



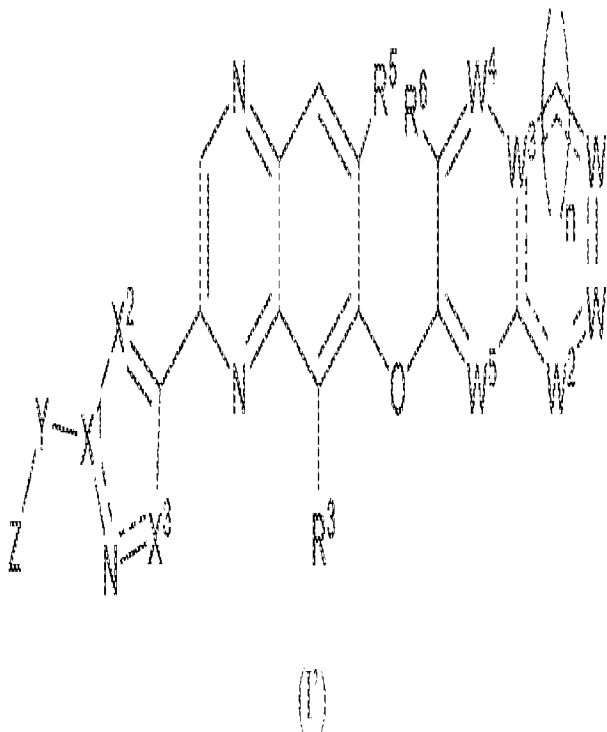
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(54) **Titre : DERIVES DE QUINOXALINE ET LEURS UTILISATIONS**
(54) **Title: QUINOXALINE DERIVATIVES AND USES THEREOF**



(57) **Abstrégé/Abstract:**

The present disclosure relates compounds of Formula (I'): and pharmaceutically acceptable salts and stereoisomers thereof. The present disclosure also relates to methods of preparing the compounds, compositions comprising the compounds, and methods of using the compounds, e.g., in the treatment of cancer.



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Abstract:

The present disclosure relates compounds of Formula (I'): and pharmaceutically acceptable salts and stereoisomers thereof. The present disclosure also relates to methods of preparing the compounds, compositions comprising the compounds, and methods of using the compounds, e.g., in the treatment of cancer.

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

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QUINOXALINE DERIVATIVES AND USES THEREOF

RELATED APPLICATIONS

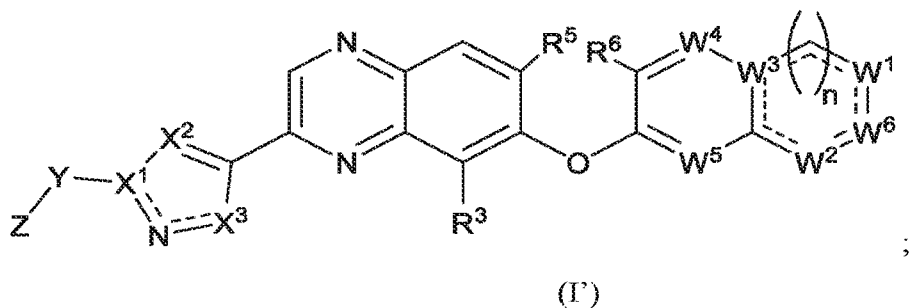
[0001] The application claims priority to, and the benefit of, U.S. Provisional Application Nos. 63/146,312, filed on February 5, 2021, 63/223,255, filed on July 19, 2021, and 63/242,260, filed September 9, 2021, the contents of each of which are incorporated herein by reference in their entirety.

BACKGROUND

[0002] Specific mutations in the human genes *FGFR2* and *FGFR3*, which encode for the proteins FGFR2 and FGFR3 respectively, have been associated with several different types of cancers. A variety of different inhibitors for FGFR2 and/or FGFR3 have been developed for the treatment of cancer, including FDA-approved drugs such as erdafitinib and pemigatinib. However, existing inhibitors exhibit a variety of flaws that limit their effectiveness in the clinical. First, some of the existing inhibitors target only FGFR2 and fail to inhibit FGFR3, limiting their ability to treat certain types of cancers. Additionally, several of the existing inhibitors also target FGFR1, leading to dose-limiting toxicities such as hyperphosphatemia. Finally, following administration of some existing inhibitors, many patients develop additional mutations in FGFR2 and/or FGFR3, referred to as gatekeeper mutations, that results in resistance to the existing inhibitors. Thus, there is a long-felt need in the art for new therapies that specifically target FGFR2 and FGFR3. The present disclosure provides compositions and methods for preventing or treating cancer in patients with overexpression of and/or oncogenic mutations in *FGFR2* and/or *FGFR3*, and the FGFR2 and/or FGFR3.

SUMMARY

[0003] In some aspects, the present disclosure provides a compound of Formula (I):



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

each $\equiv$ independently represents a single bond or a double bond;

n is 0 or 1;

W^1 is $C(R^{W1})$ when connected to one double bond and one single bond, $N(R^{W1})$ when connected to two single bonds, or N when connected to one double bond and one single bond;

R^{W1} is H, C₁-C₆ alkyl, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^2 is $C(R^{W2})$ when connected to one double bond and one single bond, $N(R^{W2})$ or O when connected to two single bonds, or N when connected to one double bond and one single bond;

R^{W2} is H, C₁-C₆ alkyl, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^3 is C or N;

W^4 is $C(R^{W4})$ or N;

R^{W4} is H, halogen, cyano, C₁-C₆ alkyl, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^5 is $C(R^{W5})$ or N;

R^{W5} is H, halogen, cyano, C₁-C₆ alkyl, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^6 is $C(R^{W6})$ when connected to one double bond and one single bond, $N(R^{W6})$ when connected to two single bonds, or N when connected to one double bond and one single bond;

R^{W6} is H, halogen, cyano, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

X^1 is C or N;

X^2 is N, O, or $C(R^{X2})$;

R^{X2} is H or C₁-C₆ alkyl;

X^3 is N, O, or $C(R^{X3})$;

R^{X3} is H or C₁-C₆ alkyl;

R^3 is H, halogen, cyano, NH_2 , $-NH(C_1-C_6 \text{ alkyl})$, $-NHC(=O)(C_1-C_6 \text{ haloalkyl})$, $-NHC(=O)O(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)H$, $-C(=O)(C_1-C_6 \text{ alkyl})$, $-C(=O)O(C_1-C_6 \text{ alkyl})$, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the $-NH(C_1-C_6 \text{ alkyl})$, $-NHC(=O)(C_1-C_6 \text{ haloalkyl})$, $-NHC(=O)O(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)H$, $-C(=O)(C_1-C_6 \text{ alkyl})$, $-C(=O)O(C_1-C_6 \text{ alkyl})$, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered

heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, is optionally substituted with one or more R^{3a};

each R^{3a} independently is halogen, cyano, oxo, -OH, NH₂, -NH(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the NHC(=O)O(C₁-C₆ alkyl) is optionally substituted with one or more halogen;

R⁵ is H, halogen, cyano, or C₁-C₆ alkyl;

R⁶ is H, halogen, cyano, or C₁-C₆ alkyl;

Y is absent, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₁-C₆ alkoxy, wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₁-C₆ alkoxy is optionally substituted with one or more halogen, oxo, cyano, -OH, NH₂, -NH(C₁-C₆ alkyl)-OH, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy optionally substituted with -(C₁-C₆ alkyl)(C₆-C₁₀ aryl), or C₃-C₁₂ cycloalkyl;

Z is absent, H, C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl or 5- to 10-membered heteroaryl, is optionally substituted with one or more R^Z;

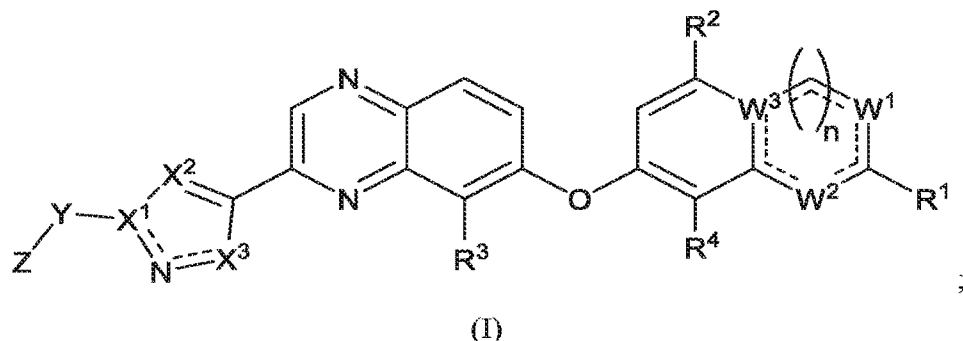
each R^Z independently is oxo, halogen, cyano, -OH, =NR^{Za}, NH₂, NHR^{Za}, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(C₁-C₆ alkyl), -S(=O)(=NR^{Za})-(C₁-C₆ alkyl), -S(=O)₂-(C₁-C₆ alkyl), -S(=O)₂-(C₂-C₆ alkenyl), -C(=O)(3- to 12-membered heterocycloalkyl), -C(=O)NH(C₁-C₆ alkyl), -C(=O)NR^{Za}, -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), -C(=O)-(C₁-C₆ alkoxy), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, or 5- to 10-membered heteroaryl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{Za};

each R^{Za} independently is H, oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, or 3- to 12-membered heterocycloalkyl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -

C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, or 3- to 12-membered heterocycloalkyl is optionally substituted with one or more R^{Zb}; and

each R^{Zb} independently is oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, or C₁-C₆ alkoxy.

[0004] In some aspects, the present disclosure provides compound of Formula (I):



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

each $\equiv$ independently represents a single bond or a double bond;

n is 0 or 1;

W¹ is C(R^{W1}) when connected to one double bond and one single bond, N(R^{W1}) when connected to two single bonds, or N when connected to one double bond and one single bond;

R^{W1} is H, C₁-C₆ alkyl, or -S(=O)₂-(C₁-C₆ alkyl);

W² is C(R^{W2}) when connected to one double bond and one single bond, N(R^{W2}) when connected to two single bonds, or N when connected to one double bond and one single bond;

R^{W2} is H, C₁-C₆ alkyl, or -S(=O)₂-(C₁-C₆ alkyl);

W³ is C or N;

X¹ is C or N;

X² is N, O, or C(R^{X2});

R^{X2} is H or C₁-C₆ alkyl;

X³ is N, O, or C(R^{X3});

R^{X3} is H or C₁-C₆ alkyl;

R¹ is H, halogen, cyano, or C₁-C₆ alkyl;

R² is H, halogen, cyano, or C₁-C₆ alkyl;

R³ is H, halogen, cyano, or C₁-C₆ alkyl;

R⁴ is H, halogen, cyano, or C₁-C₆ alkyl;

Y is absent or C₁-C₆ alkyl optionally substituted with one or more oxo or -OH;

Z is H, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl, wherein the C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^Z;

each R^Z independently is oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{Za};

each R^{Za} independently is oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{Zb};

and

each R^{Zb} independently is oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, or C₁-C₆ alkoxy.

[0005] In some aspects, the present disclosure provides an isotopic derivative of a compound described herein.

[0006] In some aspects, the present disclosure provides a method of preparing a compound described herein.

[0007] In some aspects, the present disclosure provides a pharmaceutical composition comprising a compound described herein and one or more pharmaceutically acceptable carriers or excipients.

[0008] In some aspects, the present disclosure provides a method of treating or preventing cancer in a subject, the method comprising administering to the subject a therapeutically effective amount of a compound described herein.

[0009] In some aspects, the present disclosure provides a compound described herein for treating

or preventing cancer in a subject.

[0010] In some aspects, the present disclosure provides a use of a compound described herein in the manufacture of a medicament for treating or preventing cancer in a subject.

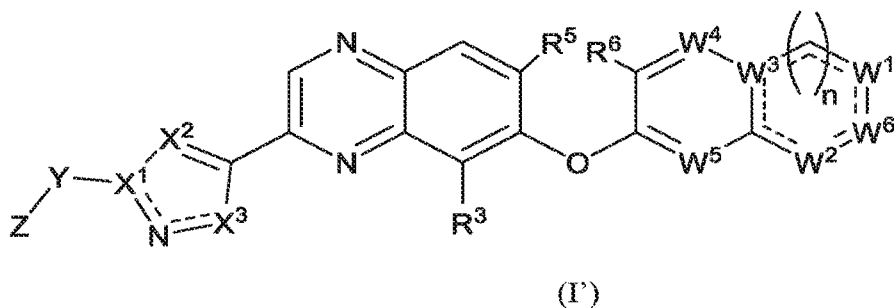
[0011] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below. All publications, patent applications, patents and other references mentioned herein are incorporated by reference. The references cited herein are not admitted to be prior art to the claimed invention. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods and examples are illustrative only and are not intended to be limiting. In the case of conflict between the chemical structures and names of the compounds disclosed herein, the chemical structures will control.

[0012] Other features and advantages of the disclosure will be apparent from the following detailed description and claims.

DETAILED DESCRIPTION

Compounds of the Present Disclosure

[0013] In some aspects, the present disclosure provides a compound of Formula (I'):



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

each $\equiv$ independently represents a single bond or a double bond;

n is 0 or 1;

W^1 is $C(R^{W1})$ when connected to one double bond and one single bond, $N(R^{W1})$ when connected to two single bonds, or N when connected to one double bond and one single bond;

R^{W1} is H, C_1 - C_6 alkyl, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^2 is $C(R^{W2})$ when connected to one double bond and one single bond, $N(R^{W2})$ or O when connected to two single bonds, or N when connected to one double bond and one single bond;

R^{W2} is H, C₁-C₆ alkyl, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^3 is C or N;

W^4 is $C(R^{W4})$ or N;

R^{W4} is H, halogen, cyano, C₁-C₆ alkyl, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^5 is $C(R^{W5})$ or N;

R^{W5} is H, halogen, cyano, C₁-C₆ alkyl, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^6 is $C(R^{W6})$ when connected to one double bond and one single bond, $N(R^{W6})$ when connected to two single bonds, or N when connected to one double bond and one single bond;

R^{W6} is H, halogen, cyano, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

X^1 is C or N;

X^2 is N, O, or $C(R^{X2})$;

R^{X2} is H or C₁-C₆ alkyl;

X^3 is N, O, or $C(R^{X3})$;

R^{X3} is H or C₁-C₆ alkyl;

R^3 is H, halogen, cyano, NH_2 , $-NH(C_1-C_6 \text{ alkyl})$, $-NHC(=O)(C_1-C_6 \text{ haloalkyl})$, $-NHC(=O)O(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)H$, $-C(=O)(C_1-C_6 \text{ alkyl})$, $-C(=O)O(C_1-C_6 \text{ alkyl})$, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the $-NH(C_1-C_6 \text{ alkyl})$, $-NHC(=O)(C_1-C_6 \text{ haloalkyl})$, $-NHC(=O)O(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)H$, $-C(=O)(C_1-C_6 \text{ alkyl})$, $-C(=O)O(C_1-C_6 \text{ alkyl})$, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, is optionally substituted with one or more R^{3a} ;

each R^{3a} independently is halogen, cyano, oxo, $-OH$, NH_2 , $-NH(C_1-C_6 \text{ alkyl})$, $-NHC(=O)O(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)(C_1-C_6 \text{ alkyl})$, $-C(=O)O(C_1-C_6 \text{ alkyl})$, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl,

3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the NHC(=O)O(C₁-C₆ alkyl) is optionally substituted with one or more halogen;

R⁵ is H, halogen, cyano, or C₁-C₆ alkyl;

R⁶ is H, halogen, cyano, or C₁-C₆ alkyl;

Y is absent, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₁-C₆ alkoxy, wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₁-C₆ alkoxy is optionally substituted with one or more halogen, oxo, cyano, -OH, NH₂, -NH(C₁-C₆ alkyl)-OH, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy optionally substituted with -(C₁-C₆ alkyl)(C₆-C₁₀ aryl), or C₃-C₁₂ cycloalkyl;

Z is absent, H, C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl or 5- to 10-membered heteroaryl, is optionally substituted with one or more R^Z;

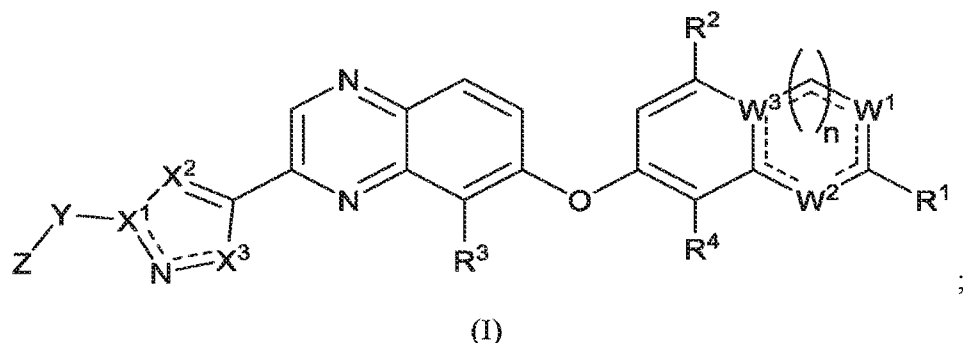
each R^Z independently is oxo, halogen, cyano, -OH, =NR^{Za}, NH₂, NHR^{Za}, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(C₁-C₆ alkyl), -S(=O)(=NR^{Za})-(C₁-C₆ alkyl), -S(=O)₂-(C₁-C₆ alkyl), -S(=O)₂-(C₂-C₆ alkenyl), -C(=O)(3- to 12-membered heterocycloalkyl), -C(=O)NH(C₁-C₆ alkyl), -C(=O)NR^{Za}, -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), -C(=O)-(C₁-C₆ alkoxy), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, or 5- to 10-membered heteroaryl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{Za};

each R^{Za} independently is H, oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, or 3- to 12-membered heterocycloalkyl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, or 3- to 12-membered heterocycloalkyl is optionally substituted with one or more R^{Zb};

and

each R^{Zb} independently is oxo, halogen, cyano, -OH, NH_2 , $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, or $C_1-C_6 \text{ alkoxy}$.

[0014] In some aspects, the present disclosure provides a compound of Formula (I):



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

each $\equiv$ independently represents a single bond or a double bond;

n is 0 or 1;

W^1 is $C(R^{W1})$ when connected to one double bond and one single bond, $N(R^{W1})$ when connected to two single bonds, or N when connected to one double bond and one single bond;

R^{W1} is H , $C_1-C_6 \text{ alkyl}$, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^2 is $C(R^{W2})$ when connected to one double bond and one single bond, $N(R^{W2})$ when connected to two single bonds, or N when connected to one double bond and one single bond;

R^{W2} is H , $C_1-C_6 \text{ alkyl}$, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^3 is C or N ;

X^1 is C or N ;

X^2 is N , O , or $C(R^{X2})$;

R^{X2} is H or $C_1-C_6 \text{ alkyl}$;

X^3 is N , O , or $C(R^{X3})$;

R^{X3} is H or $C_1-C_6 \text{ alkyl}$;

R^1 is H , halogen, cyano, or $C_1-C_6 \text{ alkyl}$;

R^2 is H , halogen, cyano, or $C_1-C_6 \text{ alkyl}$;

R^3 is H , halogen, cyano, or $C_1-C_6 \text{ alkyl}$;

R^4 is H , halogen, cyano, or $C_1-C_6 \text{ alkyl}$;

Y is absent or $C_1-C_6 \text{ alkyl}$ optionally substituted with one or more oxo or -OH;

Z is H, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl, wherein the C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^Z;

each R^Z independently is oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxyl, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxyl, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{Za};

each R^{Za} independently is oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxyl, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxyl, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{Zb}; and

each R^{Zb} independently is oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, or C₁-C₆ alkoxyl.

[0015] In some aspects, the present disclosure provides a compound of Formula (I'), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

each $\equiv$ independently represents a single bond or a double bond;

n is 0;

W¹ is C(R^{W1}) when connected to one double bond and one single bond, N(R^{W1}) when connected to two single bonds, or N when connected to one double bond and one single bond;

R^{W1} is H;

W² is C(R^{W2}) when connected to one double bond and one single bond, N(R^{W2}) or O when connected to two single bonds, or N when connected to one double bond and one single bond;

R^{W2} is H;

W³ is N;

W⁴ is C(R^{W4});

R^{W4} is H or halogen;

W^5 is $C(R^{W5})$;

R^{W5} is H or halogen;

W^6 is $C(R^{W6})$ when connected to one double bond and one single bond, $N(R^{W6})$ when connected to two single bonds, or N when connected to one double bond and one single bond;

R^{W6} is H or C₁-C₆ alkyl;

X^1 is N;

X^2 is $C(R^{X2})$;

R^{X2} is H or C₁-C₆ alkyl;

X^3 is $C(R^{X3})$;

R^{X3} is H or C₁-C₆ alkyl;

R^3 is H, halogen, cyano, NH_2 , $NHC(=O)O(C_1-C_6 \text{ alkyl})$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)(C_1-C_6 \text{ alkyl})$, $-C(=O)O(C_1-C_6 \text{ alkyl})$, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, or 5- to 10-membered heteroaryl, wherein the $NHC(=O)O(C_1-C_6 \text{ alkyl})$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)(C_1-C_6 \text{ alkyl})$, $-C(=O)O(C_1-C_6 \text{ alkyl})$, C₁-C₆ alkyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, or 5- to 10-membered heteroaryl, is optionally substituted with one or more R^{3a} ;

each R^{3a} independently is halogen, oxo, $NHC(=O)O(C_1-C_6 \text{ alkyl})$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)(C_1-C_6 \text{ alkyl})$, $-C(=O)O(C_1-C_6 \text{ alkyl})$, C₁-C₆ alkyl, or C₂-C₆ alkenyl, wherein the $NHC(=O)O(C_1-C_6 \text{ alkyl})$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)(C_1-C_6 \text{ alkyl})$, $-C(=O)O(C_1-C_6 \text{ alkyl})$, C₁-C₆ alkyl, or C₂-C₆ alkenyl is optionally substituted with one or more halogen;

R^5 is H or C₁-C₆ alkyl;

R^6 is H or halogen;

Y is absent, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₁-C₆ alkoxy, wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₁-C₆ alkoxy is optionally substituted with one or more halogen, oxo, cyano, -OH, NH_2 , C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy optionally substituted with $-(C_1-C_6 \text{ alkyl})(C_6-C_{10} \text{ aryl})$, or C₃-C₁₂ cycloalkyl;

Z is absent, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the C₃-C₁₂ cycloalkyl,

3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl or 5- to 10-membered heteroaryl is optionally substituted with one or more R^Z;

each R^Z independently is oxo, halogen, -OH, =NR^{Za}, NH₂, NHR^{Za}, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(C₁-C₆ alkyl), -S(=O)(=NR^{Za})-(C₁-C₆ alkyl), -S(=O)₂-(C₁-C₆ alkyl), -S(=O)₂-(C₂-C₆ alkenyl), -C(=O)NH(C₁-C₆ alkyl), -C(=O)NR^{Za}, -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), -C(=O)-(C₁-C₆ alkoxy), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, or 5- to 10-membered heteroaryl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(C₁-C₆ alkyl), -S(=O)(=NR^{Za})-(C₁-C₆ alkyl), -S(=O)₂-(C₁-C₆ alkyl), -S(=O)₂-(C₂-C₆ alkenyl), -C(=O)NH(C₁-C₆ alkyl), -C(=O)NR^{Za}, -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), -C(=O)-(C₁-C₆ alkoxy), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{Za};

each R^{Za} independently is H, oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, or 3- to 12-membered heterocycloalkyl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, or 3- to 12-membered heterocycloalkyl is optionally substituted with one or more R^{Zb}; and

each R^{Zb} independently is oxo, halogen, -OH.

[0016] In some aspects, the present disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

each $\equiv$ independently represents a single bond or a double bond;

n is 0 or 1;

W¹ is C(R^{W1}) or N(R^{W1}) when connected to two single bonds, or C or N when connected to one double bond and one single bond;

R^{W1} is H, C₁-C₆ alkyl, or -S(=O)₂-(C₁-C₆ alkyl);

W² is C(R^{W2}) or N(R^{W2}) when connected to two single bonds, or C or N when connected to one double bond and one single bond;

R^{W2} is H, C₁-C₆ alkyl, or -S(=O)₂-(C₁-C₆ alkyl);

W³ is C or N;

X¹ is C or N;

X^2 is N, O, or $C(R^{X2})$;

R^{X2} is H or C₁-C₆ alkyl;

X^3 is N, O, or $C(R^{X3})$;

R^{X3} is H or C₁-C₆ alkyl;

R^1 is H, halogen, cyano, or C₁-C₆ alkyl;

R^2 is H, halogen, cyano, or C₁-C₆ alkyl;

R^3 is H, halogen, cyano, or C₁-C₆ alkyl;

R^4 is H, halogen, cyano, or C₁-C₆ alkyl;

Y is absent or C₁-C₆ alkyl optionally substituted with one or more oxo or -OH;

Z is C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl, wherein the C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^Z ;

each R^Z independently is oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{Za} ;

each R^{Za} independently is oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{Zb} ;

and

each R^{Zb} independently is oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, or C₁-C₆ alkoxy.

[0017] In some aspects, the present disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

each $\equiv$ independently represents a single bond or a double bond;

n is 0 or 1;

W^1 is $C(R^{W1})$ or $N(R^{W1})$ when connected to two single bonds, or C or N when connected to one double bond and one single bond;

R^{W1} is H, C_1 - C_6 alkyl, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^2 is $C(R^{W2})$ or $N(R^{W2})$ when connected to two single bonds, or C or N when connected to one double bond and one single bond;

R^{W2} is H, C_1 - C_6 alkyl, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^3 is C or N;

X^1 is C or N;

X^2 is N, O, or $C(R^{X2})$;

R^{X2} is H or C_1 - C_6 alkyl;

X^3 is N, O, or $C(R^{X3})$;

R^{X3} is H or C_1 - C_6 alkyl;

R^1 is H, halogen, cyano, or C_1 - C_6 alkyl;

R^2 is H, halogen, cyano, or C_1 - C_6 alkyl;

R^3 is H, halogen, cyano, or C_1 - C_6 alkyl;

R^4 is H, halogen, cyano, or C_1 - C_6 alkyl;

Y is C_1 - C_6 alkyl optionally substituted with one or more oxo or -OH;

Z is C_3 - C_8 cycloalkyl or 3- to 8-membered heterocycloalkyl, wherein the C_3 - C_8 cycloalkyl or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^Z ;

each R^Z independently is oxo, halogen, cyano, -OH, NH_2 , $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_3 - C_8 cycloalkyl, or 3- to 8-membered heterocycloalkyl, wherein the $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_3 - C_8 cycloalkyl, or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{Za} ;

each R^{Za} independently is oxo, halogen, cyano, -OH, NH_2 , $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_3 - C_8 cycloalkyl, or 3- to 8-membered heterocycloalkyl, wherein the $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_3 - C_8

cycloalkyl, or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{Zb} , and

each R^{Zb} independently is oxo, halogen, cyano, -OH, NH_2 , $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, or $C_1-C_6 \text{ alkoxyl}$.

