C1-C6 alkyl optionally substituted with hydroxyl, hydroxyl, $-C(=O)NR^A R^B$, $-NR^A R^B$, or 4-10 membered heterocyclyl optionally substituted with hydroxyl or C1-C6 alkyl.

28. The compound of any one of Claims 1-27, wherein X is a bond.

29. The compound of any one of Claims 1-27, wherein X is CH_2 .

30. The compound of any one of Claims 1-27, wherein X is $CH(CH_3)$.

31. The compound of any one of Claims 1-27, wherein X is $C(CH_3)_2$.

32. The compound of any one of Claims 1-27, wherein X is .

33. The compound of any one of Claims 1-32, wherein W is O.

34. The compound of any one of Claims 1-33, wherein R^{3A} is hydrogen.

35. The compound of any one of Claims 1-33, wherein R^{3A} is C1-C6 alkyl.

36. The compound of any one of Claims 1-33, wherein R^{3A} is C1-C6 alkoxy.

37. The compound of any one of Claims 1-33, wherein R^{3A} is C1-C6 haloalkyl.

38. The compound of any one of Claims 1-32, wherein W is NR^{3B} .

39. The compound of any one of Claims 1-32 or 38, wherein R^{3B} is hydrogen.

40. The compound of any one of Claims 1-32 or 38, wherein R^{3B} is methyl.

41. The compound of any one of Claims 1-40, wherein Y is unsubstituted 5-10 membered heteroaryl.

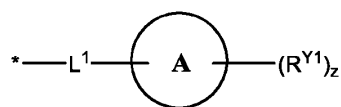
42. The compound of any one of Claims 1-40, wherein Y is phenyl optionally substituted with 1-3 independently selected R^Y .

43. The compound of any one of Claims 1-40, wherein Y is naphthyl optionally substituted with 1-3 independently selected R^Y .

44. The compound of any one of Claims 1-40, wherein Y is 5-10 membered heteroaryl optionally substituted with 1-3 independently selected R^Y .

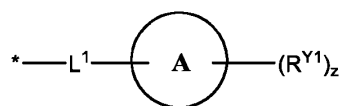
45. The compound of any one of Claims 1-40 or 42-44, wherein each R^Y is independently selected from: halogen, $-\text{CO}_2\text{H}$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{CH}_3$, $-\text{C}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{O})\text{NHR}^H$, $-(\text{CH}_2)_n-\text{C}(=\text{O})\text{NHOR}^I$ and $-(\text{CH}_2)_n-\text{S}(=\text{O})(=\text{NH})\text{R}^J$.

46. The compound of any one of Claims 1-40, wherein Y is phenyl substituted with



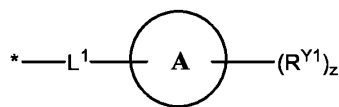
, wherein * represents the connection of L^1 to the remainder of the compound of Formula (I).

47. The compound of any one of Claims 1-40, wherein Y is naphthyl substituted with



, wherein * represents the connection of L^1 to the remainder of the compound of Formula (I).

48. The compound of any one of Claims 1-40, wherein Y is 5-10 membered heteroaryl



substituted with, wherein * represents the connection of L^1 to the remainder of the compound of Formula (I).

49. The compound of any one of Claims 1-40 or 46-48, wherein each R^{Y1} is independently selected from: hydroxyl, cyano, $-\text{SO}_2\text{NH}_2$, $-\text{C}(=\text{O})\text{R}^F$, $-\text{C}(=\text{O})\text{NH}_2$, C1-C3 alkoxy optionally substituted with hydroxyl, and C1-C3 alkyl optionally substituted with hydroxyl.

50. The compound of any one of Claims 1-49, wherein R^4 is hydrogen.

51. The compound of any one of Claims 1-49, wherein R^4 is halogen.

52. The compound of any one of Claims 1-49, wherein R^4 is C1-C6 alkyl.
53. The compound of any one of Claims 1-49, wherein R^4 is acrylamido.
54. The compound of any one of Claims 1-53, wherein R^5 is hydrogen.
55. The compound of any one of Claims 1-53, wherein R^5 is halogen.
- 5 56. The compound of any one of Claims 1-53, wherein R^5 is C1-C6 alkyl.
57. The compound of any one of Claims 1-53, wherein R^5 is cyano.
58. The compound of any one of Claims 1-53, wherein R^5 is $-NR^{5A}R^{5B}$.
59. The compound of any one of Claims 1-53, wherein R^5 is $-C(=O)NR^{5A}R^{5B}$.
- 10 60. The compound of any one of Claims 1-53, wherein R^5 is $-NR^{5A}C(=O)R^{5B}$.
61. The compound of any one of Claims 1-60, wherein R^6 is hydrogen.
62. The compound of any one of Claims 1-60, wherein R^6 is halogen.
63. The compound of any one of Claims 1-60, wherein R^6 is C1-C6 alkyl.
64. The compound of any one of Claims 1-50, wherein R^4 is hydrogen, R^5 is methyl,
15 and R^6 is hydrogen.
65. The compound of any one of Claims 1-50, wherein R^4 is hydrogen, R^5 is chloro,
and R^6 is hydrogen.
66. The compound of Claim 64 or 65, wherein R^1 is methyl or cyano.
67. A compound selected from the group consisting of the compounds in Table A, or a
20 pharmaceutically acceptable salt thereof.
68. A pharmaceutical composition comprising a compound of any one of Claims 1-67,
or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable
excipients.
69. A method for treating cancer in a subject in need thereof, comprising administering
25 to the subject a therapeutically effective amount of a compound of any one of Claims 1-67, or a
pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 68.
70. A method for treating cancer in a subject in need thereof, the method comprising
(a) determining that the cancer is associated with a dysregulation of a *PIK3CA* gene, a PI3K α
protein, or expression or activity or level of any of the same; and (b) administering to the subject
30 a therapeutically effective amount of a compound of any one of Claims 1-67, or a pharmaceutically
acceptable salt thereof, or a pharmaceutical composition of Claim 68.

71. A method of treating a PI3K α -associated cancer in a subject, comprising administering to a subject identified or diagnosed as having a PI3K α -associated cancer a therapeutically effective amount of a compound of any one of Claims 1-67 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 68.

5 72. A method for inhibiting mutant PI3K α activity in a mammalian cell, the method comprising contacting the mammalian cell with an effective amount of a compound of any one of Claims 1-67, or a pharmaceutically acceptable salt thereof.