Variables n , W^1 , R^{W1} , W^2 , R^{W2} , W^3 , W^4 , R^{W4} , W^5 , R^{W5} , W^6 , and R^{W6}

[0018] In some embodiments, each $\equiv$ independently represents a single bond or a double bond.

[0019] In some embodiments, each $\equiv$ independently represents a single bond. In some embodiments, each $\equiv$ independently represents a double bond.

[0020] In some embodiments, n is 0. In some embodiments, n is 1.

[0021] In some embodiments, W^1 is $C(R^{W1})$ when connected to one double bond and one single bond, $N(R^{W1})$ when connected to two single bonds, or N when connected to one double bond and one single bond.

[0022] In some embodiments, W^1 is $C(R^{W1})$ when connected to one double bond and one single bond.

[0023] In some embodiments, W^1 is $N(R^{W1})$ when connected to two single bonds.

[0024] In some embodiments, W^1 is N when connected to one double bond and one single bond.

[0025] In some embodiments, W^1 is $C(R^{W1})$ or $N(R^{W1})$.

[0026] In some embodiments, W^1 is $C(R^{W1})$. In some embodiments, W^1 is CH .

[0027] In some embodiments, W^1 is $N(R^{W1})$. In some embodiments, W^1 is NH .

[0028] In some embodiments, W^1 is $N(-S(=O)_2-(C_1-C_6 \text{ alkyl}))$. In some embodiments, W^1 is $N(-S(=O)_2-CH_3)$.

[0029] In some embodiments, W^1 is N .

[0030] In some embodiments, R^{W1} is H .

[0031] In some embodiments, R^{W1} is $C_1-C_6 \text{ alkyl}$ or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$.

[0032] In some embodiments, R^{W1} is $C_1-C_6 \text{ alkyl}$.

[0033] In some embodiments, R^{W1} is $-S(=O)_2-(C_1-C_6 \text{ alkyl})$. In some embodiments, R^{W1} is $-S(=O)_2-CH_3$.

[0034] In some embodiments, W^2 is $C(R^{W2})$ when connected to one double bond and one single bond, $N(R^{W2})$ when connected to two single bonds, or N when connected to one double bond and

one single bond.

[0035] In some embodiments, W^2 is $C(R^{W2})$ when connected to one double bond and one single bond.

[0036] In some embodiments, W^2 is $N(R^{W2})$ when connected to two single bonds.

[0037] In some embodiments, W^2 is N when connected to one double bond and one single bond.

[0038] In some embodiments, W^2 is $C(R^{W2})$ or $N(R^{W2})$.

[0039] In some embodiments, W^2 is $C(R^{W2})$. In some embodiments, W^2 is CH.

[0040] In some embodiments, W^2 is $N(R^{W2})$. In some embodiments, W^2 is NH.

[0041] In some embodiments, W^2 is $N(-S(=O)_2-(C_1-C_6 \text{ alkyl}))$. In some embodiments, W^2 is $N(-S(=O)_2-CH_3)$.

[0042] In some embodiments, W^2 is N.

[0043] In some embodiments, R^{W2} is H.

[0044] In some embodiments, R^{W2} is $C_1-C_6 \text{ alkyl}$ or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$.

[0045] In some embodiments, R^{W2} is $C_1-C_6 \text{ alkyl}$.

[0046] In some embodiments, R^{W2} is $-S(=O)_2-(C_1-C_6 \text{ alkyl})$. In some embodiments, R^{W2} is $-S(=O)_2-CH_3$.

[0047] In some embodiments, W^3 is C. In some embodiments, W^3 is N.

[0048] In some embodiments, W^4 is $C(R^{W4})$. In some embodiments, W^4 is CH. In some embodiments, W^4 is $C(\text{halogen})$.

[0049] In some embodiments, W^4 is N.

[0050] In some embodiments, R^{W4} is H.

[0051] In some embodiments, R^{W4} is halogen, cyano, $C_1-C_6 \text{ alkyl}$ or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$.

[0052] In some embodiments, R^{W4} is halogen or cyano.

[0053] In some embodiments, R^{W4} is halogen. In some embodiments, R^{W4} is F, Cl, Br, or I. In some embodiments, R^{W4} is F. In some embodiments, R^{W4} is Cl. In some embodiments, R^{W4} is Br. In some embodiments, R^{W4} is I.

[0054] In some embodiments, R^{W4} is cyano.

[0055] In some embodiments, R^{W4} is $C_1-C_6 \text{ alkyl}$.

[0056] In some embodiments, R^{W4} is $-S(=O)_2-(C_1-C_6 \text{ alkyl})$. In some embodiments, R^{W4} is $-S(=O)_2-CH_3$.

[0057] In some embodiments, W^5 is $C(R^{W5})$. In some embodiments, W^5 is CH. In some

embodiments, W^5 is C(halogen).

[0058] In some embodiments, W^5 is N.

[0059] In some embodiments, R^{W5} is H.

[0060] In some embodiments, R^{W5} is halogen, cyano, C₁-C₆ alkyl or -S(=O)₂-(C₁-C₆ alkyl).

[0061] In some embodiments, R^{W5} is halogen or cyano.

[0062] In some embodiments, R^{W5} is halogen. In some embodiments, R^{W5} is F, Cl, Br, or I. In some embodiments, R^{W5} is F. In some embodiments, R^{W5} is Cl. In some embodiments, R^{W5} is Br. In some embodiments, R^{W5} is I.

[0063] In some embodiments, R^{W5} is cyano.

[0064] In some embodiments, R^{W5} is C₁-C₆ alkyl.

[0065] In some embodiments, R^{W5} is -S(=O)₂-(C₁-C₆ alkyl). In some embodiments, R^{W5} is -S(=O)₂-CH₃.

[0066] In some embodiments, W^6 is C(R^{W6}) when connected to one double bond and one single bond, N(R^{W6}) when connected to two single bonds, or N when connected to one double bond and one single bond.

[0067] In some embodiments, W^6 is C(R^{W6}) when connected to one double bond and one single bond.

[0068] In some embodiments, W^6 is N(R^{W6}) when connected to two single bonds.

[0069] In some embodiments, W^6 is N when connected to one double bond and one single bond.

[0070] In some embodiments, W^6 is C(R^{W6}) or N(R^{W6}).

[0071] In some embodiments, W^6 is C(R^{W6}). In some embodiments, W^6 is CH.

[0072] In some embodiments, W^6 is N(R^{W6}). In some embodiments, W^6 is NH.

[0073] In some embodiments, W^6 is N(-S(=O)₂-(C₁-C₆ alkyl)). In some embodiments, W^6 is N(-S(=O)₂-CH₃).

[0074] In some embodiments, W^6 is N.

[0075] In some embodiments, R^{W6} is H.

[0076] In some embodiments, R^{W6} is halogen, cyano, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, or -S(=O)₂-(C₁-C₆ alkyl).

[0077] In some embodiments, R^{W6} is halogen or cyano.

[0078] In some embodiments, R^{W6} is halogen. In some embodiments, R^{W6} is F, Cl, Br, or I. In some embodiments, R^{W6} is F. In some embodiments, R^{W6} is Cl. In some embodiments, R^{W6} is Br.

In some embodiments, R^{W6} is H.

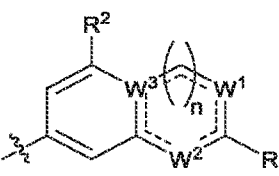
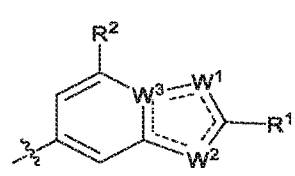
[0079] In some embodiments, R^{W6} is cyano.

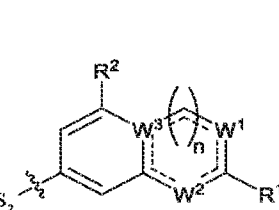
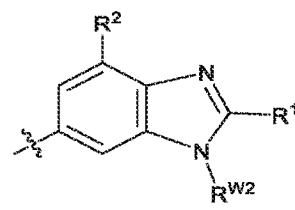
[0080] In some embodiments, R^{W6} is C₁-C₆ alkyl.

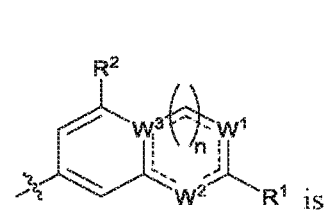
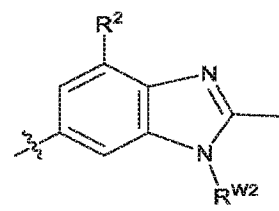
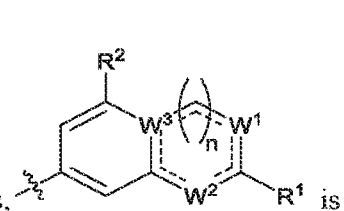
[0081] In some embodiments, R^{W6} is C₁-C₆ alkoxy.

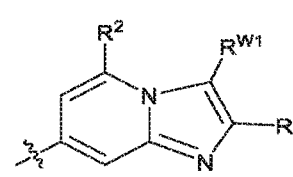
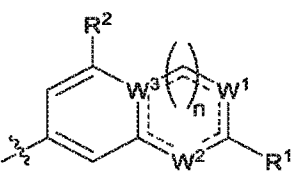
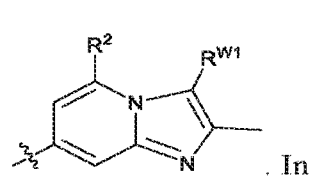
[0082] In some embodiments, R^{W6} is C₁-C₆ haloalkyl.

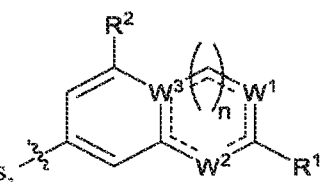
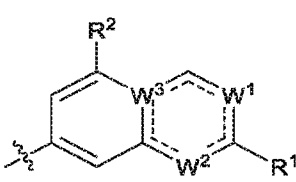
[0083] In some embodiments, R^{W6} is $-S(=O)_2-(C_1-C_6 \text{ alkyl})$. In some embodiments, R^{W1} is $-S(=O)_2-CH_3$.

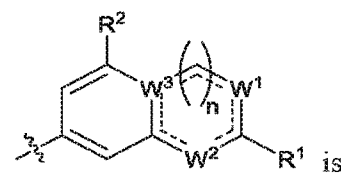
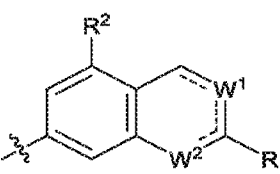
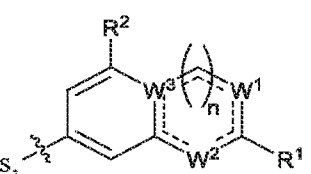
[0084] In some embodiments,  is . In some

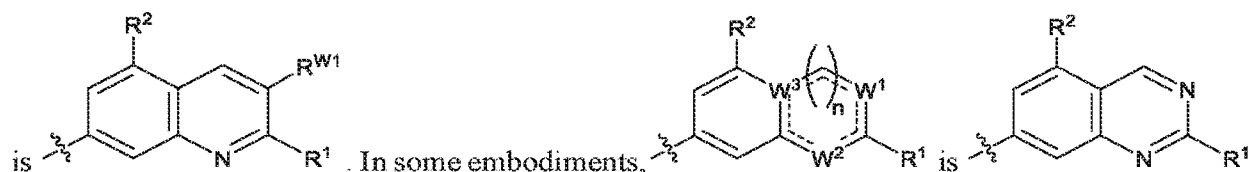
embodiments,  is . In some embodiments,

 is . In some embodiments,  is

. In some embodiments,  is . In

some embodiments,  is . In some embodiments,

 is . In some embodiments, 



Variables X^1 , X^2 , R^{X2} , X^3 , and R^{X3}

[0085] In some embodiments, X^1 is C. In some embodiments, X^1 is N.

[0086] In some embodiments, X^2 is N. In some embodiments, X^2 is O.

[0087] In some embodiments, X^2 is $C(R^{X2})$. In some embodiments, X^2 is CH. In some embodiments, X^2 is $C(C_1-C_6 \text{ alkyl})$. In some embodiments, X^2 is $C(CH_3)$.

[0088] In some embodiments, R^{X2} is H.

[0089] In some embodiments, R^{X2} is $C_1-C_6 \text{ alkyl}$. In some embodiments, R^{X2} is CH_3 .

[0090] In some embodiments, X^3 is N. In some embodiments, X^3 is O.

[0091] In some embodiments, X^3 is $C(R^{X3})$. In some embodiments, X^3 is CH. In some embodiments, X^3 is $C(C_1-C_6 \text{ alkyl})$. In some embodiments, X^3 is $C(CH_3)$.

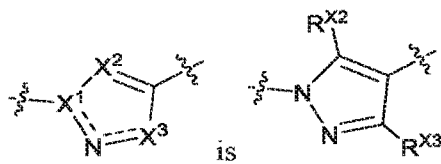
[0092] In some embodiments, R^{X3} is H.

[0093] In some embodiments, R^{X3} is $C_1-C_6 \text{ alkyl}$. In some embodiments, R^{X3} is CH_3 .

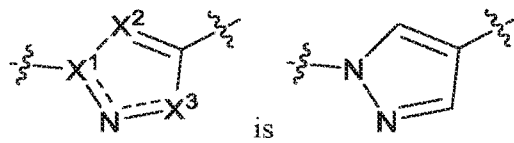
[0094] In some embodiments, X^1 is N, X^2 is $C(R^{X2})$, and X^3 is $C(R^{X3})$.

[0095] In some embodiments, X^1 is C, X^2 is $C(R^{X2})$, and X^3 is O.

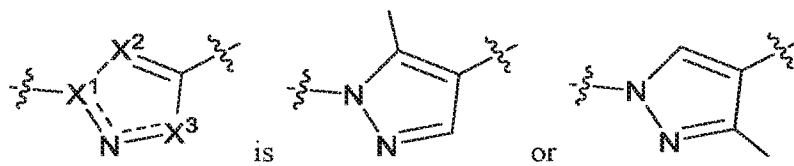
[0096] In some embodiments,

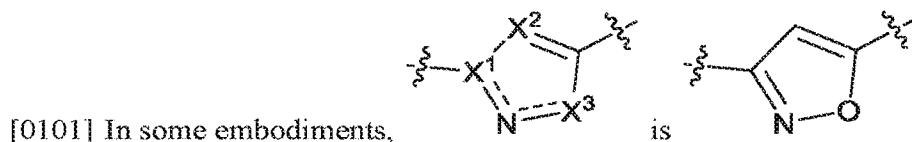
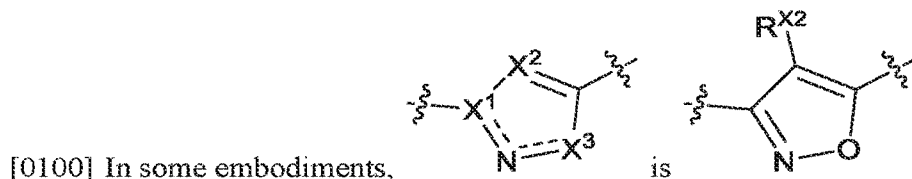
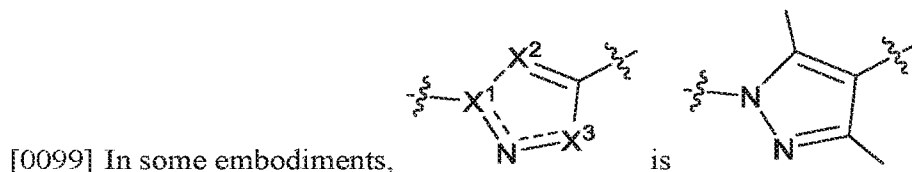


[0097] In some embodiments,



[0098] In some embodiments,





Variables R^1 , R^2 , R^3 , R^{3a} , R^4 , R^5 , and R^6

[0102] In some embodiments, R^1 is H.

[0103] In some embodiments, R^1 is halogen, cyano, or C₁-C₆ alkyl.

[0104] In some embodiments, R^1 is halogen. In some embodiments, R^1 is F or Cl.

[0105] In some embodiments, R^1 is F. In some embodiments, R^1 is Cl.

[0106] In some embodiments, R^1 is cyano.

[0107] In some embodiments, R^1 is C₁-C₆ alkyl. In some embodiments, R^1 is CH₃.

[0108] In some embodiments, R^2 is H.

[0109] In some embodiments, R^2 is halogen, cyano, or C₁-C₆ alkyl.

[0110] In some embodiments, R^2 is halogen. In some embodiments, R^2 is F or Cl.

[0111] In some embodiments, R^2 is F. In some embodiments, R^2 is Cl.

[0112] In some embodiments, R^2 is cyano.

[0113] In some embodiments, R^2 is C₁-C₆ alkyl. In some embodiments, R^2 is CH₃.

[0114] In some embodiments, R^3 is H, halogen, cyano, NH₂, -NH(C₁-C₆ alkyl), -NHC(=O)(C₁-C₆ haloalkyl), -NHC(=O)O(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)H, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the -NH(C₁-C₆ alkyl), -NHC(=O)(C₁-C₆ haloalkyl), -NHC(=O)O(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-

C₆ alkyl), -C(=O)H, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, is optionally substituted with one or more R^{3a}.

[0115] In some embodiments, R³ is H, halogen, cyano, NH₂, -NH(C₁-C₆ alkyl), -NHC(=O)(C₁-C₆ haloalkyl), -NHC(=O)O(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)H, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl.

[0116] In some embodiments, R³ is H.

[0117] In some embodiments, R³ is halogen, cyano, NH₂, -NH(C₁-C₆ alkyl), -NHC(=O)(C₁-C₆ haloalkyl), -NHC(=O)O(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)H, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the -NH(C₁-C₆ alkyl), -NHC(=O)(C₁-C₆ haloalkyl), -NHC(=O)O(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)H, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, is optionally substituted with one or more R^{3a}.

[0118] In some embodiments, R³ is halogen, cyano, NH₂, -NH(C₁-C₆ alkyl), -NHC(=O)(C₁-C₆ haloalkyl), -NHC(=O)O(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)H, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl.

[0119] In some embodiments, R³ is halogen, cyano, NH₂, -NH(C₁-C₆ alkyl), -NHC(=O)(C₁-C₆ haloalkyl), -NHC(=O)O(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)H, -C(=O)(C₁-C₆ alkyl), or -C(=O)O(C₁-C₆ alkyl), wherein the -NH(C₁-C₆ alkyl), -NHC(=O)(C₁-C₆ haloalkyl), -NHC(=O)O(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)H, -C(=O)(C₁-C₆ alkyl), or -C(=O)O(C₁-C₆ alkyl) is optionally substituted with one or more R^{3a}.

[0120] In some embodiments, R³ is halogen, cyano, NH₂, -NH(C₁-C₆ alkyl), -NHC(=O)(C₁-C₆

haloalkyl), -NHC(=O)O(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)H, -C(=O)(C₁-C₆ alkyl), or -C(=O)O(C₁-C₆ alkyl).

[0121] In some embodiments, R³ is NH₂, -NH(C₁-C₆ alkyl), -NHC(=O)(C₁-C₆ haloalkyl), -NHC(=O)O(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)H, -C(=O)(C₁-C₆ alkyl), or -C(=O)O(C₁-C₆ alkyl), wherein the -NH(C₁-C₆ alkyl), -NHC(=O)(C₁-C₆ haloalkyl), -NHC(=O)O(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)H, -C(=O)(C₁-C₆ alkyl), or -C(=O)O(C₁-C₆ alkyl) is optionally substituted with one or more R^{3a}.

[0122] In some embodiments, R³ is NH₂, -NH(C₁-C₆ alkyl), -NHC(=O)(C₁-C₆ haloalkyl), -NHC(=O)O(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)H, -C(=O)(C₁-C₆ alkyl), or -C(=O)O(C₁-C₆ alkyl).

[0123] In some embodiments, R³ is NH₂, -NH(C₁-C₆ alkyl), -NHC(=O)(C₁-C₆ haloalkyl), -NHC(=O)O(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂, wherein the -NH(C₁-C₆ alkyl), -NHC(=O)(C₁-C₆ haloalkyl), -NHC(=O)O(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂ is optionally substituted with one or more R^{3a}.

[0124] In some embodiments, R³ is NH₂, -NH(C₁-C₆ alkyl), -NHC(=O)(C₁-C₆ haloalkyl), -NHC(=O)O(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂.

[0125] In some embodiments, R³ is NH₂.

[0126] In some embodiments, R³ is -NH(C₁-C₆ alkyl) optionally substituted with one or more R^{3a}.

[0127] In some embodiments, R³ is -NH(C₁-C₆ alkyl).

[0128] In some embodiments, R³ is -NHC(=O)(C₁-C₆ haloalkyl) optionally substituted with one or more R^{3a}.

[0129] In some embodiments, R³ is -NHC(=O)(C₁-C₆ haloalkyl).

[0130] In some embodiments, R³ is -NHC(=O)O(C₁-C₆ alkyl) optionally substituted with one or more R^{3a}.

[0131] In some embodiments, R³ is -NHC(=O)O(C₁-C₆ alkyl).

[0132] In some embodiments, R³ is N(C₁-C₆ alkyl)₂ optionally substituted with one or more R^{3a}.

[0133] In some embodiments, R³ is N(C₁-C₆ alkyl)₂.

[0134] In some embodiments, R³ is -S(=O)₂-(C₁-C₆ alkyl), -C(=O)H, -C(=O)(C₁-C₆ alkyl), or -C(=O)O(C₁-C₆ alkyl), wherein the -S(=O)₂-(C₁-C₆ alkyl), -C(=O)H, -C(=O)(C₁-C₆ alkyl), or -C(=O)O(C₁-C₆ alkyl) is optionally substituted with one or more R^{3a}.

[0135] In some embodiments, R³ is -S(=O)₂-(C₁-C₆ alkyl), -C(=O)H, -C(=O)(C₁-C₆ alkyl), or -

C(=O)O(C₁-C₆ alkyl).

[0136] In some embodiments, R³ is -S(=O)₂-(C₁-C₆ alkyl) optionally substituted with one or more R^{3a}.

[0137] In some embodiments, R³ is -S(=O)₂-(C₁-C₆ alkyl).

[0138] In some embodiments, R³ is -C(=O)H.

[0139] In some embodiments, R³ is -C(=O)(C₁-C₆ alkyl) optionally substituted with one or more R^{3a}.

[0140] In some embodiments, R³ is -C(=O)(C₁-C₆ alkyl).

[0141] In some embodiments, R³ is -C(=O)O(C₁-C₆ alkyl) optionally substituted with one or more R^{3a}.

[0142] In some embodiments, R³ is -C(=O)O(C₁-C₆ alkyl).

[0143] In some embodiments, R³ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, is optionally substituted with one or more R^{3a}.

[0144] In some embodiments, R³ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl.

[0145] In some embodiments, R³ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, or C₁-C₆ alkoxy, wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, or C₁-C₆ alkoxy is optionally substituted with one or more R^{3a}.

[0146] In some embodiments, R³ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, or C₁-C₆ alkoxy.

[0147] In some embodiments, R³ is C₁-C₆ alkyl optionally substituted with one or more R^{3a}.

[0148] In some embodiments, R³ is C₂-C₆ alkenyl optionally substituted with one or more R^{3a}.

[0149] In some embodiments, R³ is C₂-C₆ alkenyl.

[0150] In some embodiments, R³ is C₂-C₆ alkynyl optionally substituted with one or more R^{3a}.

[0151] In some embodiments, R³ is C₂-C₆ alkynyl.

[0152] In some embodiments, R³ is C₁-C₆ alkoxy optionally substituted with one or more R^{3a}.

[0153] In some embodiments, R³ is C₁-C₆ alkoxy.

[0154] In some embodiments, R^3 is C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, is optionally substituted with one or more R^{3a} .

[0155] In some embodiments, R^3 is C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl.

[0156] In some embodiments, R^3 is C₃-C₁₂ cycloalkyl optionally substituted with one or more R^{3a} .

[0157] In some embodiments, R^3 is C₃-C₁₂ cycloalkyl.

[0158] In some embodiments, R^3 is C₃-C₁₂ cycloalkenyl optionally substituted with one or more R^{3a} .

[0159] In some embodiments, R^3 is C₃-C₁₂ cycloalkenyl.

[0160] In some embodiments, R^3 is 3- to 12-membered heterocycloalkyl optionally substituted with one or more R^{3a} .

[0161] In some embodiments, R^3 is 3- to 12-membered heterocycloalkyl.

[0162] In some embodiments, R^3 is 3- to 12-membered heterocycloalkenyl optionally substituted with one or more R^{3a} .

[0163] In some embodiments, R^3 is 3- to 12-membered heterocycloalkenyl.

[0164] In some embodiments, R^3 is C₆-C₁₀ aryl optionally substituted with one or more R^{3a} .

[0165] In some embodiments, R^3 is C₆-C₁₀ aryl.

[0166] In some embodiments, R^3 is 5- to 10-membered heteroaryl optionally substituted with one or more R^{3a} .

[0167] In some embodiments, R^3 is 5- to 10-membered heteroaryl.

[0168] In some embodiments, R^3 is halogen, cyano, or C₁-C₆ alkyl.

[0169] In some embodiments, R^3 is halogen. In some embodiments, R^3 is F or Cl.

[0170] In some embodiments, R^3 is F. In some embodiments, R^3 is Cl.

[0171] In some embodiments, R^3 is cyano.

[0172] In some embodiments, R^3 is C₁-C₆ alkyl. In some embodiments, R^3 is CH₃.

[0173] In some embodiments, each R^{3a} independently is halogen, cyano, oxo, -OH, NH₂, -NH(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)(C₁-C₆ alkyl),

-C(=O)O(C₁-C₆ alkyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the -NH(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more halogen.

[0174] In some embodiments, each R^{3a} independently is halogen, cyano, oxo, -OH, NH₂, -NH(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the NHC(=O)O(C₁-C₆ alkyl) is optionally substituted with one or more halogen.

[0175] In some embodiments, each R^{3a} independently is halogen, cyano, oxo, -OH, NH₂, -NH(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)(C₁-C₆ alkyl), or -C(=O)O(C₁-C₆ alkyl), wherein the NHC(=O)O(C₁-C₆ alkyl) is optionally substituted with one or more halogen.

[0176] In some embodiments, each R^{3a} independently is halogen, cyano, oxo, or -OH.

[0177] In some embodiments, each R^{3a} independently is halogen. In some embodiments, each R^{3a} independently is cyano. In some embodiments, each R^{3a} independently is oxo. In some embodiments, each R^{3a} independently is -OH.

[0178] In some embodiments, each R^{3a} independently is NH₂, -NH(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)(C₁-C₆ alkyl), or -C(=O)O(C₁-C₆ alkyl), wherein the NHC(=O)O(C₁-C₆ alkyl) is optionally substituted with one or more halogen.

[0179] In some embodiments, each R^{3a} independently is NH₂.

[0180] In some embodiments, each R^{3a} independently is -NH(C₁-C₆ alkyl).

[0181] In some embodiments, each R^{3a} independently is -NHC(=O)O(C₁-C₆ alkyl) optionally substituted with one or more halogen.

[0182] In some embodiments, each R^{3a} independently is -NHC(=O)O(C₁-C₆ alkyl).

[0183] In some embodiments, each R^{3a} independently is N(C₁-C₆ alkyl)₂.

[0184] In some embodiments, each R^{3a} independently is -S(=O)₂-(C₁-C₆ alkyl).

[0185] In some embodiments, each R^{3a} independently is -C(=O)(C₁-C₆ alkyl).

[0186] In some embodiments, each R^{3a} independently is -C(=O)O(C₁-C₆ alkyl).

- [0187] In some embodiments, each R^{3a} independently is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, or C₁-C₆ alkoxy.
- [0188] In some embodiments, each R^{3a} independently is C₁-C₆ alkyl.
- [0189] In some embodiments, each R^{3a} independently is C₂-C₆ alkenyl.
- [0190] In some embodiments, each R^{3a} independently is C₂-C₆ alkynyl.
- [0191] In some embodiments, each R^{3a} independently is C₁-C₆ alkoxy.
- [0192] In some embodiments, each R^{3a} independently is C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl.
- [0193] In some embodiments, each R^{3a} independently is C₃-C₁₂ cycloalkyl.
- [0194] In some embodiments, each R^{3a} independently is 3- to 12-membered heterocycloalkyl.
- [0195] In some embodiments, each R^{3a} independently is C₆-C₁₀ aryl.
- [0196] In some embodiments, each R^{3a} independently is 5- to 10-membered heteroaryl.
- [0197] In some embodiments, R^4 is H.
- [0198] In some embodiments, R^4 is halogen, cyano, or C₁-C₆ alkyl.
- [0199] In some embodiments, R^4 is halogen. In some embodiments, R^4 is F or Cl.
- [0200] In some embodiments, R^4 is F. In some embodiments, R^4 is Cl.
- [0201] In some embodiments, R^4 is cyano.
- [0202] In some embodiments, R^4 is C₁-C₆ alkyl. In some embodiments, R^4 is CH₃.
- [0203] In some embodiments, R^5 is H.
- [0204] In some embodiments, R^5 is halogen, cyano, or C₁-C₆ alkyl.
- [0205] In some embodiments, R^5 is halogen. In some embodiments, R^5 is F or Cl.
- [0206] In some embodiments, R^5 is F. In some embodiments, R^5 is Cl.
- [0207] In some embodiments, R^5 is cyano.
- [0208] In some embodiments, R^5 is C₁-C₆ alkyl. In some embodiments, R^5 is CH₃.
- [0209] In some embodiments, R^6 is H.
- [0210] In some embodiments, R^6 is halogen, cyano, or C₁-C₆ alkyl.
- [0211] In some embodiments, R^6 is halogen. In some embodiments, R^6 is F or Cl.
- [0212] In some embodiments, R^6 is F. In some embodiments, R^6 is Cl.
- [0213] In some embodiments, R^6 is cyano.
- [0214] In some embodiments, R^6 is C₁-C₆ alkyl. In some embodiments, R^6 is CH₃.

Variables Y, Z, R^Z, R^{Za}, and R^{Zb}

[0215] In some embodiments, Y is absent, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₁-C₆ alkoxy, wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₁-C₆ alkoxy is optionally substituted with one or more halogen, oxo, cyano, -OH, NH₂, -NH(C₁-C₆ alkyl)-OH, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy optionally substituted with -(C₁-C₆ alkyl)(C₆-C₁₀ aryl), or C₃-C₁₂ cycloalkyl.

[0216] In some embodiments, Y is absent.

[0217] In some embodiments, Y is C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₁-C₆ alkoxy, wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₁-C₆ alkoxy is optionally substituted with one or more halogen, oxo, cyano, -OH, NH₂, -NH(C₁-C₆ alkyl)-OH, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy optionally substituted with -(C₁-C₆ alkyl)(C₆-C₁₀ aryl), or C₃-C₁₂ cycloalkyl.

[0218] In some embodiments, Y is C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₁-C₆ alkoxy.

[0219] In some embodiments, Y is C₁-C₆ alkyl optionally substituted with one or more halogen, oxo, cyano, -OH, NH₂, -NH(C₁-C₆ alkyl)-OH, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy.

[0220] In some embodiments, Y is C₁-C₆ alkyl. In some embodiments, Y is -CH₂-.

[0221] In some embodiments, Y is C₁-C₆ alkyl optionally substituted with one or more oxo, cyano, or -OH.

[0222] In some embodiments, Y is C₁-C₆ alkyl optionally substituted with one or more oxo.

[0223] In some embodiments, Y is C₁-C₆ alkyl substituted with one or more oxo.

[0224] In some embodiments, Y is methyl optionally substituted with one or more oxo.

[0225] In some embodiments, Y is methyl substituted oxo, *i.e.*, Y is -C(=O)-.

[0226] In some embodiments, Y is C₁-C₆ alkyl optionally substituted with one or more cyano.

[0227] In some embodiments, Y is C₁-C₆ alkyl substituted with one or more cyano.

[0228] In some embodiments, Y is methyl optionally substituted with one or more cyano.

[0229] In some embodiments, Y is C₁-C₆ alkyl optionally substituted with one or more -OH.

[0230] In some embodiments, Y is C₁-C₆ alkyl substituted with one or more -OH.

[0231] In some embodiments, Z is H.

[0232] In some embodiments, Z is C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl or 5- to 10-membered heteroaryl, is optionally substituted with one or more R^Z.

[0233] In some embodiments, Z is C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl.

[0234] In some embodiments, Z is C₃-C₁₂ cycloalkyl optionally substituted with one or more R^Z.

[0235] In some embodiments, Z is C₃-C₁₂ cycloalkyl.

[0236] In some embodiments, Z is C₃-C₁₂ cycloalkenyl optionally substituted with one or more R^Z.

[0237] In some embodiments, Z is C₃-C₁₂ cycloalkenyl.

[0238] In some embodiments, Z is 3- to 12-membered heterocycloalkyl optionally substituted with one or more R^Z.

[0239] In some embodiments, Z is 3- to 12-membered heterocycloalkyl.

[0240] In some embodiments, Z is 3- to 12-membered heterocycloalkenyl optionally substituted with one or more R^Z.

[0241] In some embodiments, Z is 3- to 12-membered heterocycloalkenyl.

[0242] In some embodiments, Z is C₆-C₁₀ aryl optionally substituted with one or more R^Z.

[0243] In some embodiments, Z is C₆-C₁₀ aryl.

[0244] In some embodiments, Z is 5- to 10-membered heteroaryl optionally substituted with one or more R^Z.

[0245] In some embodiments, Z is 5- to 10-membered heteroaryl.

[0246] In some embodiments, Z is C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl, wherein the C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^Z.

[0247] In some embodiments, Z is C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl.

[0248] In some embodiments, Z is C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl, wherein the C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl is substituted with one or more R^Z.

[0249] In some embodiments, Z is C₃-C₈ cycloalkyl optionally substituted with one or more R^Z.

[0250] In some embodiments, Z is C₃-C₈ cycloalkyl.

[0251] In some embodiments, Z is C₃-C₈ cycloalkyl substituted with one or more R^Z.

[0252] In some embodiments, Z is cyclopropyl optionally substituted with one or more R^Z.

[0253] In some embodiments, Z is cyclobutyl optionally substituted with one or more R^Z.

- [0254] In some embodiments, Z is cyclohexyl optionally substituted with one or more R^Z .
- [0255] In some embodiments, Z is 3- to 8-membered heterocycloalkyl optionally substituted with one or more R^Z .
- [0256] In some embodiments, Z is 3- to 8-membered heterocycloalkyl.
- [0257] In some embodiments, Z is 3- to 8-membered heterocycloalkyl substituted with one or more R^Z .
- [0258] In some embodiments, Z is azetidinyll or oxetanyl, wherein the azetidinyll or oxetanyl is optionally substituted with one or more R^Z .
- [0259] In some embodiments, Z is azetidinyll or oxetanyl.
- [0260] In some embodiments, Z is azetidinyll or oxetanyl, wherein the azetidinyll or oxetanyl is substituted with one or more R^Z .
- [0261] In some embodiments, Z is pyrrolidinyl or tetrahydrofuranyl, wherein the pyrrolidinyl or tetrahydrofuranyl is optionally substituted with one or more R^Z .
- [0262] In some embodiments, Z is pyrrolidinyl or tetrahydrofuranyl.
- [0263] In some embodiments, Z is pyrrolidinyl or tetrahydrofuranyl, wherein the pyrrolidinyl or tetrahydrofuranyl is substituted with one or more R^Z .
- [0264] In some embodiments, Z is piperidinyl or tetrahydropyranyl, wherein the piperidinyl or tetrahydropyranyl is optionally substituted with one or more R^Z .
- [0265] In some embodiments, Z is piperidinyl or tetrahydropyranyl.
- [0266] In some embodiments, Z is piperidinyl or tetrahydropyranyl, wherein the piperidinyl or tetrahydropyranyl is substituted with one or more R^Z .
- [0267] In some embodiments, each R^Z independently is oxo, halogen, cyano, -OH, $=NR^{Za}$, NH_2 , NHR^{Za} , $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(C_1-C_6 \text{ alkyl})$, $-S(=O)(=NR^{Za})(C_1-C_6 \text{ alkyl})$, $-S(=O)_2(C_1-C_6 \text{ alkyl})$, $-S(=O)_2(C_2-C_6 \text{ alkenyl})$, $-C(=O)(3\text{- to }12\text{-membered heterocycloalkyl})$, $-C(=O)NH(C_1-C_6 \text{ alkyl})$, $-C(=O)NR^{Za}$, $-C(=O)(C_1-C_6 \text{ alkyl})$, $-C(=O)(C_2-C_6 \text{ alkenyl})$, $-C(=O)(C_1-C_6 \text{ alkoxy})$, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, $C_1-C_6 \text{ alkoxy}$, $C_3-C_{12} \text{ cycloalkyl}$, 3- to 12-membered heterocycloalkyl, or 5- to 10-membered heteroaryl, wherein the $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2(C_1-C_6 \text{ alkyl})$, $-C(=O)(C_1-C_6 \text{ alkyl})$, $-C(=O)(C_2-C_6 \text{ alkenyl})$, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, $C_1-C_6 \text{ alkoxy}$, $C_3-C_{12} \text{ cycloalkyl}$, 3- to 12-membered heterocycloalkyl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{Za} .
- [0268] In some embodiments, each R^Z independently is oxo, halogen, cyano, -OH, $=NR^{Za}$, NH_2 ,

NHR^{Za}, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(C₁-C₆ alkyl), -S(=O)(=NR^{Za})-(C₁-C₆ alkyl), -S(=O)₂-(C₁-C₆ alkyl), -S(=O)₂-(C₂-C₆ alkenyl), -C(=O)(3- to 12-membered heterocycloalkyl), -C(=O)NH(C₁-C₆ alkyl), -C(=O)NR^{Za}, -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), -C(=O)-(C₁-C₆ alkoxy), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, or 5- to 10-membered heteroaryl.

[0269] In some embodiments, each R^Z independently is oxo, halogen, cyano, -OH.

[0270] In some embodiments, each R^Z independently is R^Z is oxo.

[0271] In some embodiments, each R^Z independently is R^Z is halogen. In some embodiments, each R^Z independently is F or Cl.

[0272] In some embodiments, each R^Z independently is F. In some embodiments, each R^Z independently is Cl.

[0273] In some embodiments, each R^Z independently is cyano. In some embodiments, each R^Z independently is -OH.

[0274] In some embodiments, each R^Z independently is =NR^{Za}. In some embodiments, each R^Z independently is NHR^{Za}.

[0275] In some embodiments, each R^Z independently is NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂, wherein the NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)₂ is optionally substituted with one or more R^{Za}.

[0276] In some embodiments, each R^Z independently is NH₂.

[0277] In some embodiments, each R^Z independently is NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂, wherein the NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)₂ is optionally substituted with one or more R^{Za}.

[0278] In some embodiments, each R^Z independently is NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂.

[0279] In some embodiments, each R^Z independently is NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂, wherein the NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)₂ is substituted with one or more R^{Za}.

[0280] In some embodiments, each R^Z independently is -S(=O)₂-(C₁-C₆ alkyl) optionally substituted with one or more R^{Za}.

[0281] In some embodiments, each R^Z independently is -S(=O)₂-(C₁-C₆ alkyl).

[0282] In some embodiments, each R^Z independently is -S(=O)₂-CH₃.

[0283] In some embodiments, each R^Z independently is -S(C₁-C₆ alkyl) optionally substituted with one or more R^{Za}.

[0284] In some embodiments, each R^Z independently is -S(C₁-C₆ alkyl) substituted with one or more R^{Za}.

- [0285] In some embodiments, each R^Z independently is $-S(C_1-C_6 \text{ alkyl})$.
- [0286] In some embodiments, each R^Z independently is $-S(=NR^{Za})(C_1-C_6 \text{ alkyl})$ optionally substituted with one or more R^{Za} .
- [0287] In some embodiments, each R^Z independently is $-S(=NR^{Za})(C_1-C_6 \text{ alkyl})$ substituted with one or more R^{Za} .
- [0288] In some embodiments, each R^Z independently is $-S(=NR^{Za})(C_1-C_6 \text{ alkyl})$.
- [0289] In some embodiments, each R^Z independently is $-S(C_2-C_6 \text{ alkenyl})$ optionally substituted with one or more R^{Za} .
- [0290] In some embodiments, each R^Z independently is $-S(C_2-C_6 \text{ alkenyl})$ substituted with one or more R^{Za} .
- [0291] In some embodiments, each R^Z independently is $-S(C_2-C_6 \text{ alkenyl})$.
- [0292] In some embodiments, at least one R^Z is $-C(=O)-(C_1-C_6 \text{ alkyl})$ or $-C(=O)-(C_2-C_6 \text{ alkenyl})$, wherein the $-C(=O)-(C_1-C_6 \text{ alkyl})$ or $-C(=O)-(C_2-C_6 \text{ alkenyl})$ is optionally substituted with one or more R^{Za} .
- [0293] In some embodiments, each R^Z independently is $-C(=O)-(C_1-C_6 \text{ alkyl})$ or $-C(=O)-(C_2-C_6 \text{ alkenyl})$.
- [0294] In some embodiments, each R^Z independently is $-C(=O)-(C_1-C_6 \text{ alkyl})$.
- [0295] In some embodiments, each R^Z independently is $-C(=O)-(C_1-C_6 \text{ alkyl})$.
- [0296] In some embodiments, each R^Z independently is $-C(=O)-CH=CH_2$.
- [0297] In some embodiments, each R^Z independently is $-C(=O)-(C_1-C_6 \text{ alkyl})$ or $-C(=O)-(C_2-C_6 \text{ alkenyl})$, wherein the $-C(=O)-(C_1-C_6 \text{ alkyl})$ or $-C(=O)-(C_2-C_6 \text{ alkenyl})$ is substituted with one or more R^{Za} .
- [0298] In some embodiments, each R^Z independently is $-S(=O)_2-(C_2-C_6 \text{ alkenyl})$, $-C(=O)(3\text{- to }12\text{-membered heterocycloalkyl})$, $-C(=O)NH(C_1-C_6 \text{ alkyl})$, $-C(=O)NR^{Za}$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, or $-C(=O)-(C_1-C_6 \text{ alkoxy})$, wherein the $-S(=O)_2-(C_2-C_6 \text{ alkenyl})$, $-C(=O)(3\text{- to }12\text{-membered heterocycloalkyl})$, $-C(=O)NH(C_1-C_6 \text{ alkyl})$, $-C(=O)NR^{Za}$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, or $-C(=O)-(C_1-C_6 \text{ alkoxy})$ is optionally substituted with one or more R^{Za} .
- [0299] In some embodiments, each R^Z independently is $-S(=O)_2-(C_2-C_6 \text{ alkenyl})$, $-C(=O)(3\text{- to }12\text{-membered heterocycloalkyl})$, $-C(=O)NH(C_1-C_6 \text{ alkyl})$, $-C(=O)NR^{Za}$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, or $-C(=O)-(C_1-C_6 \text{ alkoxy})$.

- [0300] In some embodiments, each R^Z independently is $-S(=O)_2-(C_2-C_6 \text{ alkenyl})$ optionally substituted with one or more R^{Za} .
- [0301] In some embodiments, each R^Z independently is $-S(=O)_2-(C_2-C_6 \text{ alkenyl})$.
- [0302] In some embodiments, each R^Z independently is $-C(=O)(3- \text{ to } 12\text{-membered heterocycloalkyl})$ optionally substituted with one or more R^{Za} .
- [0303] In some embodiments, each R^Z independently is $-C(=O)(3- \text{ to } 12\text{-membered heterocycloalkyl})$.
- [0304] In some embodiments, each R^Z independently is $-C(=O)NH(C_1-C_6 \text{ alkyl})$ optionally substituted with one or more R^{Za} .
- [0305] In some embodiments, each R^Z independently is $-C(=O)NH(C_1-C_6 \text{ alkyl})$.
- [0306] In some embodiments, each R^Z independently is $-C(=O)NR^{Za}$.
- [0307] In some embodiments, each R^Z independently is $-C(=O)-(C_1-C_6 \text{ alkyl})$ optionally substituted with one or more R^{Za} .
- [0308] In some embodiments, each R^Z independently is $C(=O)-(C_1-C_6 \text{ alkyl})$.
- [0309] In some embodiments, each R^Z independently is $-C(=O)-(C_2-C_6 \text{ alkenyl})$ optionally substituted with one or more R^{Za} .
- [0310] In some embodiments, each R^Z independently is $-C(=O)-(C_2-C_6 \text{ alkenyl})$.
- [0311] In some embodiments, each R^Z independently is $-C(=O)-(C_1-C_6 \text{ alkoxy})$ optionally substituted with one or more R^{Za} .
- [0312] In some embodiments, each R^Z independently is $-C(=O)-(C_1-C_6 \text{ alkoxy})$.
- [0313] In some embodiments, each R^Z independently is 5- to 10-membered heteroaryl optionally substituted with one or more R^{Za} .
- [0314] In some embodiments, each R^Z independently is 5- to 10-membered heteroaryl.
- [0315] In some embodiments, each R^Z independently is $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, or $C_1-C_6 \text{ alkoxy}$, wherein the $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, or $C_1-C_6 \text{ alkoxy}$ is optionally substituted with one or more R^{Za} .
- [0316] In some embodiments, each R^Z independently is $C_1-C_6 \text{ alkyl}$ optionally substituted with one or more R^{Za} .
- [0317] In some embodiments, each R^Z independently is $C_1-C_6 \text{ alkyl}$.
- [0318] In some embodiments, each R^Z independently is $C_1-C_6 \text{ alkyl}$ substituted with one or more R^{Za} .

[0319] In some embodiments, each R^Z independently is C₂-C₆ alkenyl optionally substituted with one or more R^{Za} .

[0320] In some embodiments, each R^Z independently is C₂-C₆ alkenyl.

[0321] In some embodiments, each R^Z independently is C₂-C₆ alkenyl substituted with one or more R^{Za} .

[0322] In some embodiments, each R^Z independently is C₂-C₆ alkynyl optionally substituted with one or more R^{Za} .

[0323] In some embodiments, each R^Z independently is C₂-C₆ alkynyl.

[0324] In some embodiments, each R^Z independently is C₂-C₆ alkynyl substituted with one or more R^{Za} .

[0325] In some embodiments, each R^Z independently is C₁-C₆ alkoxy is optionally substituted with one or more R^{Za} .

[0326] In some embodiments, each R^Z independently is C₁-C₆ alkoxy.

[0327] In some embodiments, each R^Z independently is C₁-C₆ alkoxy is substituted with one or more R^{Za} .

[0328] In some embodiments, each R^Z independently is C₃-C₁₂ cycloalkyl or 3- to 12-membered heterocycloalkyl, wherein the C₃-C₁₂ cycloalkyl or 3- to 12-membered heterocycloalkyl is optionally substituted with one or more R^{Za} .

[0329] In some embodiments, each R^Z independently is C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl, wherein the C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{Za} .

[0330] In some embodiments, each R^Z independently is C₃-C₁₂ cycloalkyl optionally substituted with one or more R^{Za} .

[0331] In some embodiments, each R^Z independently is C₃-C₁₂ cycloalkyl.

[0332] In some embodiments, each R^Z independently is C₃-C₁₂ cycloalkyl substituted with one or more R^{Za} .

[0333] In some embodiments, each R^Z independently is C₃-C₈ cycloalkyl optionally substituted with one or more R^{Za} .

[0334] In some embodiments, each R^Z independently is C₃-C₈ cycloalkyl.

[0335] In some embodiments, each R^Z independently is C₃-C₈ cycloalkyl substituted with one or more R^{Za} .

[0336] In some embodiments, each R^Z independently is 3- to 12-membered heterocycloalkyl optionally substituted with one or more R^{Za} .

[0337] In some embodiments, each R^Z independently is 3- to 12-membered heterocycloalkyl.

[0338] In some embodiments, each R^Z independently is 3- to 12-membered heterocycloalkyl substituted with one or more R^{Za} .

[0339] In some embodiments, each R^Z independently is 3- to 8-membered heterocycloalkyl optionally substituted with one or more R^{Za} .

[0340] In some embodiments, each R^Z independently is 3- to 8-membered heterocycloalkyl.

[0341] In some embodiments, each R^Z independently is 3- to 8-membered heterocycloalkyl substituted with one or more R^{Za} .

[0342] In some embodiments, each R^{Za} independently is H, oxo, halogen, cyano, -OH, NH_2 , $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, $C_1-C_6 \text{ alkoxy}$, $C_3-C_{12} \text{ cycloalkyl}$, or 3- to 12-membered heterocycloalkyl, wherein the $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, $C_1-C_6 \text{ alkoxy}$, $C_3-C_{12} \text{ cycloalkyl}$, or 3- to 12-membered heterocycloalkyl is optionally substituted with one or more R^{Zb} .

[0343] In some embodiments, each R^{Za} independently is H, oxo, halogen, cyano, -OH, NH_2 , $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, $C_1-C_6 \text{ alkoxy}$, $C_3-C_{12} \text{ cycloalkyl}$, or 3- to 12-membered heterocycloalkyl.

[0344] In some embodiments, each R^{Za} independently is H.

[0345] In some embodiments, each R^{Za} independently is oxo, halogen, cyano, -OH.

[0346] In some embodiments, each R^{Za} independently is oxo.

[0347] In some embodiments, each R^{Za} independently is halogen. In some embodiments, each R^{Za} independently is F or Cl.

[0348] In some embodiments, each R^{Za} independently is F. In some embodiments, each R^{Za} independently is Cl.

[0349] In some embodiments, each R^{Za} independently is cyano.

[0350] In some embodiments, each R^{Za} independently is -OH.

[0351] In some embodiments, each R^{Za} independently is NH_2 , $NH(C_1-C_6 \text{ alkyl})$, or $N(C_1-C_6$

alkyl)₂, wherein the NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)₂ is optionally substituted with one or more R^{Zb}.

[0352] In some embodiments, each R^{Za} independently is NH₂.

[0353] In some embodiments, each R^{Za} independently is NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂, wherein the NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)₂ is optionally substituted with one or more R^{Zb}.

[0354] In some embodiments, each R^{Za} independently is NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂.

[0355] In some embodiments, each R^{Za} independently is NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂, wherein the NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)₂ is substituted with one or more R^{Zb}.

[0356] In some embodiments, each R^{Za} independently is -S(=O)₂-(C₁-C₆ alkyl) optionally substituted with one or more R^{Zb}.

[0357] In some embodiments, each R^{Za} independently is -S(=O)₂-(C₁-C₆ alkyl).

[0358] In some embodiments, each R^{Za} independently is -S(=O)₂-CH₃.

[0359] In some embodiments, each R^{Za} independently is -S(=O)₂-(C₁-C₆ alkyl) substituted with one or more R^{Zb}.

[0360] In some embodiments, each R^{Za} independently is -C(=O)-(C₁-C₆ alkyl) or -C(=O)-(C₂-C₆ alkenyl), wherein the -C(=O)-(C₁-C₆ alkyl) or -C(=O)-(C₂-C₆ alkenyl) is optionally substituted with one or more R^{Zb}.

[0361] In some embodiments, each R^{Za} independently is -C(=O)-(C₁-C₆ alkyl) or -C(=O)-(C₂-C₆ alkenyl).

[0362] In some embodiments, each R^{Za} independently is -C(=O)-(C₁-C₆ alkyl).

[0363] In some embodiments, each R^{Za} independently is -C(=O)-(C₁-C₆ alkyl).

[0364] In some embodiments, each R^{Za} independently is -C(=O)-CH=CH₂.

[0365] In some embodiments, each R^{Za} independently is -C(=O)-(C₁-C₆ alkyl) or -C(=O)-(C₂-C₆ alkenyl), wherein the -C(=O)-(C₁-C₆ alkyl) or -C(=O)-(C₂-C₆ alkenyl) is substituted with one or more R^{Zb}.

[0366] In some embodiments, each R^{Za} independently is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, or C₁-C₆ alkoxy, wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, or C₁-C₆ alkoxy is optionally substituted with one or more R^{Zb}.

[0367] In some embodiments, each R^{Za} independently is C₁-C₆ alkyl optionally substituted with one or more R^{Zb}.

[0368] In some embodiments, each R^{Za} independently is C₁-C₆ alkyl.

[0369] In some embodiments, each R^{Za} independently is C₁-C₆ alkyl substituted with one or more R^{Zb} .

[0370] In some embodiments, each R^{Za} independently is C₂-C₆ alkenyl optionally substituted with one or more R^{Zb} .

[0371] In some embodiments, each R^{Za} independently is C₂-C₆ alkenyl.

[0372] In some embodiments, each R^{Za} independently is C₂-C₆ alkenyl substituted with one or more R^{Zb} .

[0373] In some embodiments, each R^{Za} independently is C₂-C₆ alkynyl optionally substituted with one or more R^{Zb} .

[0374] In some embodiments, each R^{Za} independently is C₂-C₆ alkynyl.

[0375] In some embodiments, each R^{Za} independently is C₂-C₆ alkynyl substituted with one or more R^{Zb} .

[0376] In some embodiments, each R^{Za} independently is C₁-C₆ alkoxy is optionally substituted with one or more R^{Zb} .

[0377] In some embodiments, each R^{Za} independently is C₁-C₆ alkoxy.

[0378] In some embodiments, each R^{Za} independently is C₁-C₆ alkoxy is substituted with one or more R^{Zb} .

[0379] In some embodiments, each R^{Za} independently is C₃-C₁₂ cycloalkyl or 3- to 12-membered heterocycloalkyl, wherein the C₃-C₁₂ cycloalkyl or 3- to 12-membered heterocycloalkyl is optionally substituted with one or more R^{Zb} .

[0380] In some embodiments, each R^{Za} independently is C₃-C₁₂ cycloalkyl optionally substituted with one or more R^{Zb} .

[0381] In some embodiments, each R^{Za} independently is C₃-C₁₂ cycloalkyl.

[0382] In some embodiments, each R^{Za} independently is C₃-C₁₂ cycloalkyl substituted with one or more R^{Zb} .

[0383] In some embodiments, each R^{Za} independently is 3- to 12-membered heterocycloalkyl optionally substituted with one or more R^{Zb} .

[0384] In some embodiments, each R^{Za} independently is 3- to 12-membered heterocycloalkyl.

[0385] In some embodiments, each R^{Za} independently is 3- to 12-membered heterocycloalkyl substituted with one or more R^{Zb} .

[0386] In some embodiments, each R^{Za} independently is C₃-C₈ cycloalkyl or 3- to 8-membered

heterocycloalkyl, wherein the C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{Zb}.

[0387] In some embodiments, each R^{Za} independently is C₃-C₈ cycloalkyl optionally substituted with one or more R^{Zb}.

[0388] In some embodiments, each R^{Za} independently is C₃-C₈ cycloalkyl.

[0389] In some embodiments, each R^{Za} independently is C₃-C₈ cycloalkyl substituted with one or more R^{Zb}.

[0390] In some embodiments, each R^{Za} independently is 3- to 8-membered heterocycloalkyl optionally substituted with one or more R^{Zb}.

[0391] In some embodiments, each R^{Za} independently is 3- to 8-membered heterocycloalkyl.

[0392] In some embodiments, each R^{Za} independently is 3- to 8-membered heterocycloalkyl substituted with one or more R^{Zb}.

[0393] In some embodiments, each R^{Zb} independently is oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, or C₁-C₆ alkoxyl.

[0394] In some embodiments, each R^{Zb} independently is oxo, halogen, cyano, or -OH.

[0395] In some embodiments, each R^{Zb} independently is oxo.

[0396] In some embodiments, each R^{Zb} independently is halogen. In some embodiments, each R^{Zb} independently is F or Cl.

[0397] In some embodiments, each R^{Zb} independently is F. In some embodiments, each R^{Zb} independently is Cl.

[0398] In some embodiments, each R^{Zb} independently is cyano. In some embodiments, each R^{Zb} independently is -OH.

[0399] In some embodiments, each R^{Zb} independently is NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂.

[0400] In some embodiments, each R^{Zb} independently is NH₂.

[0401] In some embodiments, each R^{Zb} independently is NH(C₁-C₆ alkyl).

[0402] In some embodiments, each R^{Zb} independently is N(C₁-C₆ alkyl)₂.

[0403] In some embodiments, each R^{Zb} independently is -S(=O)₂-(C₁-C₆ alkyl).

[0404] In some embodiments, each R^{Zb} independently is -C(=O)-(C₁-C₆ alkyl) or -C(=O)-(C₂-C₆ alkenyl).

[0405] In some embodiments, each R^{Zb} independently is $-C(=O)-(C_1-C_6 \text{ alkyl})$.

[0406] In some embodiments, each R^{Zb} independently is $-C(=O)-(C_2-C_6 \text{ alkenyl})$.

[0407] In some embodiments, each R^{Zb} independently is $-C(=O)-CH=CH_2$.

[0408] In some embodiments, each R^{Zb} independently is $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, or $C_1-C_6 \text{ alkoxy}$.

[0409] In some embodiments, each R^{Zb} independently is $C_1-C_6 \text{ alkyl}$.

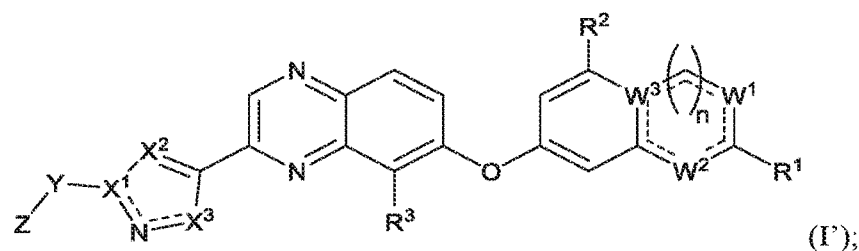
[0410] In some embodiments, each R^{Zb} independently is $C_2-C_6 \text{ alkenyl}$.

[0411] In some embodiments, each R^{Zb} independently is $C_2-C_6 \text{ alkynyl}$.

[0412] In some embodiments, each R^{Zb} independently is $C_1-C_6 \text{ alkoxy}$.

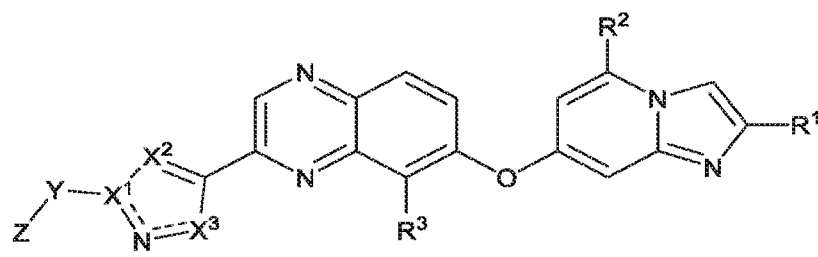
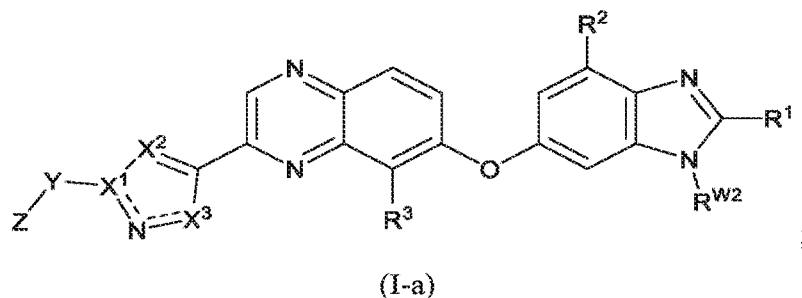
Exemplary Embodiments of the Compounds

[0413] In some embodiments, the compound is of Formula (I'):

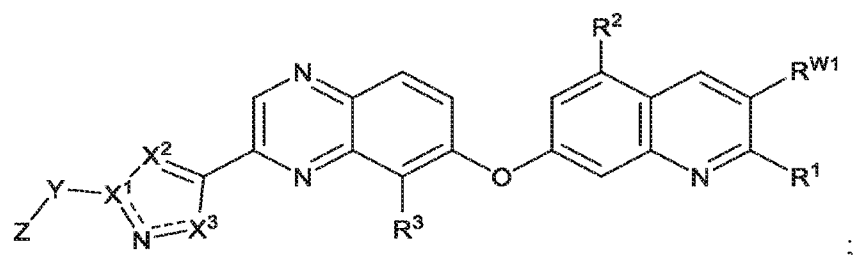


or a pharmaceutically acceptable salt or stereoisomer thereof.

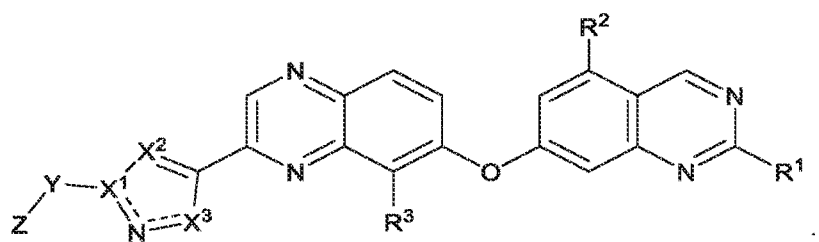
[0414] In some embodiments, the compound is of Formula (I-a), (I-b), (I-c), or (I-d):



(I-b)



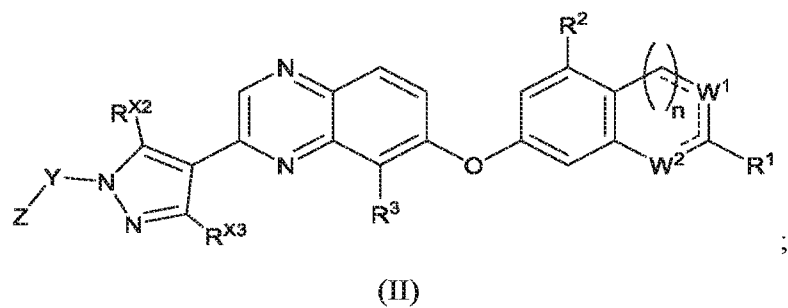
(I-c)



(I-d)

or a pharmaceutically acceptable salt or stereoisomer thereof.

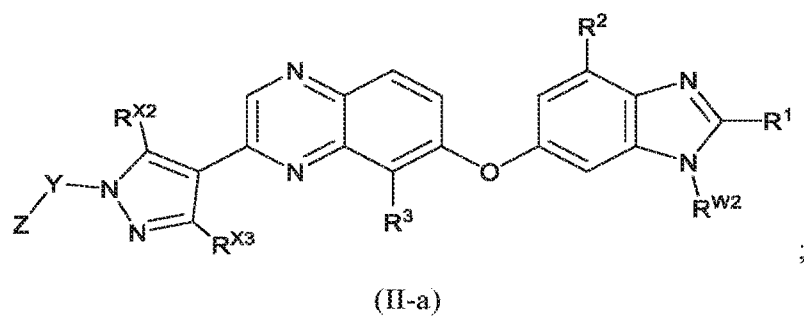
[0415] In some embodiments, the compound is of Formula (II):



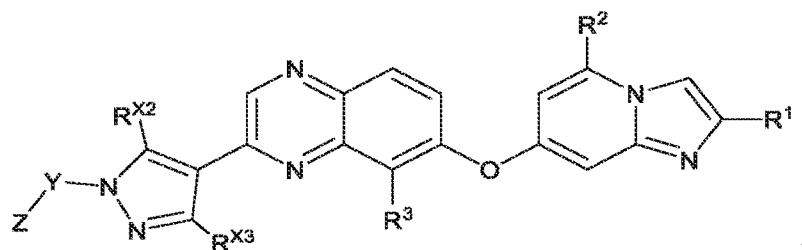
(II)

or a pharmaceutically acceptable salt or stereoisomer thereof.

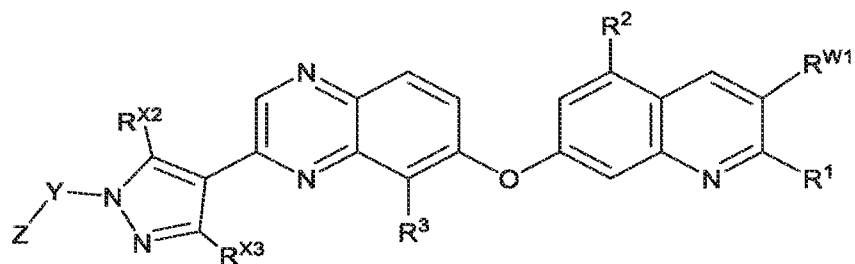
[0416] In some embodiments, the compound is of Formula (II-a), (II-b), (II-c), or (II-d):



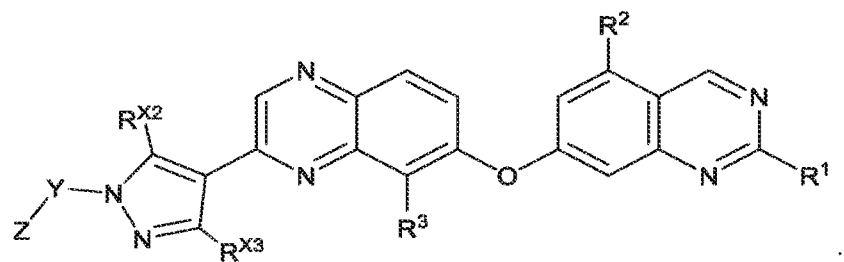
(II-a)



(II-b)



(II-c)



(II-d)

or a pharmaceutically acceptable salt or stereoisomer thereof.

[0417] In some embodiments, the compound is a compounds described in Table I and II, or a pharmaceutically acceptable salt or stereoisomer thereof.

[0418] In some embodiments, the compound is a compounds described in Table I and II, or a pharmaceutically acceptable salt thereof.

[0419] In some embodiments, the compound is a compounds described in Table I and II.

[0420] In some embodiments, the compound is a compounds described in Table II, or a pharmaceutically acceptable salt or stereoisomer thereof.

[0421] In some embodiments, the compound is a compounds described in Table II, or a pharmaceutically acceptable salt thereof.

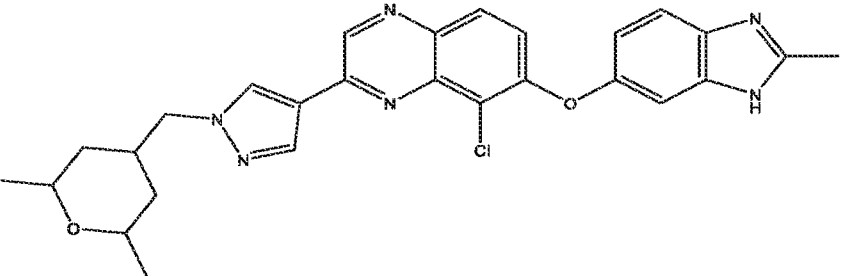
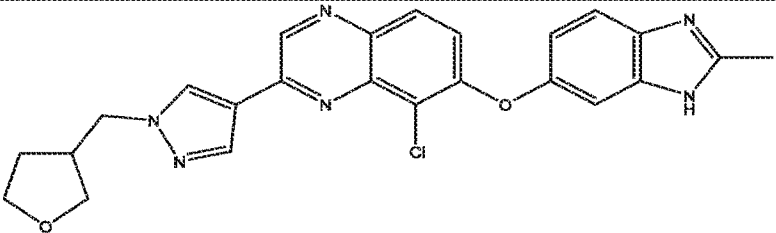
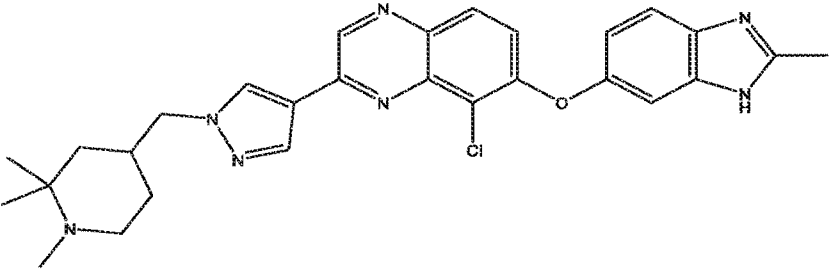
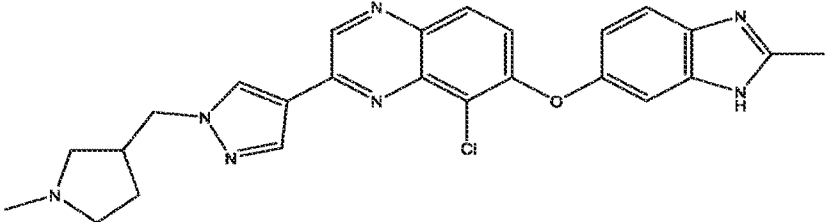
[0422] In some embodiments, the compound is a compounds described in Table II.

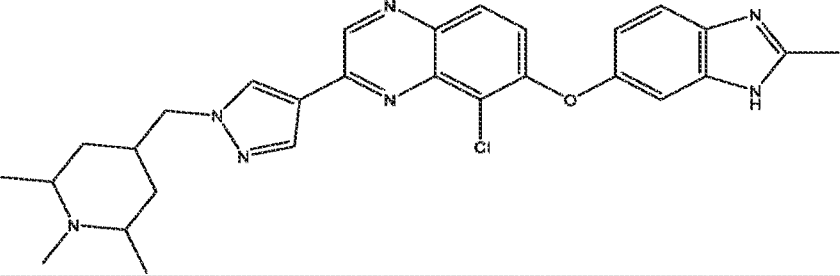
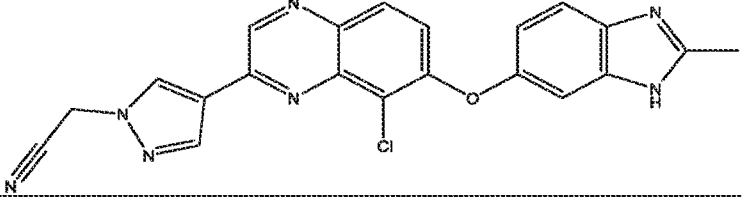
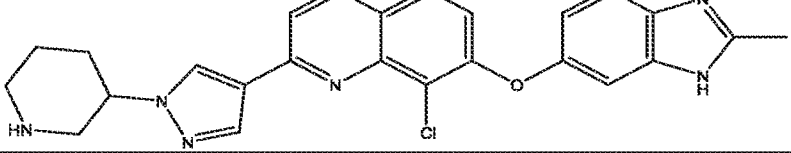
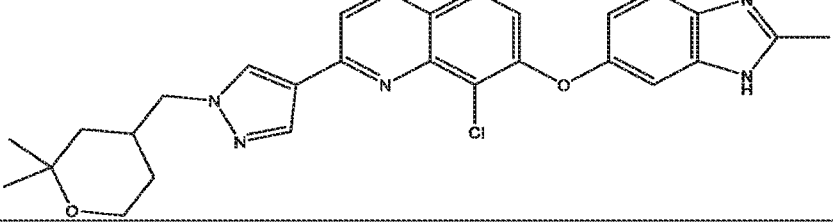
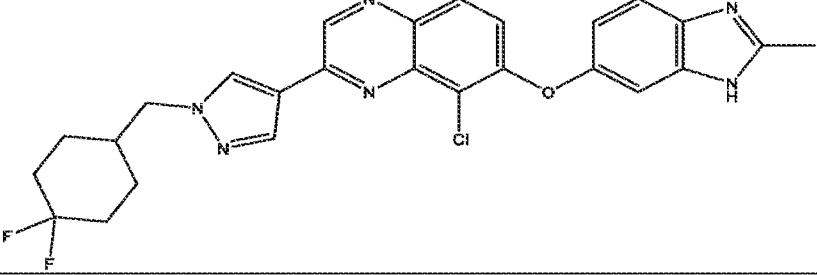
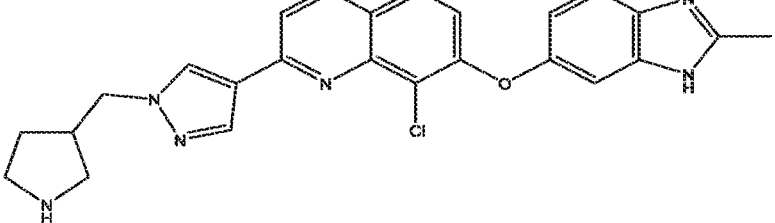
[0423] In some embodiments, the compound is a compounds described in Table I, or a pharmaceutically acceptable salt or stereoisomer thereof.

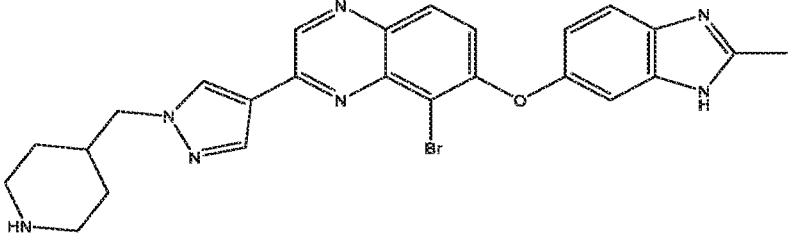
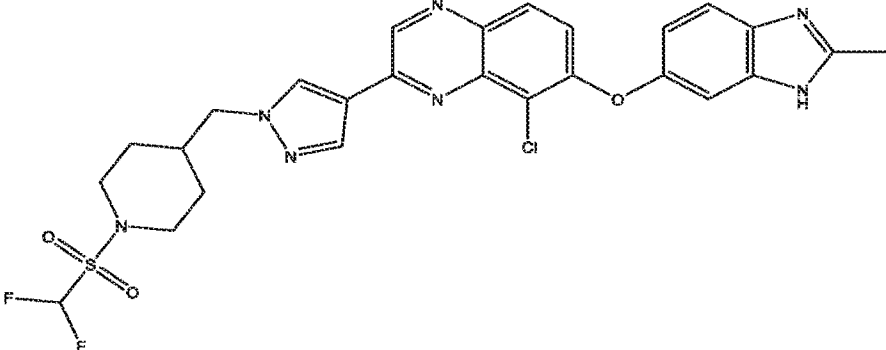
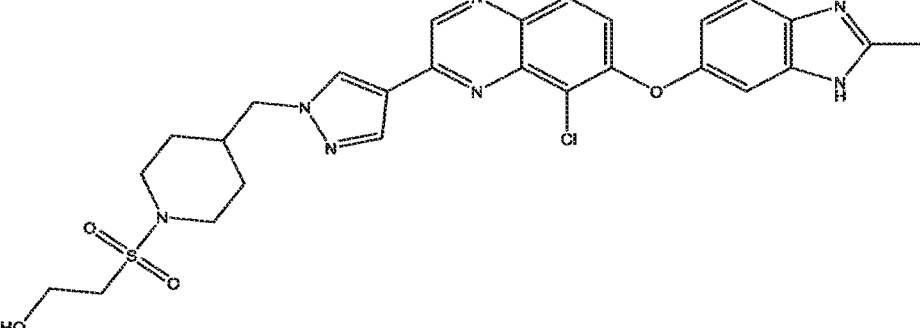
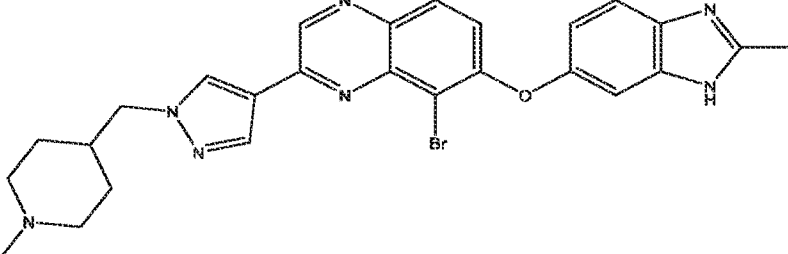
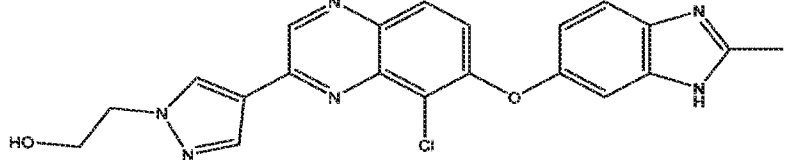
[0424] In some embodiments, the compound is a compounds described in Table I, or a pharmaceutically acceptable salt thereof.

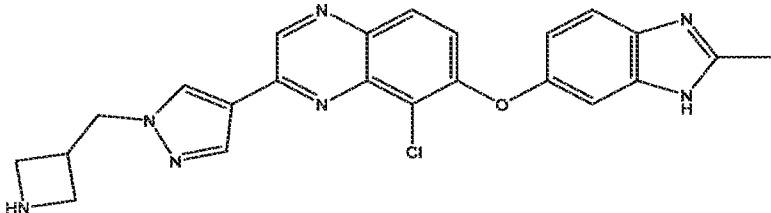
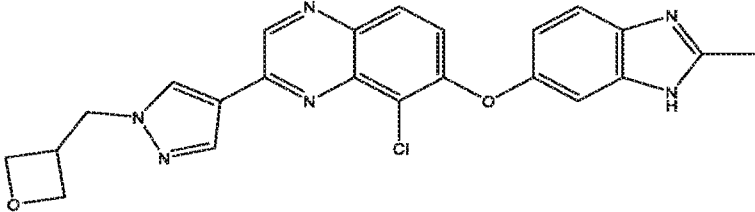
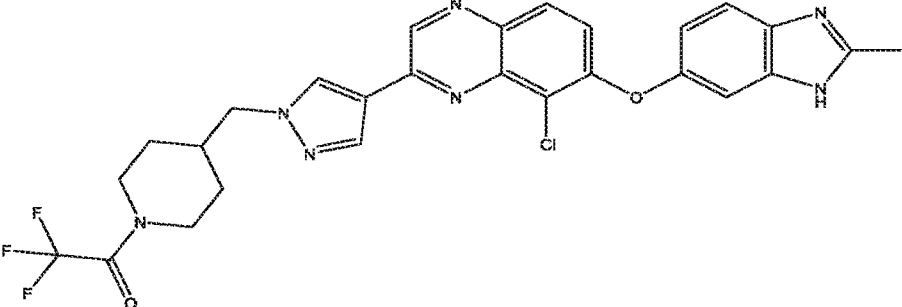
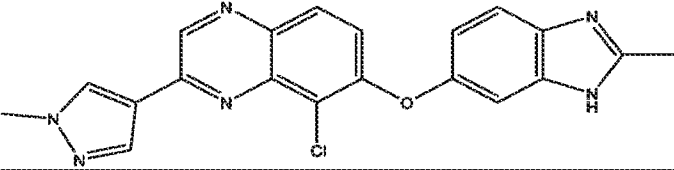
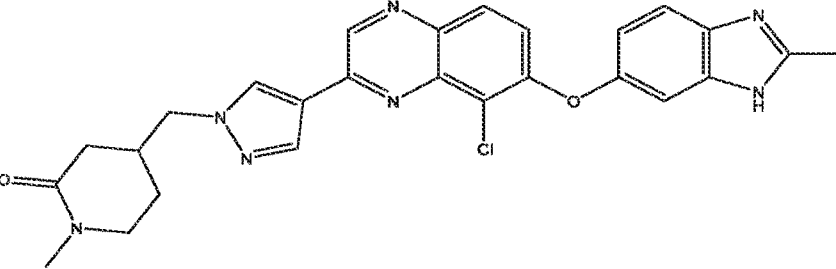
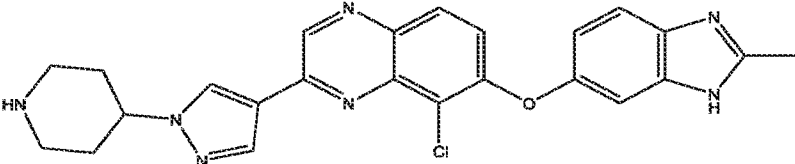
[0425] In some embodiments, the compound is a compounds described in Table I.

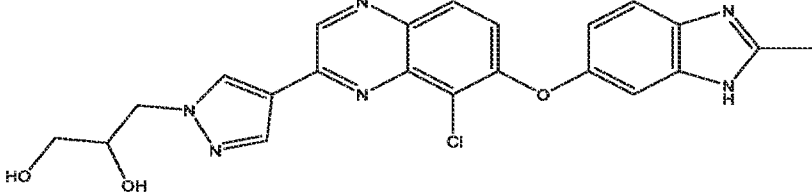
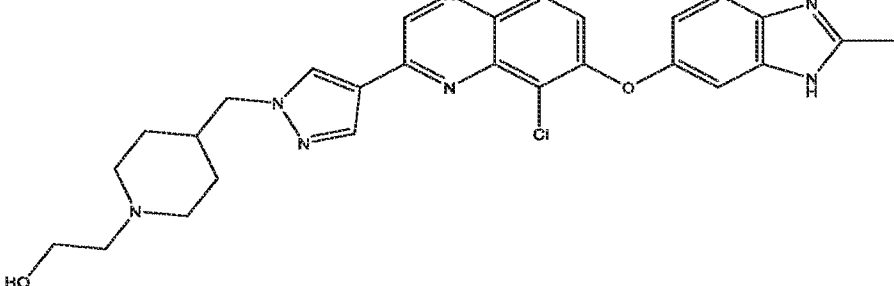
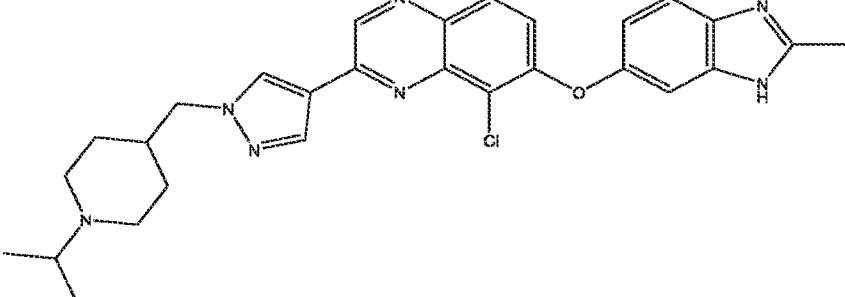
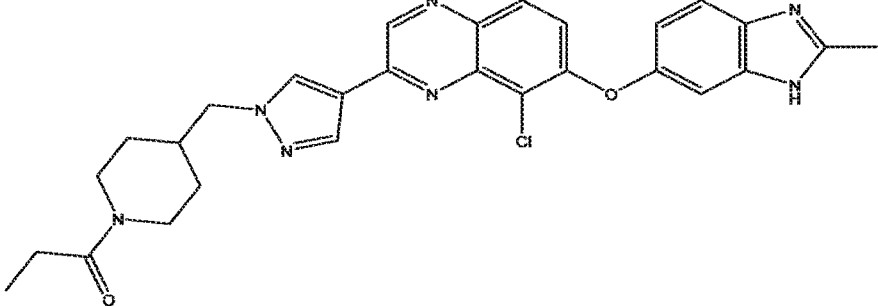
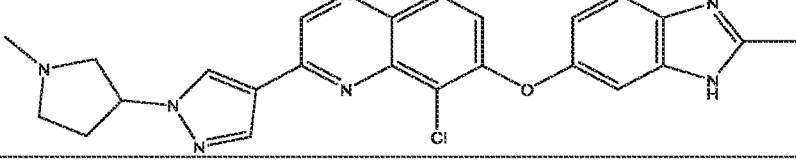
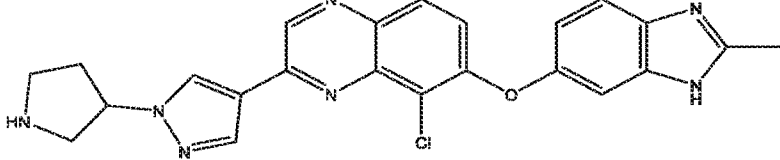
Table I

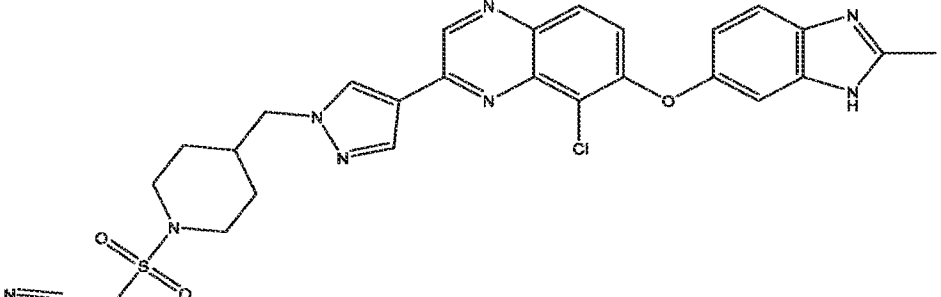
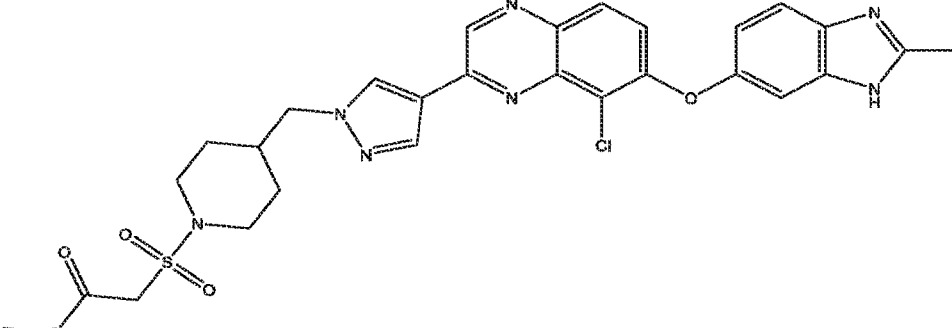
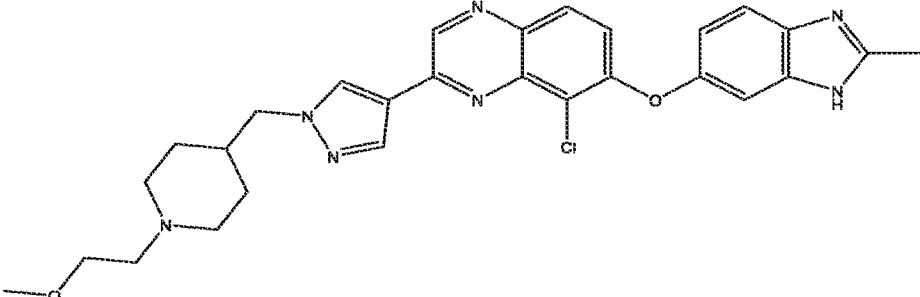
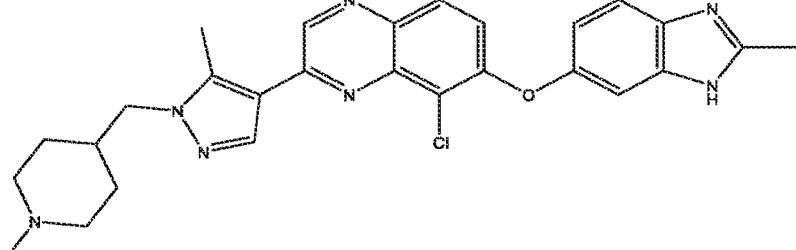
Compound No.	Structure
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2	
3	
4	

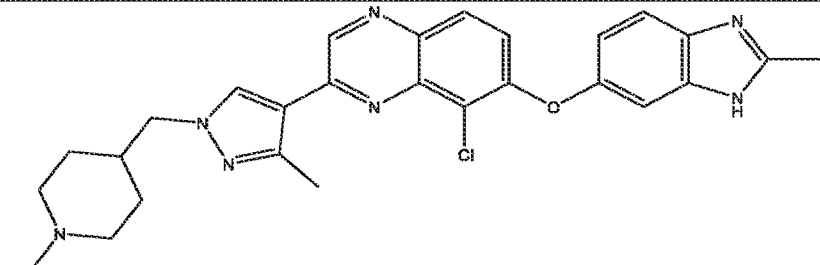
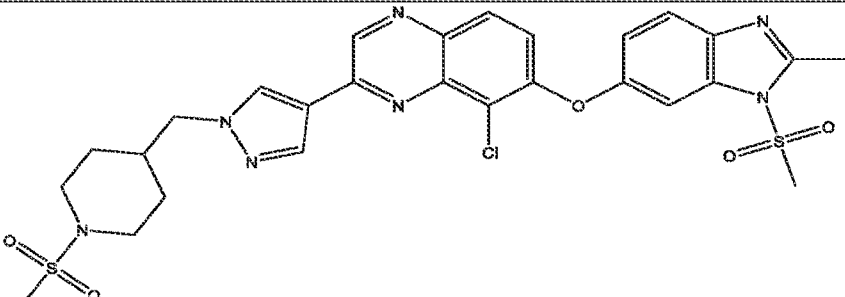
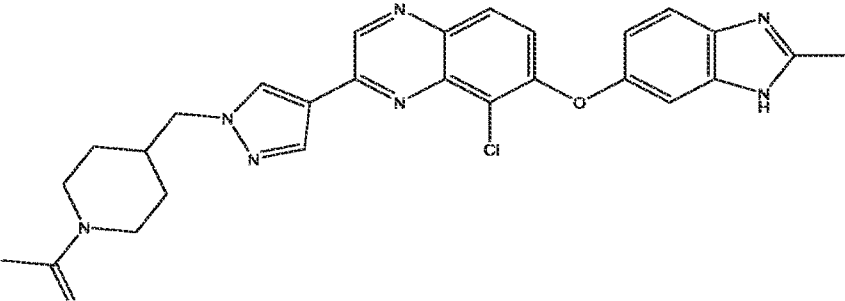
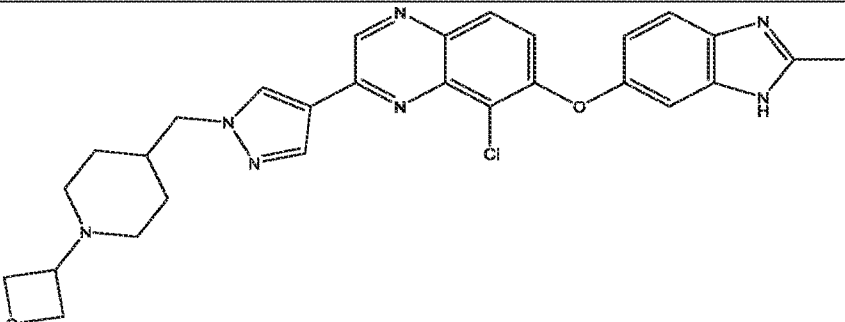
Compound No.	Structure
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6	
7	
8	
9	
10	

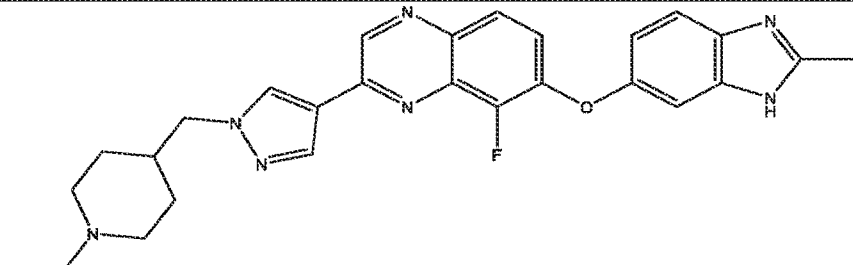
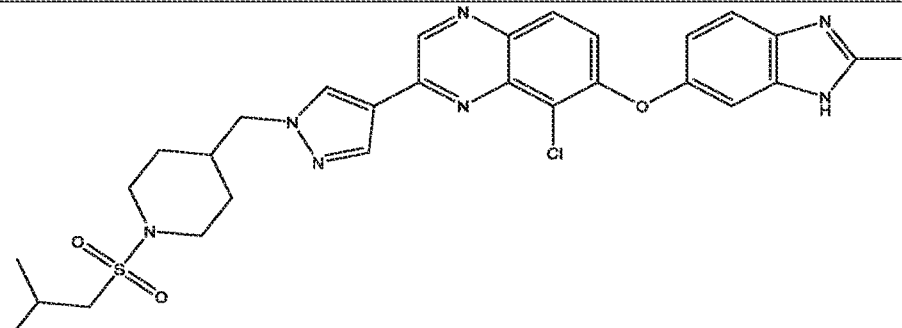
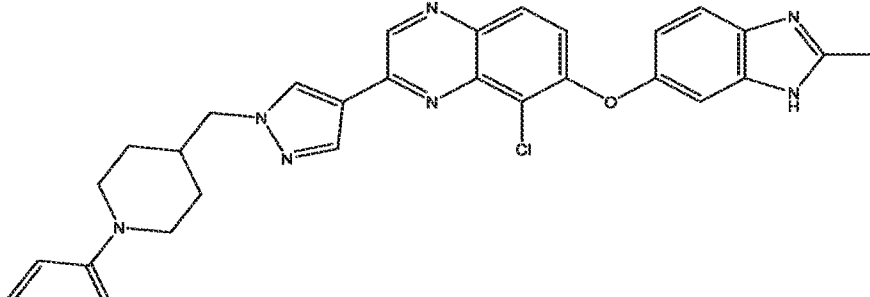
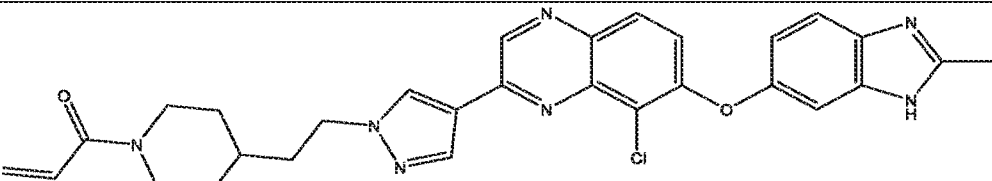
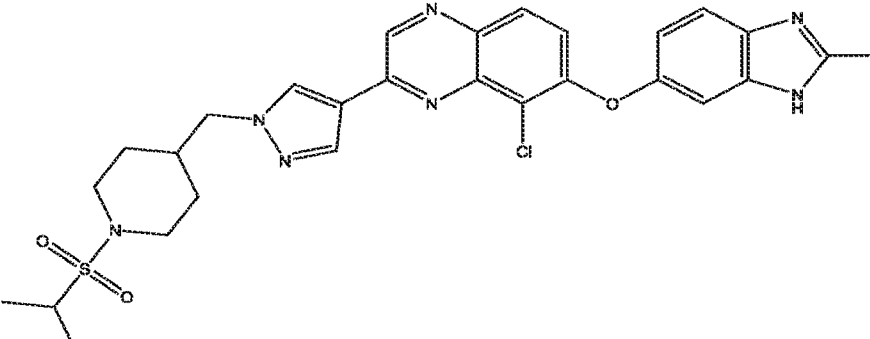
Compound No.	Structure
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12	
13	
14	
15	

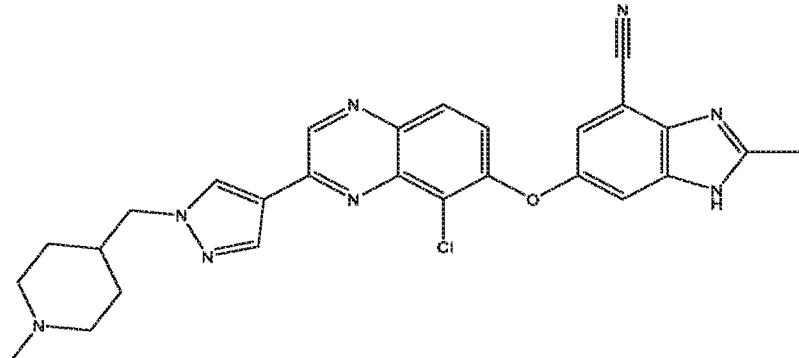
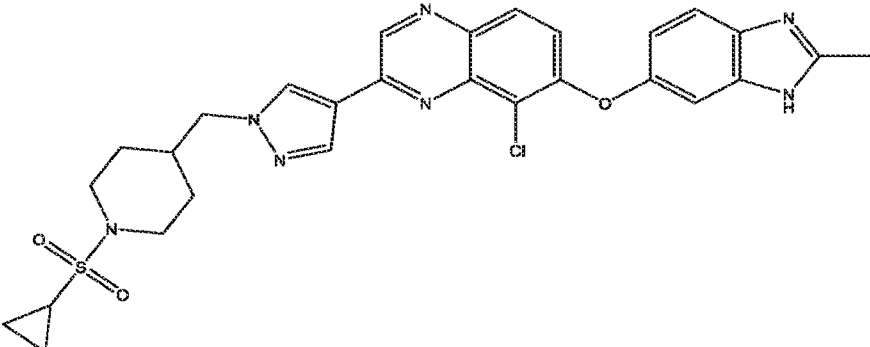
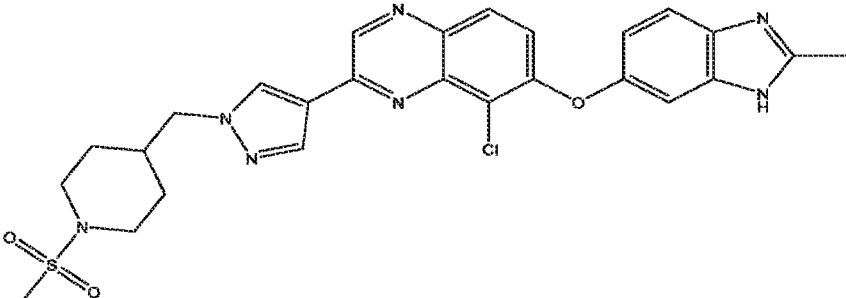
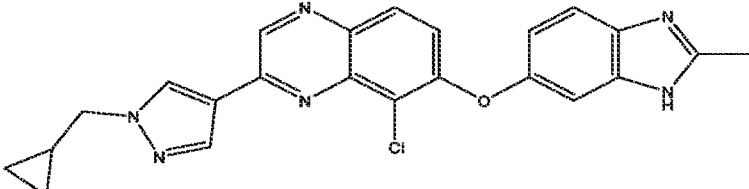
Compound No.	Structure
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17	
18	
19	
20	
21	

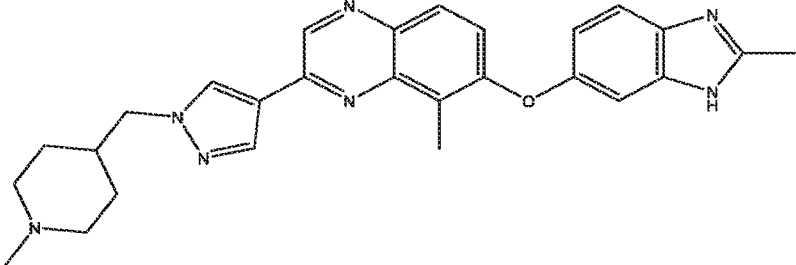
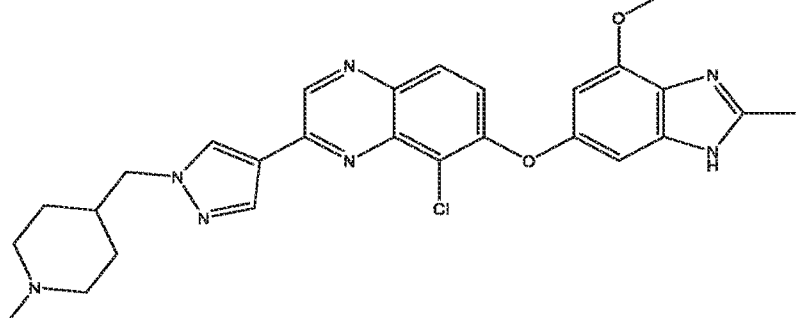
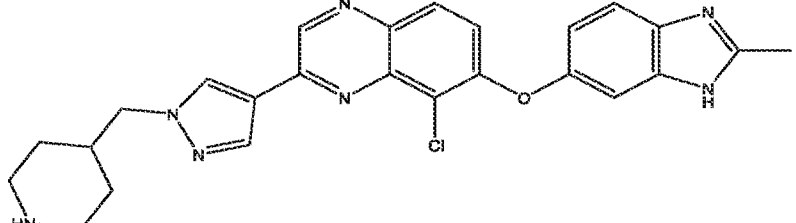
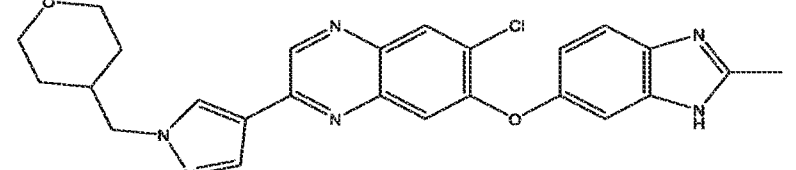
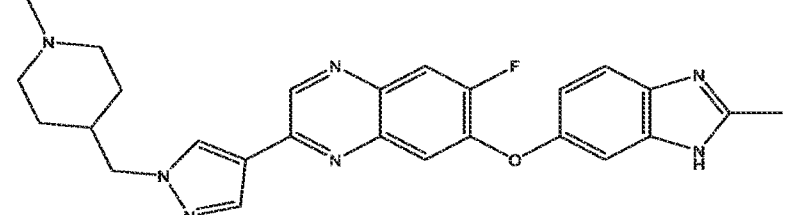
Compound No.	Structure
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23	
24	
25	
26	
27	

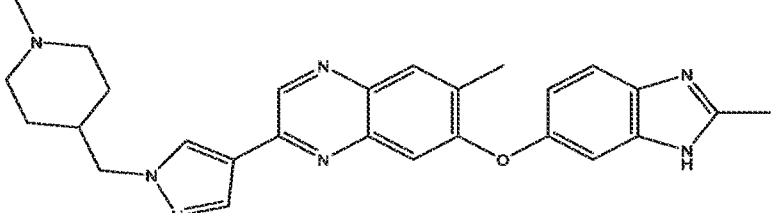
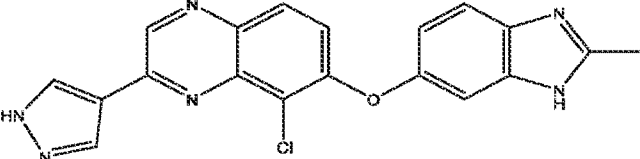
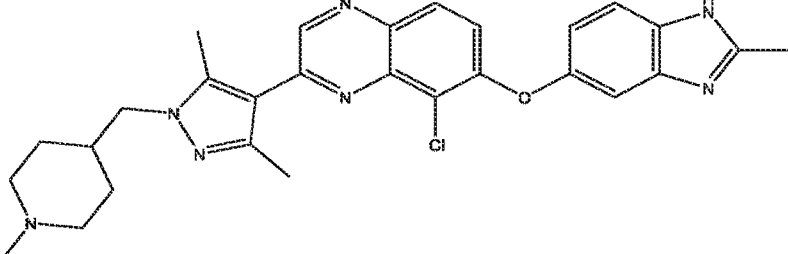
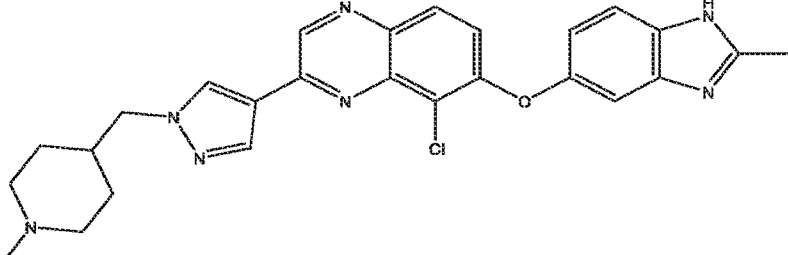
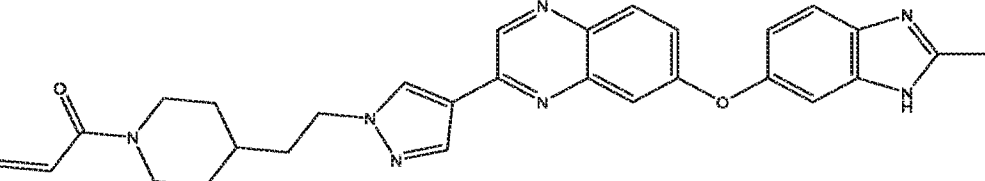
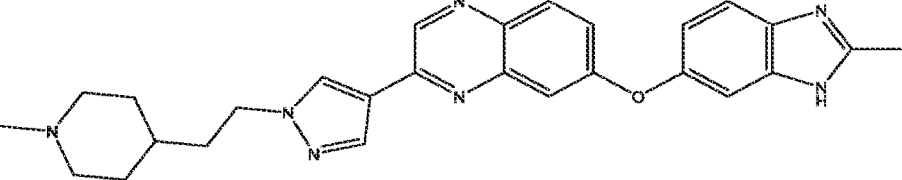
Compound No.	Structure
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29	
30	
31	

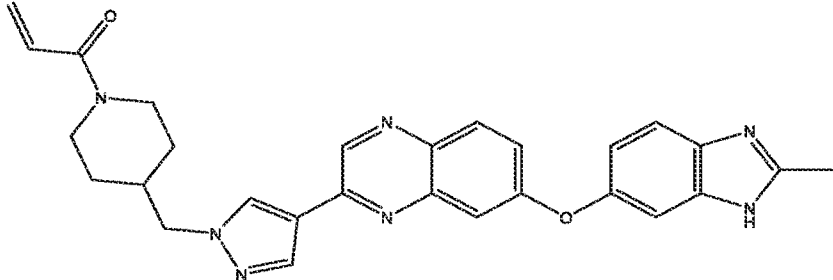
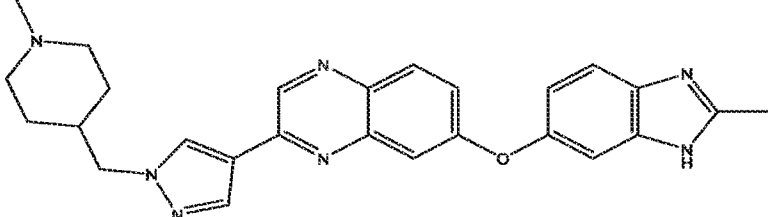
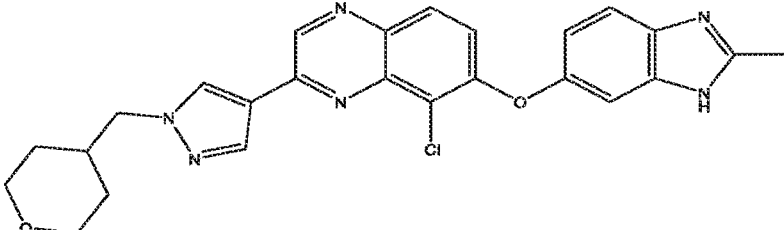
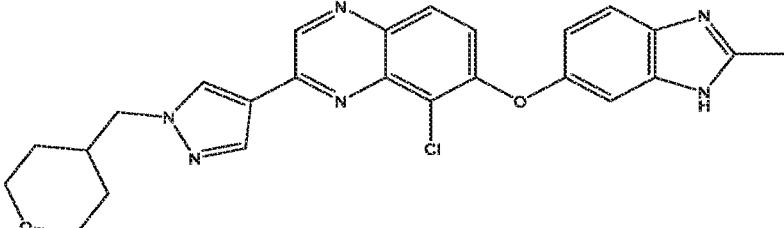
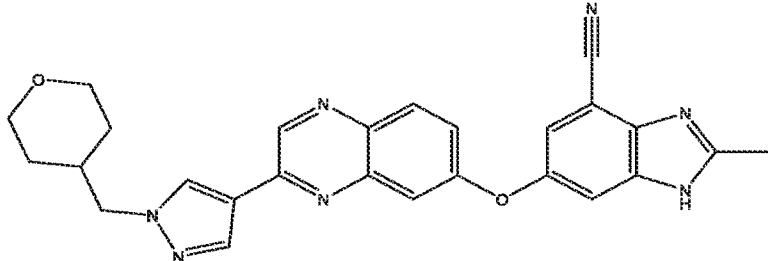
Compound No.	Structure
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33	
34	
35	

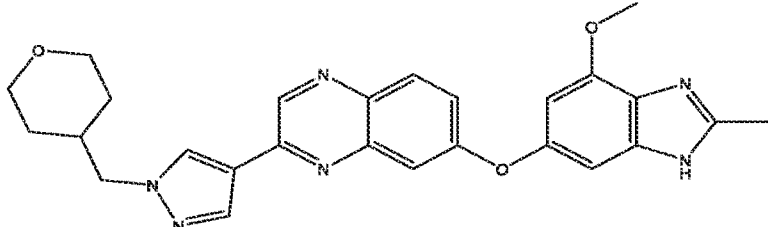
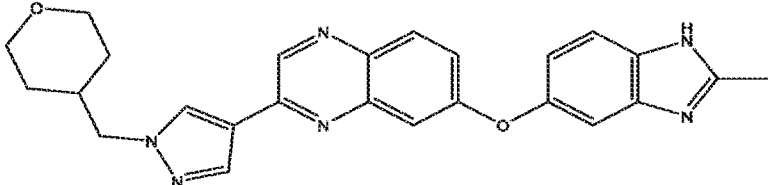
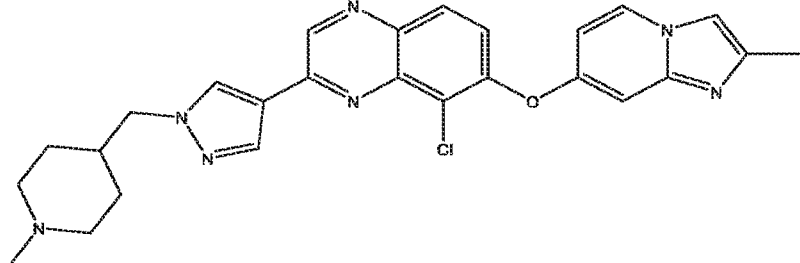
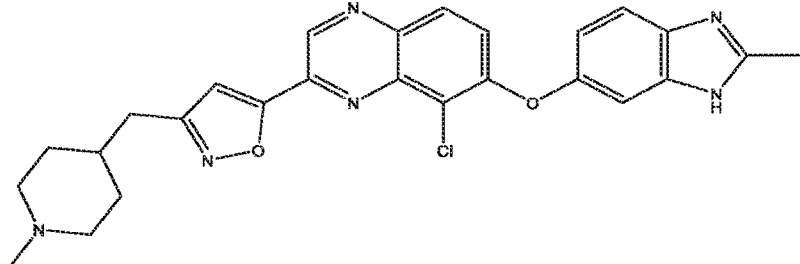
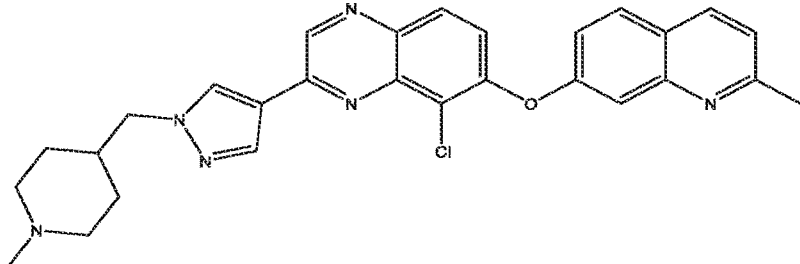
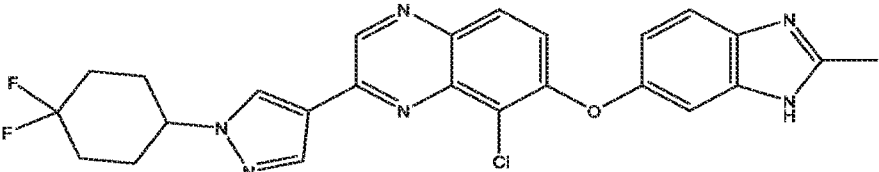
Compound No.	Structure
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37	 <chem>CC1=CN2C(=N1)C3=CC=C(C=C3)OC4=CC=C(C=C4)c5nc6c(ncn6)C5</chem>
38	 <chem>CC1=CN2C(=N1)C3=CC=C(C=C3)OC4=CC=C(C=C4)c5nc6c(ncn6)C5</chem>
39	 <chem>CC1=CN2C(=N1)C3=CC=C(C=C3)OC4=CC=C(C=C4)c5nc6c(ncn6)C5</chem>
40	 <chem>CC1=CN2C(=N1)C3=CC=C(C=C3)OC4=CC=C(C=C4)c5nc6c(ncn6)C5</chem>

Compound No.	Structure
41	
42	
43	
44	

Compound No.	Structure
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Compound No.	Structure
50	
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Compound No.	Structure
56	
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Compound No.	Structure
61	
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65	
66	

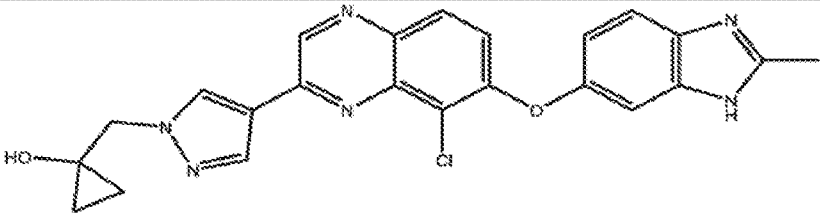
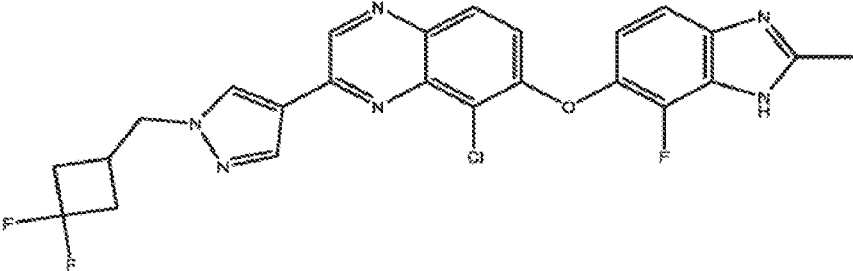
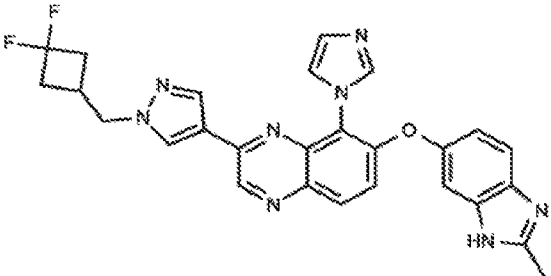
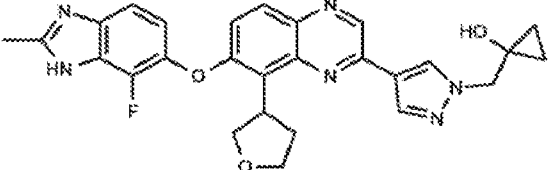
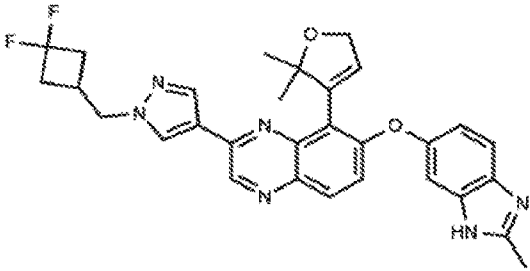
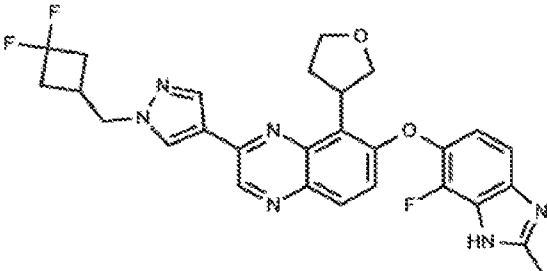
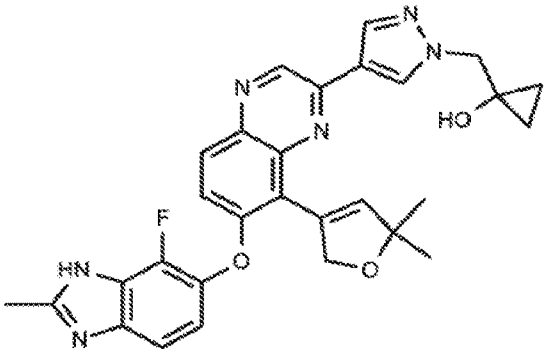
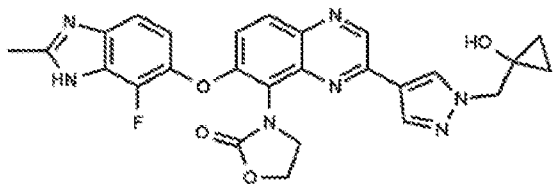
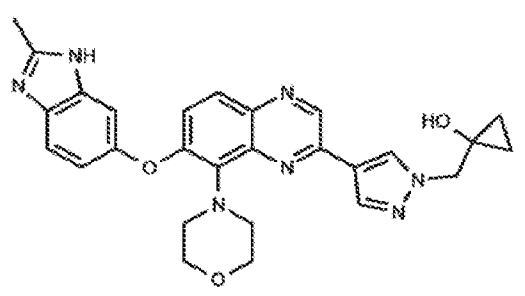
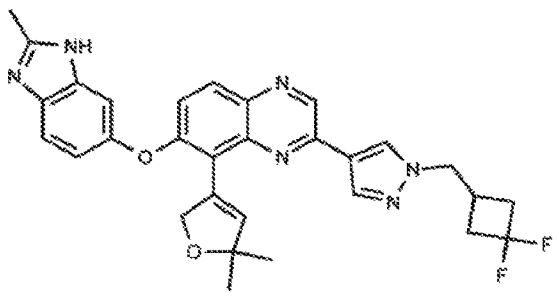
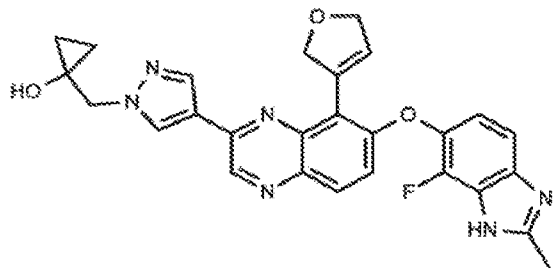
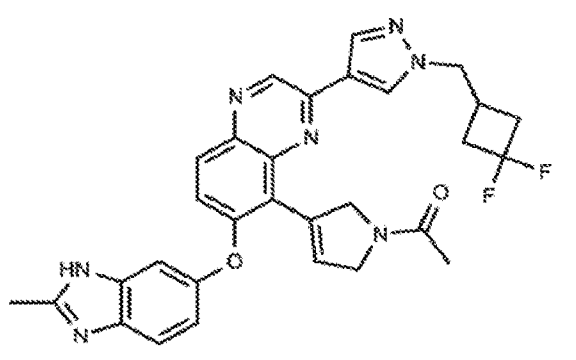
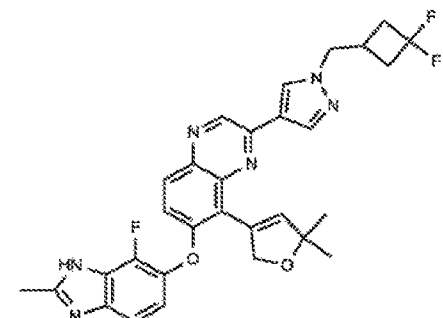
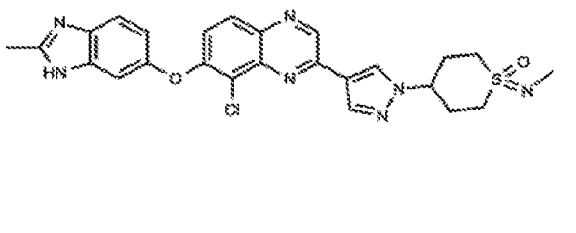
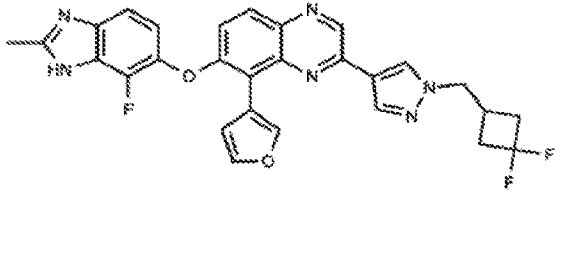
Compound No.	Structure
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68	

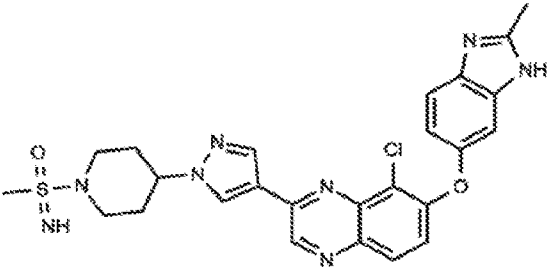
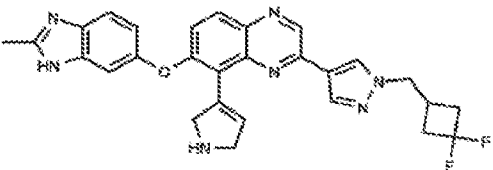
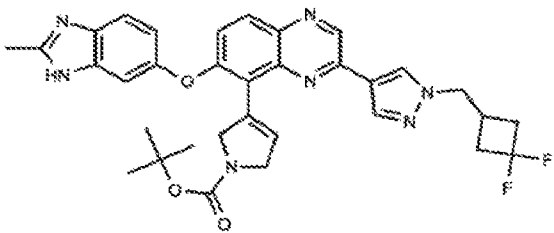
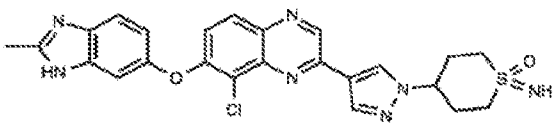
Table II

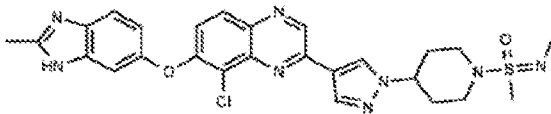
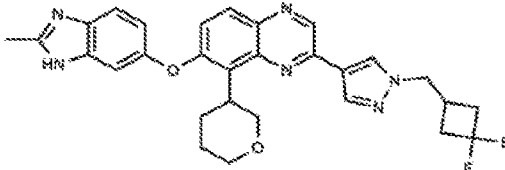
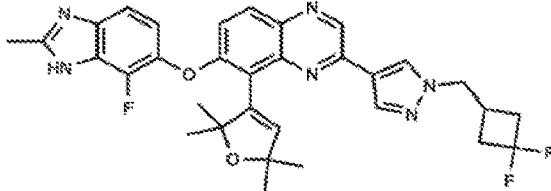
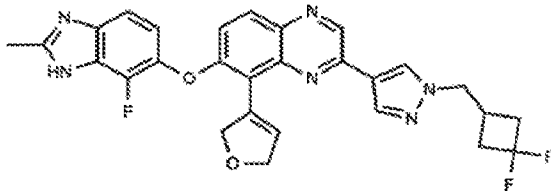
Compound No.	Structure
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70	

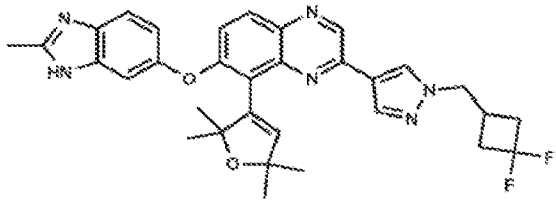
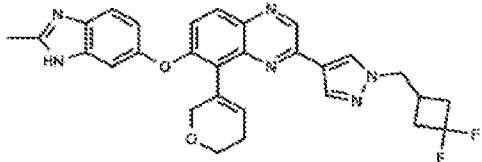
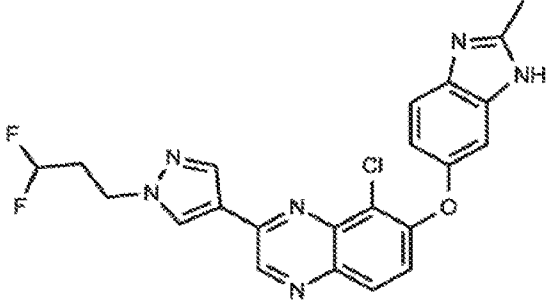
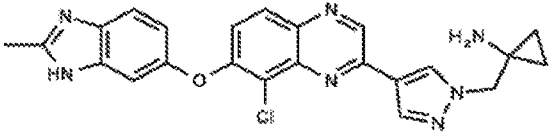
Compound No.	Structure
71	 Chemical structure of compound 71: A quinoline core substituted with a 4-(difluoromethyl)-1H-imidazol-2-yl group at position 2, a 4-methyl-1H-imidazol-2-yl group at position 6, and a 4-(4-methyl-1H-imidazol-2-yloxy)phenyl group at position 7. The quinoline ring also has a 2,2-dimethyl-1,3-dioxol-5-yl group at position 5.
72	 Chemical structure of compound 72: A quinoline core substituted with a 4-(difluoromethyl)-1H-imidazol-2-yl group at position 2, a 4-methyl-1H-imidazol-2-yl group at position 6, and a 4-(4-methyl-1H-imidazol-2-yloxy)-3-fluorophenyl group at position 7. The quinoline ring also has a 2,2-dimethyl-1,3-dioxol-5-yl group at position 5.
73	 Chemical structure of compound 73: A quinoline core substituted with a 4-(4-methyl-1H-imidazol-2-yloxy)-3-fluorophenyl group at position 2, a 4-methyl-1H-imidazol-2-yl group at position 6, and a 4-(4-methyl-1H-imidazol-2-yloxy)-3-fluorophenyl group at position 7. The quinoline ring also has a 2,2-dimethyl-1,3-dioxol-5-yl group at position 5.

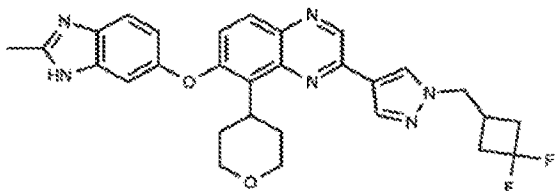
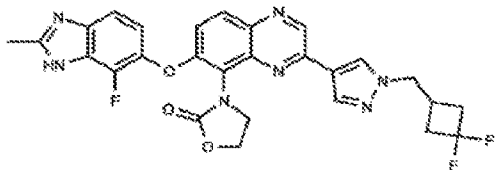
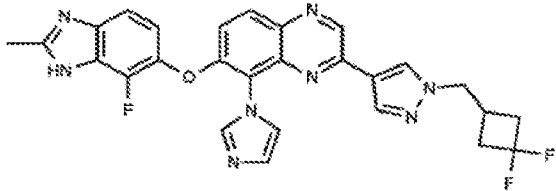
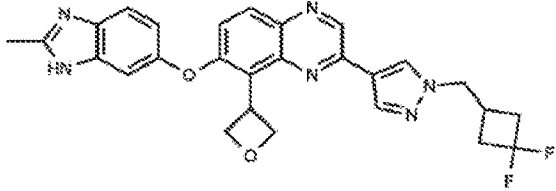
Compound No.	Structure
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75	
76	
77	

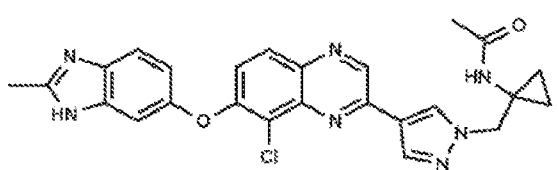
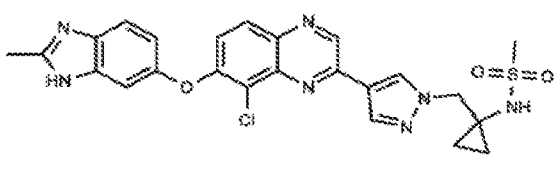
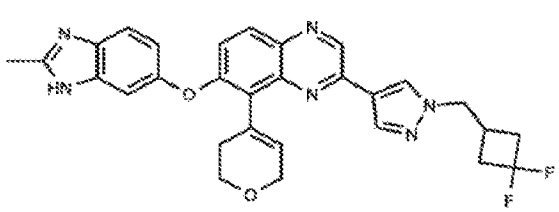
Compound No.	Structure
78	
79	
80	
81	

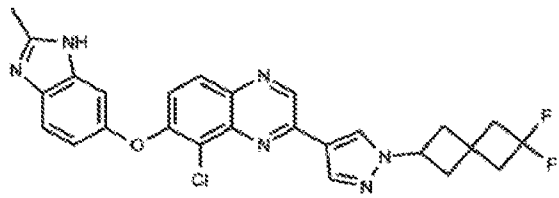
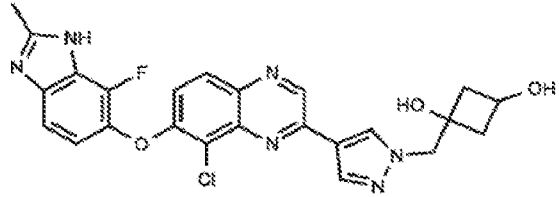
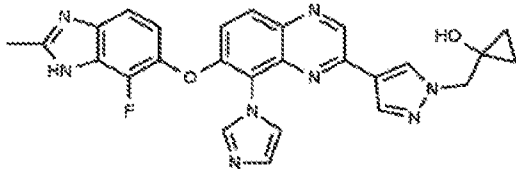
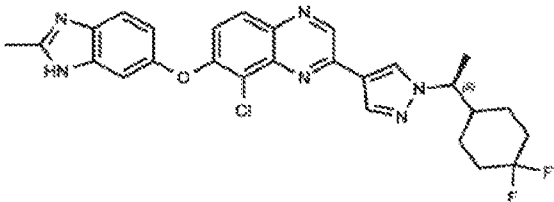
Compound No.	Structure
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83	
84	
85	

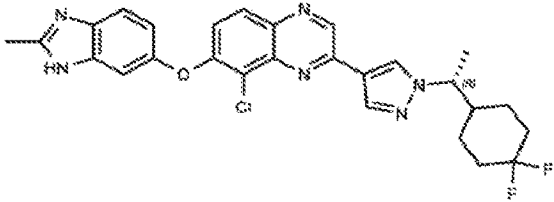
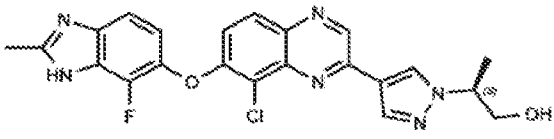
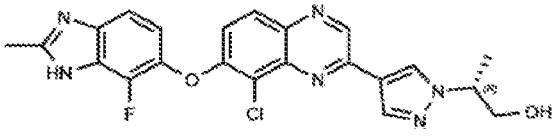
Compound No.	Structure
86	 Chemical structure of compound 86: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 8, and a 1-(1H-imidazol-2-yl)piperidin-4-yl group at position 4.
87	 Chemical structure of compound 87: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a tetrahydro-2H-pyran-2-yl group at position 8, and a 1-(2-(2,2,2-trifluoroethyl)-1H-imidazol-2-yl)methyl group at position 4.
88	 Chemical structure of compound 88: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a 2,2,4,4-tetramethyl-1,3-dioxolane-5-yl group at position 8, and a 1-(2-(2,2,2-trifluoroethyl)-1H-imidazol-2-yl)methyl group at position 4.
89	 Chemical structure of compound 89: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a 2,2,5-trimethyl-1,3-dioxolane-5-yl group at position 8, and a 1-(2-(2,2,2-trifluoroethyl)-1H-imidazol-2-yl)methyl group at position 4.

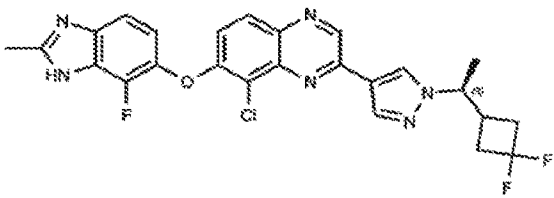
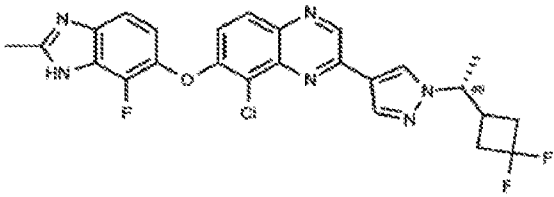
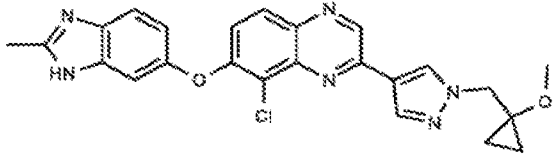
Compound No.	Structure
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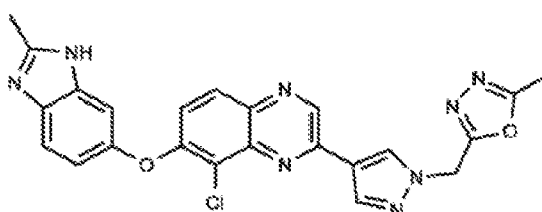
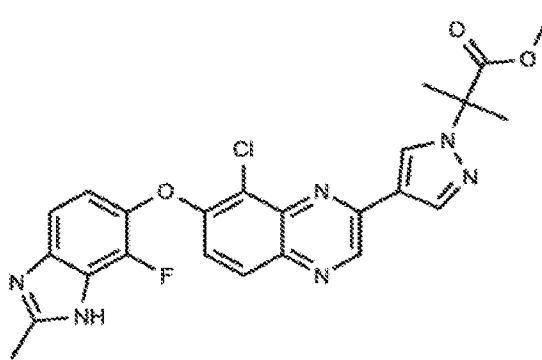
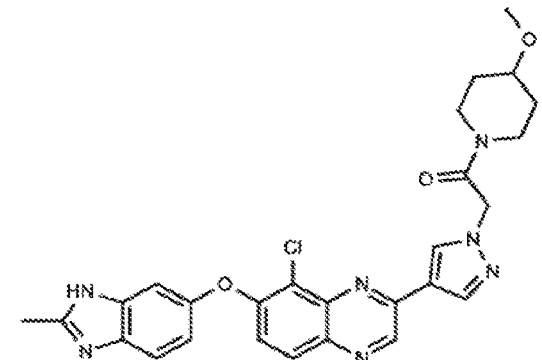
Compound No.	Structure
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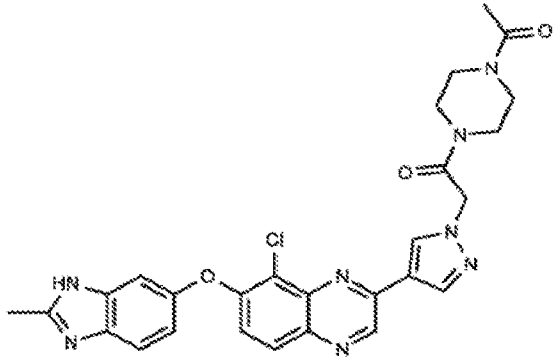
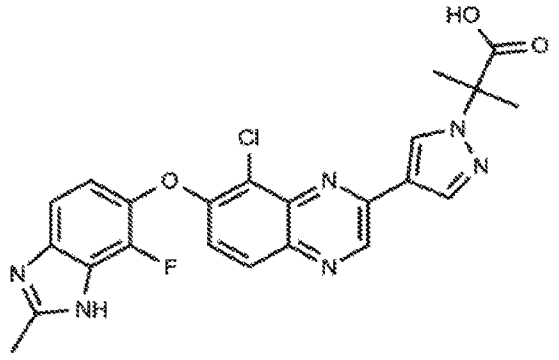
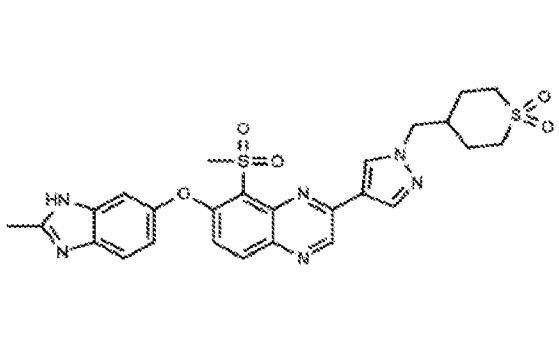
Compound No.	Structure
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100	

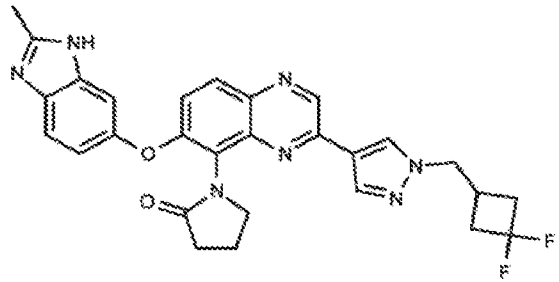
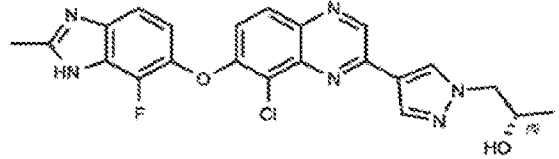
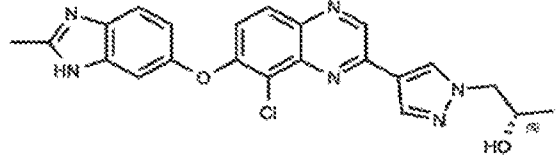
Compound No.	Structure
101	
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104	

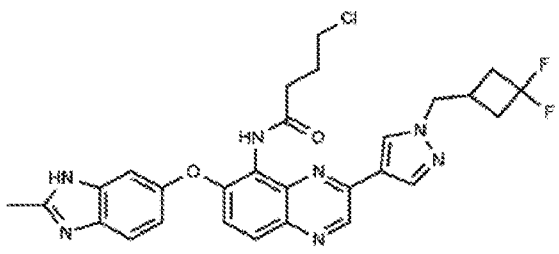
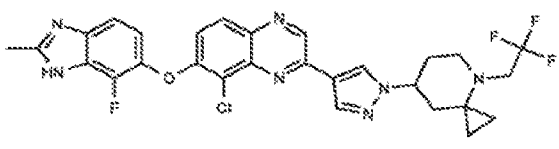
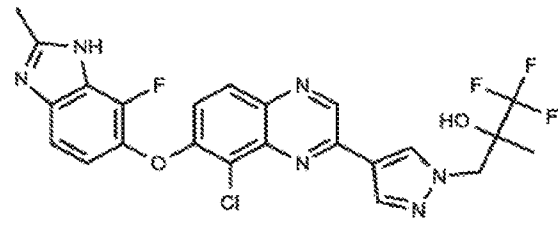
Compound No.	Structure
105	 Chemical structure of compound 105: A 4-(4-methyl-1H-imidazol-2-yl)phenyl group is linked via an ether bond to a 4-chloro-2-((1-(2,2,2-trifluorocyclohexyl)-1H-imidazol-2-yl)methyl)quinoline group.
106	 Chemical structure of compound 106: A 4-(4-methyl-1H-imidazol-2-yl)phenyl group is linked via an ether bond to a 4-chloro-2-((1-(2-hydroxypropyl)-1H-imidazol-2-yl)methyl)quinoline group.
107	 Chemical structure of compound 107: A 4-(4-methyl-1H-imidazol-2-yl)phenyl group is linked via an ether bond to a 4-chloro-2-((1-(2-hydroxypropyl)-1H-imidazol-2-yl)methyl)quinoline group.

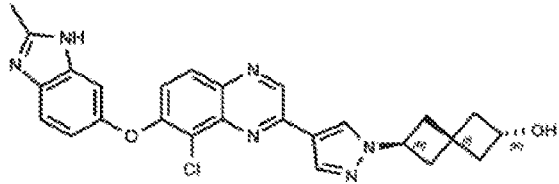
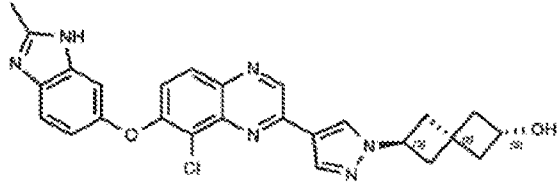
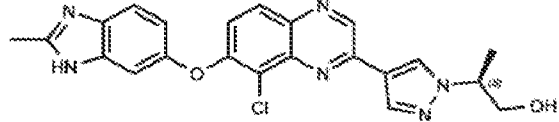
Compound No.	Structure
108	 Chemical structure of compound 108: A molecule featuring a 4-fluoro-2-methyl-1H-indazole ring connected via an ether linkage to a 4-chloro-2-((1-methyl-1H-1,2,4-triazol-5-yl)methyl)quinoline ring. The triazole ring is further substituted with a (2,2-difluorocyclobutyl)methyl group.
109	 Chemical structure of compound 109: A molecule featuring a 4-fluoro-2-methyl-1H-indazole ring connected via an ether linkage to a 4-chloro-2-((1-methyl-1H-1,2,4-triazol-5-yl)methyl)quinoline ring. The triazole ring is further substituted with a (2,2-difluorocyclobutyl)methyl group.
110	 Chemical structure of compound 110: A molecule featuring a 4-fluoro-2-methyl-1H-indazole ring connected via an ether linkage to a 4-chloro-2-((1-methyl-1H-1,2,4-triazol-5-yl)methyl)quinoline ring. The triazole ring is further substituted with a (2-iodo-2-oxiranyl)methyl group.

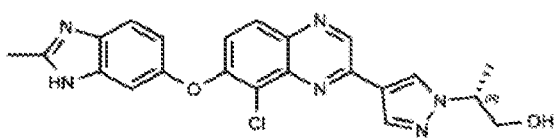
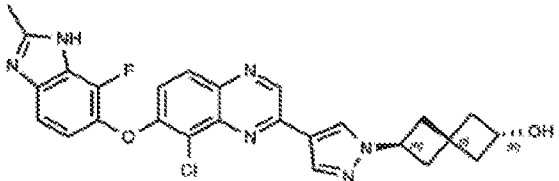
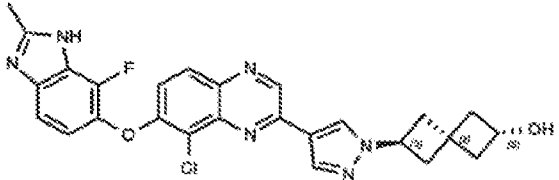
Compound No.	Structure
111	 Chemical structure of compound 111: A 4-methyl-1H-indazol-5-yl group is connected via an ether linkage to a 6-chloroquinoline ring. The quinoline ring is further connected at its 2-position to a 1,2,4-triazole ring. The triazole ring is substituted at its 4-position with a (2-methyl-1,3,4-oxadiazol-5-yl)methyl group.
112	 Chemical structure of compound 112: A 4-methyl-1H-indazol-5-yl group is connected via an ether linkage to a 6-chloroquinoline ring. The quinoline ring is further connected at its 2-position to a 1,2,4-triazole ring. The triazole ring is substituted at its 4-position with a (2-methoxy-2-methylpropanoyl) group.
113	 Chemical structure of compound 113: A 4-methyl-1H-indazol-5-yl group is connected via an ether linkage to a 6-chloroquinoline ring. The quinoline ring is further connected at its 2-position to a 1,2,4-triazole ring. The triazole ring is substituted at its 4-position with a (2-methoxy-2-methylpropanoyl) group.

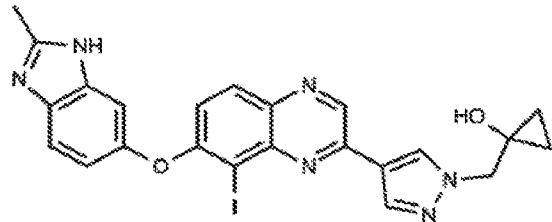
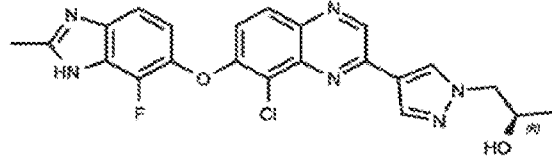
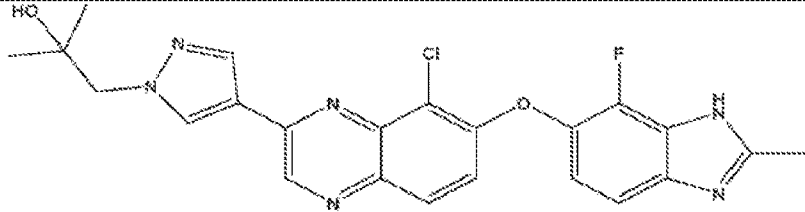
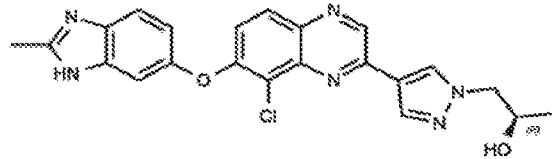
Compound No.	Structure
114	 Chemical structure of compound 114: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 8, and a 1-(2-(2-(2-(2-oxo-2-(2-methyl-2,6-piperidinediyl)ethyl)amino)ethyl)amino)ethyl)pyrazol-4-yl group at position 4.
115	 Chemical structure of compound 115: A quinazoline core substituted with a 4-(2-(4-methyl-1H-imidazol-2-yl)-6-fluorophenoxy) group at position 6, a chlorine atom at position 8, and a 1-(2-(2-(2-(2-hydroxy-2-methylpropanoyl)amino)ethyl)amino)ethyl)pyrazol-4-yl group at position 4.
116	 Chemical structure of compound 116: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a dimethylsulfonyl group at position 8, and a 1-(2-(2-(2-(2-(dimethylsulfonyl)cyclohexyl)amino)ethyl)amino)ethyl)pyrazol-4-yl group at position 4.

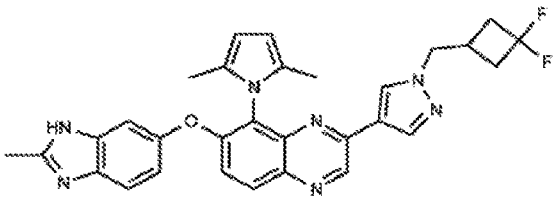
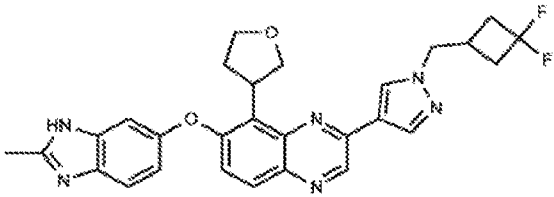
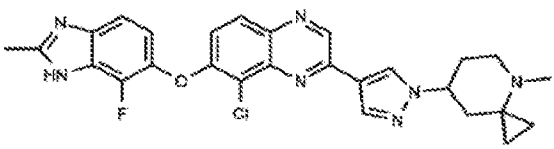
Compound No.	Structure
117	 Chemical structure of compound 117: A 4-methyl-1H-imidazo[5,4-b]pyridine ring is connected via an ether linkage to a 2-(2-oxo-2,3-dihydro-1H-pyrrol-1-yl)-6-(1,2,4-triazol-4-yl)quinoline ring. The triazole ring is further connected via a methylene group to a 1,1-difluoro-2-methylcyclobutyl group.
118	 Chemical structure of compound 118: A 4-methyl-1H-imidazo[5,4-b]pyridine ring is connected via an ether linkage to a 2-chloro-6-(1,2,4-triazol-4-yl)quinoline ring. The triazole ring is further connected via a methylene group to a 1-hydroxy-2-methylpropyl group.
119	 Chemical structure of compound 119: A 4-methyl-1H-imidazo[5,4-b]pyridine ring is connected via an ether linkage to a 2-chloro-6-(1,2,4-triazol-4-yl)quinoline ring. The triazole ring is further connected via a methylene group to a 1-hydroxy-2-methylpropyl group.

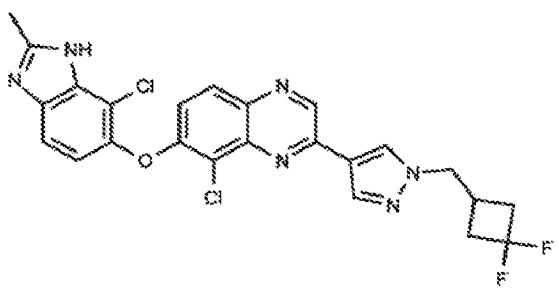
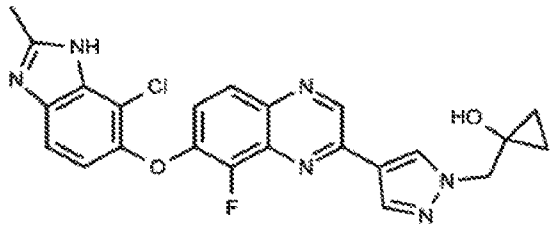
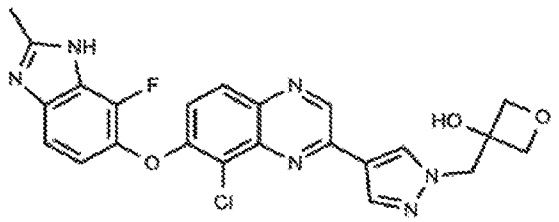
Compound No.	Structure
120	 Chemical structure of compound 120: A quinazoline core substituted at position 2 with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group, at position 4 with a 4-chlorophenyl group, and at position 6 with a 4-(4-(chloromethyl)-1H-imidazol-2-yl)phenyl group. The quinazoline core is also substituted at position 8 with a 4-(4-(chloromethyl)-1H-imidazol-2-yl)phenyl group.
121	 Chemical structure of compound 121: A quinazoline core substituted at position 2 with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group, at position 4 with a 4-chlorophenyl group, and at position 6 with a 4-(4-(chloromethyl)-1H-imidazol-2-yl)phenyl group. The quinazoline core is also substituted at position 8 with a 4-(4-(chloromethyl)-1H-imidazol-2-yl)phenyl group.
122	 Chemical structure of compound 122: A quinazoline core substituted at position 2 with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group, at position 4 with a 4-chlorophenyl group, and at position 6 with a 4-(4-(chloromethyl)-1H-imidazol-2-yl)phenyl group. The quinazoline core is also substituted at position 8 with a 4-(4-(chloromethyl)-1H-imidazol-2-yl)phenyl group.

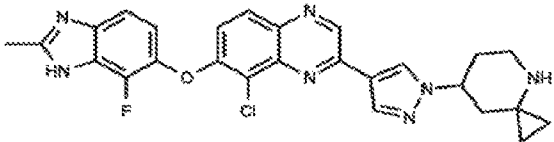
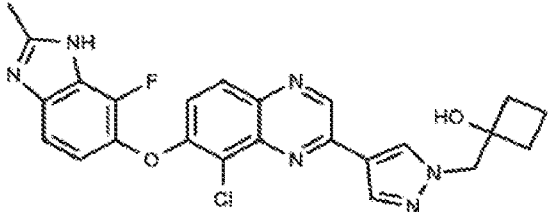
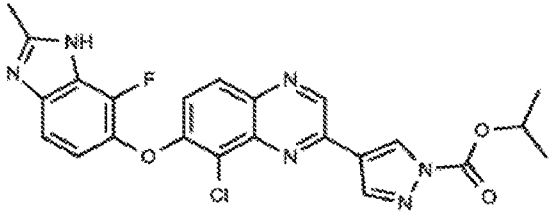
Compound No.	Structure
123	 Chemical structure of compound 123: A 4-methyl-1H-imidazo[5,4-b]pyridine ring is connected via an ether linkage to a 6-chloroquinoline ring. The quinoline ring is further connected to a 1,2,4-triazole ring, which is linked to a bicyclic system (a cyclobutane ring fused to a cyclopropane ring) with a hydroxyl group.
124	 Chemical structure of compound 124: A 4-methyl-1H-imidazo[5,4-b]pyridine ring is connected via an ether linkage to a 6-chloroquinoline ring. The quinoline ring is further connected to a 1,2,4-triazole ring, which is linked to a bicyclic system (a cyclobutane ring fused to a cyclopropane ring) with a hydroxyl group.
125	 Chemical structure of compound 125: A 4-methyl-1H-imidazo[5,4-b]pyridine ring is connected via an ether linkage to a 6-chloroquinoline ring. The quinoline ring is further connected to a 1,2,4-triazole ring, which is linked to a bicyclic system (a cyclobutane ring fused to a cyclopropane ring) with a hydroxyl group.

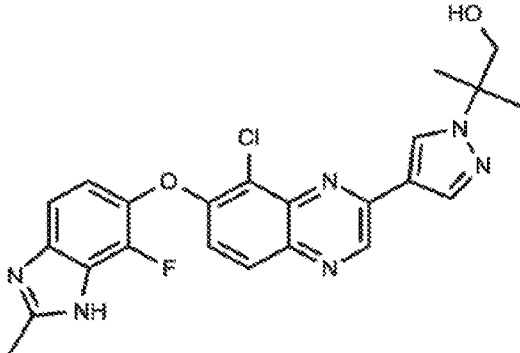
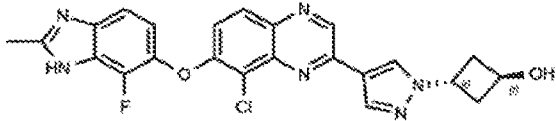
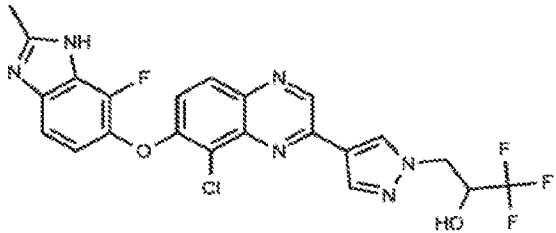
Compound No.	Structure
126	 Chemical structure of compound 126: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 8, and a 1-((R)-2-hydroxyethyl)-1H-imidazol-2-yl group at position 4.
127	 Chemical structure of compound 127: A quinazoline core substituted with a 2-fluoro-4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 8, and a 1-((R)-2-hydroxy-2,3-dihydro-1H-spiro[3.3]hept-2-yl)-1H-imidazol-2-yl group at position 4.
128	 Chemical structure of compound 128: A quinazoline core substituted with a 2-fluoro-4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 8, and a 1-((S)-2-hydroxy-2,3-dihydro-1H-spiro[3.3]hept-2-yl)-1H-imidazol-2-yl group at position 4.

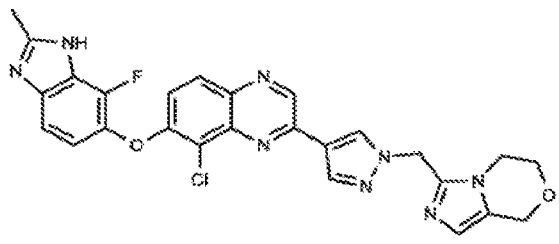
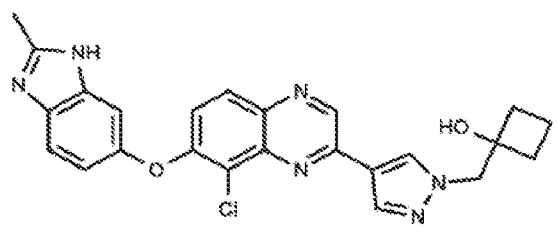
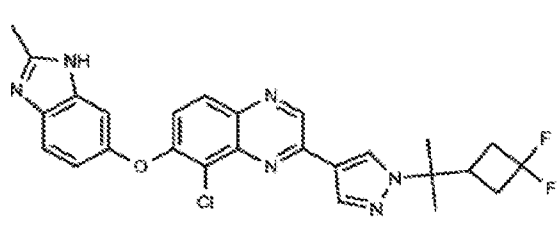
Compound No.	Structure
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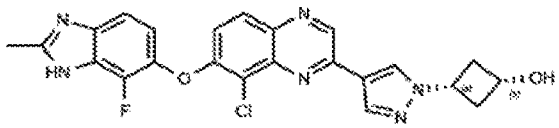
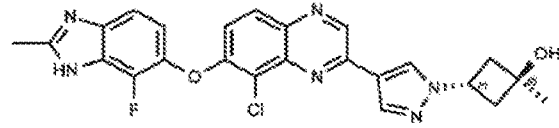
Compound No.	Structure
133	 Chemical structure of compound 133: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a 4-methyl-1H-imidazol-2-yl group at position 4, and a 1-(4,4-difluorocyclobutyl)methyl-1H-imidazol-2-yl group at position 2.
134	 Chemical structure of compound 134: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a 4-methyl-1H-imidazol-2-yl group at position 4, and a 1-(4,4-difluorocyclobutyl)methyl-1H-imidazol-2-yl group at position 2. The structure also features a 1,3-dioxolane ring attached to the quinazoline core.
135	 Chemical structure of compound 135: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a 4-methyl-1H-imidazol-2-yl group at position 4, and a 1-(4,4-difluorocyclobutyl)methyl-1H-imidazol-2-yl group at position 2. The structure also features a 1,3-dioxolane ring attached to the quinazoline core.

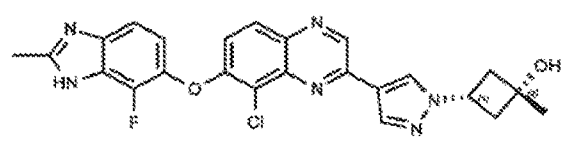
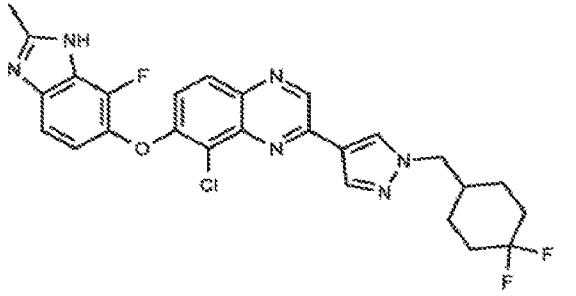
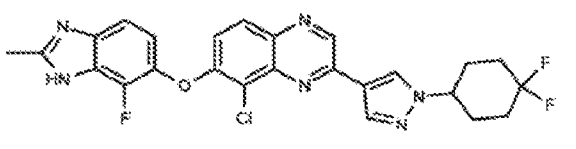
Compound No.	Structure
136	 Chemical structure of compound 136: A 2-methyl-1H-indazole ring is connected via an ether linkage to a 2,6-dichlorophenyl ring. This phenyl ring is further connected via an ether linkage to a 2,7-dichloroquinazoline ring. The quinazoline ring is connected at its 4-position to a 1,2,4-triazole ring, which is in turn connected to a 1,1-difluorocyclobutyl group.
137	 Chemical structure of compound 137: A 2-methyl-1H-indazole ring is connected via an ether linkage to a 2-chloro-6-fluorophenyl ring. This phenyl ring is further connected via an ether linkage to a 2,7-difluoroquinazoline ring. The quinazoline ring is connected at its 4-position to a 1,2,4-triazole ring, which is in turn connected to a 1-hydroxy-2-methylcyclopropyl group.
138	 Chemical structure of compound 138: A 2-methyl-1H-indazole ring is connected via an ether linkage to a 2-fluoro-6-chlorophenyl ring. This phenyl ring is further connected via an ether linkage to a 2,7-dichloroquinazoline ring. The quinazoline ring is connected at its 4-position to a 1,2,4-triazole ring, which is in turn connected to a 1-hydroxy-2-methyl-1,3-dioxolane group.

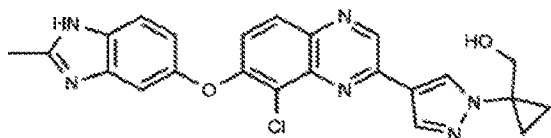
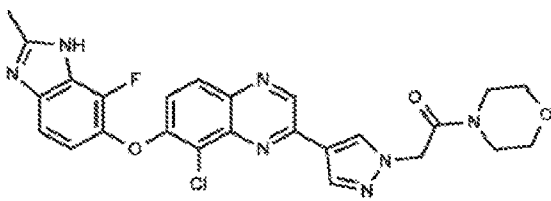
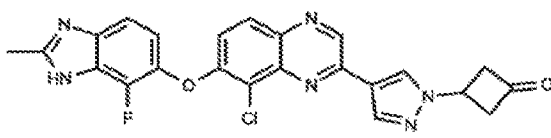
Compound No.	Structure
139	 Chemical structure of compound 139: A 4-fluoro-2-methyl-1H-indazole ring is connected via an ether linkage to a 4-chloro-2-((1H-imidazol-2-yl)methyl)quinoline ring. The imidazole ring is further substituted with a 2-azabicyclo[2.1.0]pentan-2-yl group.
140	 Chemical structure of compound 140: A 4-fluoro-2-methyl-1H-indazole ring is connected via an ether linkage to a 4-chloro-2-((1H-imidazol-2-yl)methyl)quinoline ring. The imidazole ring is further substituted with a 1-hydroxy-2,2-dimethylpropan-1-yl group.
141	 Chemical structure of compound 141: A 4-fluoro-2-methyl-1H-indazole ring is connected via an ether linkage to a 4-chloro-2-((1H-imidazol-2-yl)methyl)quinoline ring. The imidazole ring is further substituted with an isopropyl ester group.

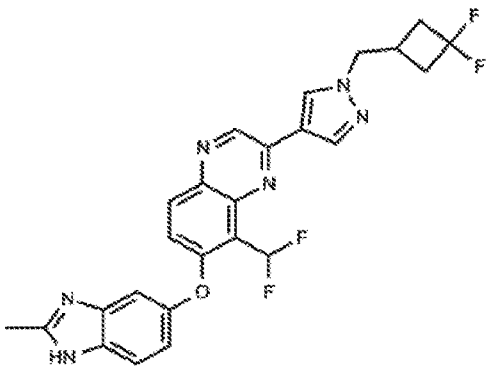
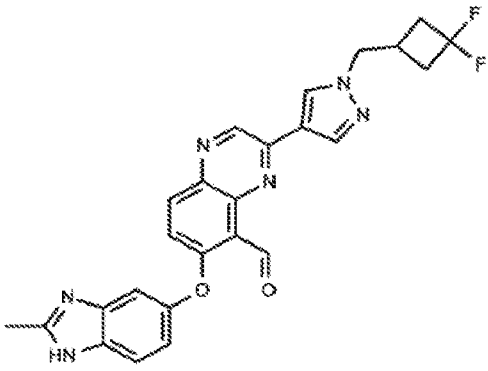
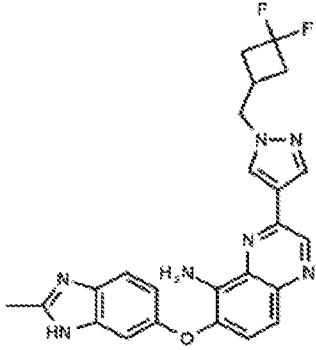
Compound No.	Structure
142	
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144	

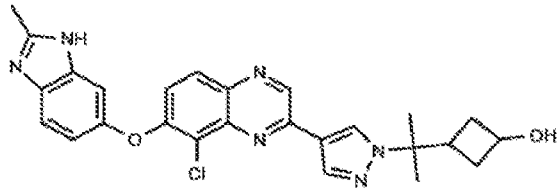
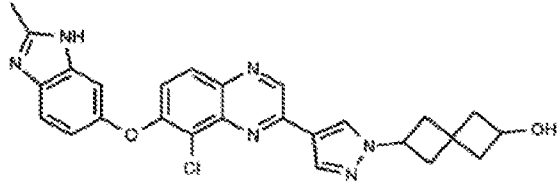
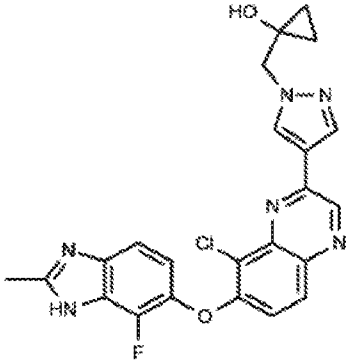
Compound No.	Structure
145	 Chemical structure of compound 145: A 4-(4-chloro-2-(4-(2-methyl-1H-imidazol-5-yl)phenoxy)quinazolin-6-yl)pyrimidin-2-ylmethyl-1,2,3,4-tetrahydro-1H-benzotriazin-5-yl group.
146	 Chemical structure of compound 146: A 4-(4-chloro-2-(4-(2-methyl-1H-imidazol-5-yl)phenoxy)quinazolin-6-yl)pyrimidin-2-ylmethyl-1,2,3,4-tetrahydro-1H-benzotriazin-5-yl group.
147	 Chemical structure of compound 147: A 4-(4-chloro-2-(4-(2-methyl-1H-imidazol-5-yl)phenoxy)quinazolin-6-yl)pyrimidin-2-ylmethyl-1,2,3,4-tetrahydro-1H-benzotriazin-5-yl group.

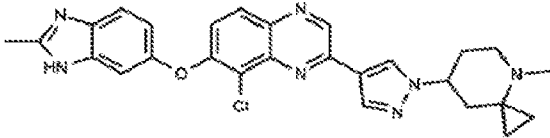
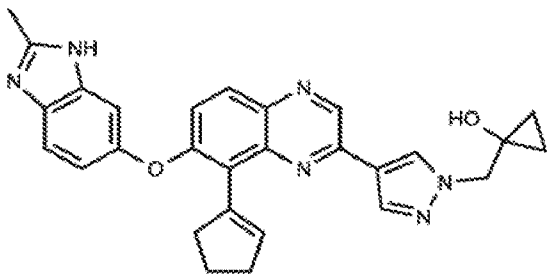
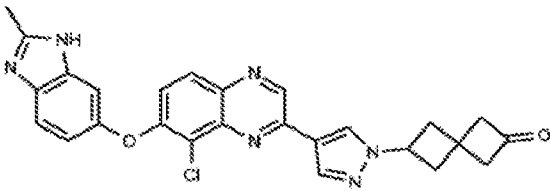
Compound No.	Structure
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149	 <chem>Cc1nc2cc(OC3=CC4=C(N2)N=CN=C3Cl)ccc2[nH]1C5=CN=C(N5)C6CC[C@H]6O</chem>
150	 <chem>Cc1nc2cc(OC3=CC4=C(N2)N=CN=C3Cl)ccc2[nH]1C5=CN=C(N5)C6CC(=O)C6</chem>

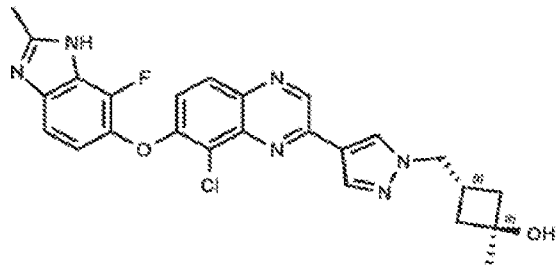
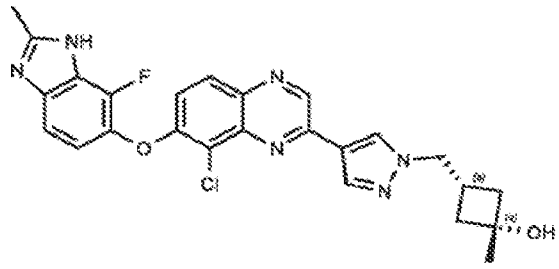
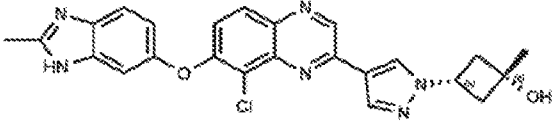
Compound No.	Structure
151	 Chemical structure of compound 151: A molecule featuring a 4-fluoro-2-methyl-1H-imidazo[5,4-b]pyridine ring connected via an ether linkage to a 4-chloro-2-(1H-imidazo[5,4-b]pyridin-2-yl)phenyl ring. This second phenyl ring is further connected via another ether linkage to a 4-(1H-imidazo[5,4-b]pyridin-2-yl)phenyl ring. The final phenyl ring is connected via a methylene group to a cyclobutane ring, which has a hydroxyl group attached to one of its carbons.
152	 Chemical structure of compound 152: A molecule featuring a 4-fluoro-2-methyl-1H-imidazo[5,4-b]pyridine ring connected via an ether linkage to a 4-chloro-2-(1H-imidazo[5,4-b]pyridin-2-yl)phenyl ring. This second phenyl ring is further connected via another ether linkage to a 4-(1H-imidazo[5,4-b]pyridin-2-yl)phenyl ring. The final phenyl ring is connected via a methylene group to a cyclohexane ring, which has two fluorine atoms attached to one of its carbons.
153	 Chemical structure of compound 153: A molecule featuring a 4-fluoro-2-methyl-1H-imidazo[5,4-b]pyridine ring connected via an ether linkage to a 4-chloro-2-(1H-imidazo[5,4-b]pyridin-2-yl)phenyl ring. This second phenyl ring is further connected via another ether linkage to a 4-(1H-imidazo[5,4-b]pyridin-2-yl)phenyl ring. The final phenyl ring is connected via a methylene group to a cyclohexane ring, which has two fluorine atoms attached to one of its carbons.

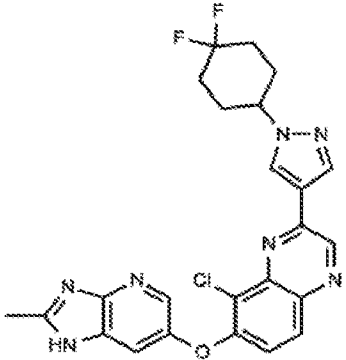
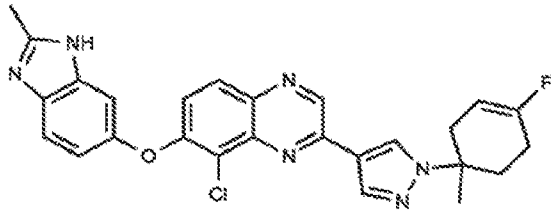
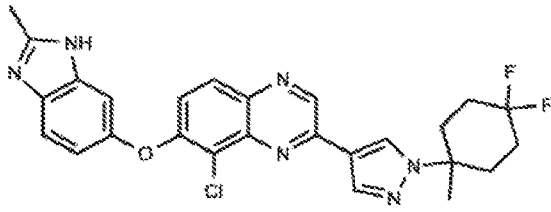
Compound No.	Structure
154	 Chemical structure of compound 154: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-chloro-2-((1-(cyclopropylmethyl)-1H-imidazol-2-yl)methyl)quinoline group.
155	 Chemical structure of compound 155: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-chloro-2-((1-(2-oxo-2-(morpholin-4-yl)ethyl)-1H-imidazol-2-yl)methyl)quinoline group.
156	 Chemical structure of compound 156: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-chloro-2-((1-(4-oxocyclobutyl)-1H-imidazol-2-yl)methyl)quinoline group.

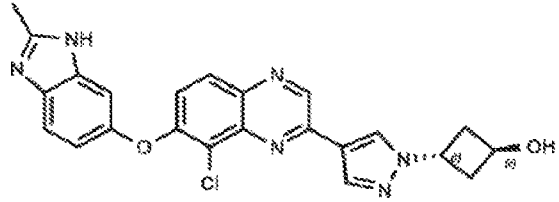
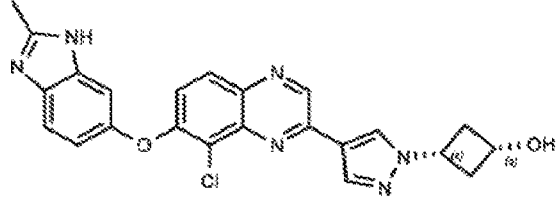
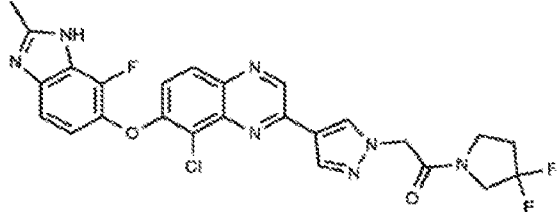
Compound No.	Structure
157	
158	
159	

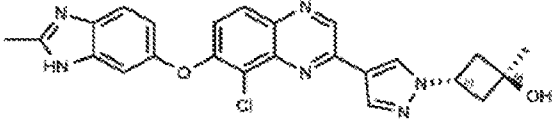
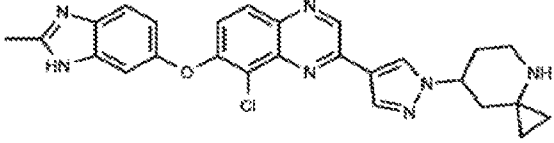
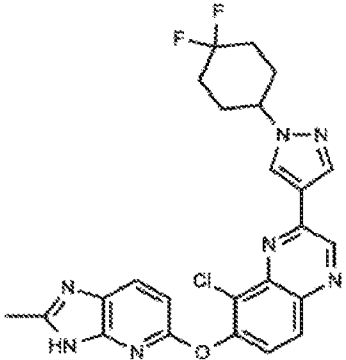
Compound No.	Structure
160	 Chemical structure of compound 160: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 7, and a 1-(4-hydroxy-4-methylcyclopentyl)-1H-imidazol-2-yl group at position 4.
161	 Chemical structure of compound 161: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 7, and a 1-(4-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1H-imidazol-2-yl group at position 4.
162	 Chemical structure of compound 162: A quinazoline core substituted with a 4-(4-fluoro-2-methyl-1H-imidazol-5-yl)phenoxy group at position 6, a chlorine atom at position 7, and a 1-(1-hydroxy-2-(1H-imidazol-2-yl)ethyl)cyclopropyl group at position 4.

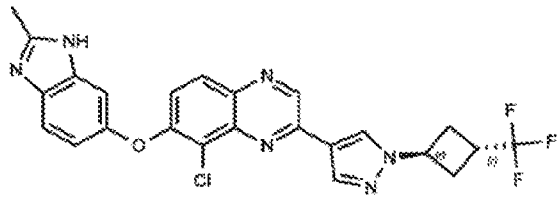
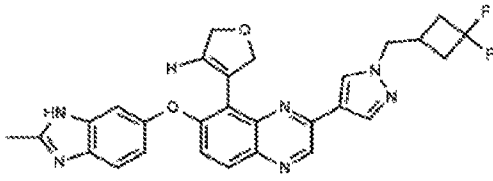
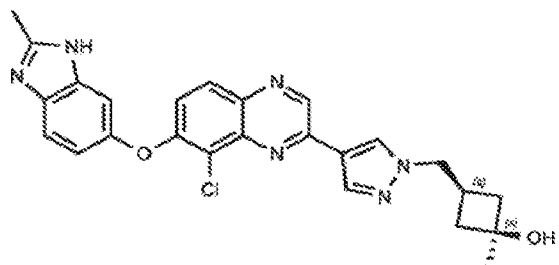
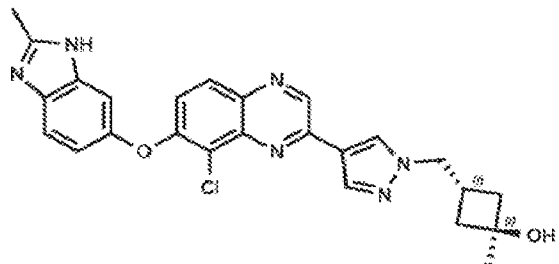
Compound No.	Structure
163	 Chemical structure of compound 163: A 4-methyl-1H-indazol-5-yl group is connected via an ether linkage to a 6-chloro-2,3-bis(4-methyl-1H-indazol-5-yloxy)quinazolin-4-yl group. This quinazolinyl group is further connected via a triazole ring to a 4-methyl-1,4,5,6-tetrahydropyridine-2-yl group.
164	 Chemical structure of compound 164: A 4-methyl-1H-indazol-5-yl group is connected via an ether linkage to a 6-cyclopentyl-2,3-bis(4-methyl-1H-indazol-5-yloxy)quinazolin-4-yl group. This quinazolinyl group is further connected via a triazole ring to a 2-(cyclopropylmethoxy)-1,4,5,6-tetrahydropyridine-4-yl group.
165	 Chemical structure of compound 165: A 4-methyl-1H-indazol-5-yl group is connected via an ether linkage to a 6-chloro-2,3-bis(4-methyl-1H-indazol-5-yloxy)quinazolin-4-yl group. This quinazolinyl group is further connected via a triazole ring to a 4-oxo-4,5,6,7-tetrahydro-1,2,3,4-tetrahydronaphthalene-1-yl group.

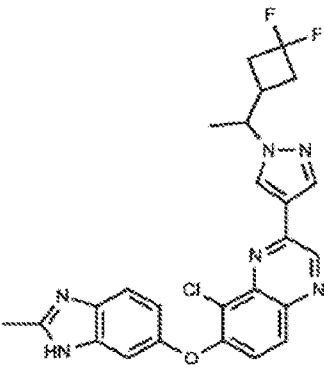
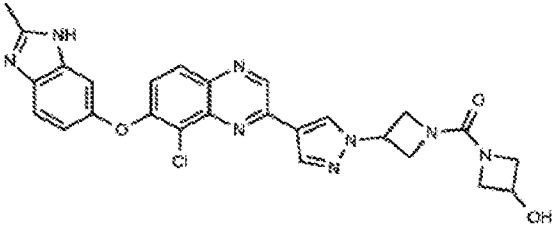
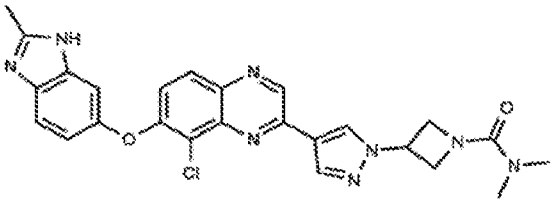
Compound No.	Structure
166	 Chemical structure of compound 166: A 2-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-chloro-2-fluorophenyl group. This phenyl group is further connected to a quinazoline ring system. The quinazoline ring is substituted with a 1,2,4-triazole ring, which is in turn connected to a cyclobutyl ring. The cyclobutyl ring has a hydroxyl group (OH) attached to one of its carbons.
167	 Chemical structure of compound 167: A 2-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-chloro-2-fluorophenyl group. This phenyl group is further connected to a quinazoline ring system. The quinazoline ring is substituted with a 1,2,4-triazole ring, which is in turn connected to a cyclobutyl ring. The cyclobutyl ring has a hydroxyl group (OH) attached to one of its carbons.
168	 Chemical structure of compound 168: A 2-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-chloro-2-fluorophenyl group. This phenyl group is further connected to a quinazoline ring system. The quinazoline ring is substituted with a 1,2,4-triazole ring, which is in turn connected to a cyclobutyl ring. The cyclobutyl ring has a hydroxyl group (OH) attached to one of its carbons.

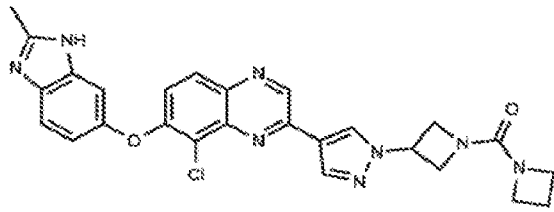
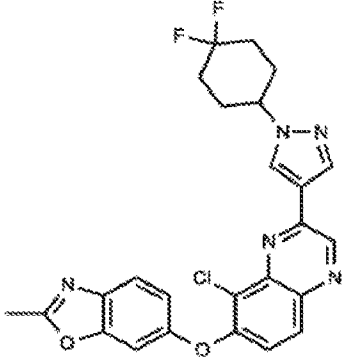
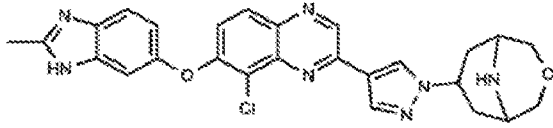
Compound No.	Structure
169	 Chemical structure of compound 169: A complex molecule featuring a central quinazoline core. The quinazoline has a chlorine atom at position 8 and a 4-methyl-1H-imidazol-2-yl group at position 6. It is linked via an ether oxygen at position 4 to a 4-methyl-1H-imidazol-2-yl group. The quinazoline is also linked at position 2 to a 1,2,4-triazole ring, which is further substituted with a 4-(difluoromethyl)cyclohexyl group.
170	 Chemical structure of compound 170: A complex molecule featuring a central quinazoline core. The quinazoline has a chlorine atom at position 8 and a 4-methyl-1H-imidazol-2-yl group at position 6. It is linked via an ether oxygen at position 4 to a 4-methyl-1H-imidazol-2-yl group. The quinazoline is also linked at position 2 to a 1,2,4-triazole ring, which is further substituted with a 4-fluorocyclohexyl group.
171	 Chemical structure of compound 171: A complex molecule featuring a central quinazoline core. The quinazoline has a chlorine atom at position 8 and a 4-methyl-1H-imidazol-2-yl group at position 6. It is linked via an ether oxygen at position 4 to a 4-methyl-1H-imidazol-2-yl group. The quinazoline is also linked at position 2 to a 1,2,4-triazole ring, which is further substituted with a 4-fluorocyclohexyl group.

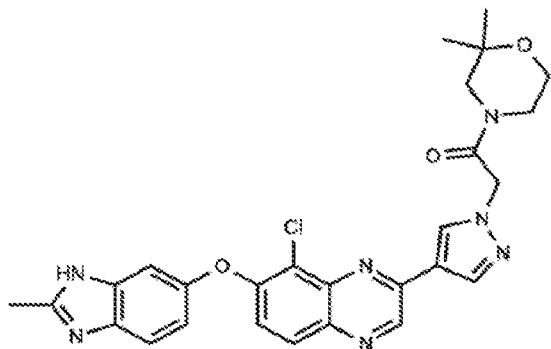
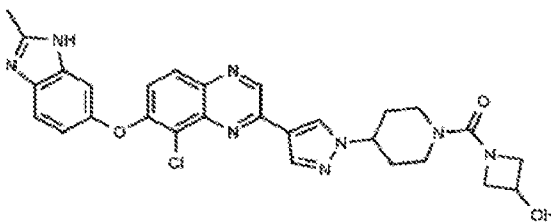
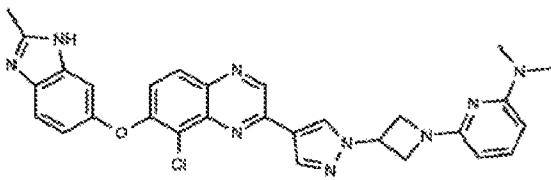
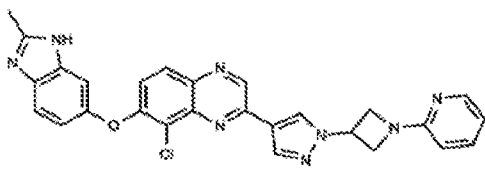
Compound No.	Structure
172	 Chemical structure of compound 172: A 4-methyl-1H-imidazo[5,1-b]pyridine ring is connected via an ether linkage to a 4-chloro-2-((1R,2R)-2-hydroxy-1,2-dihydrocyclopropyl)-1H-imidazo[5,1-b]pyridine ring.
173	 Chemical structure of compound 173: A 4-methyl-1H-imidazo[5,1-b]pyridine ring is connected via an ether linkage to a 4-chloro-2-((1S,2S)-2-hydroxy-1,2-dihydrocyclopropyl)-1H-imidazo[5,1-b]pyridine ring.
174	 Chemical structure of compound 174: A 4-fluoro-1H-imidazo[5,1-b]pyridine ring is connected via an ether linkage to a 4-chloro-2-((1S,2S)-2-(2-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-imidazo[5,1-b]pyridine ring.

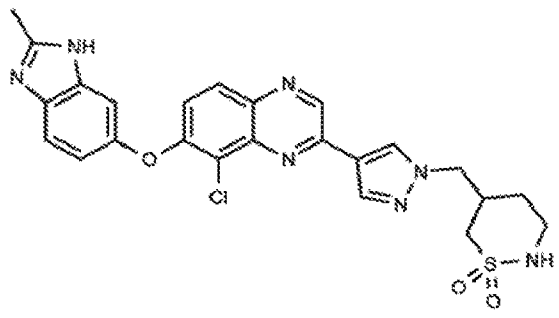
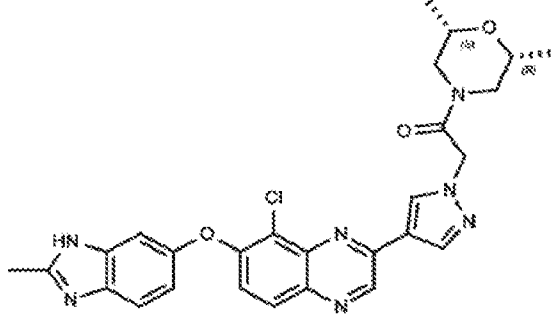
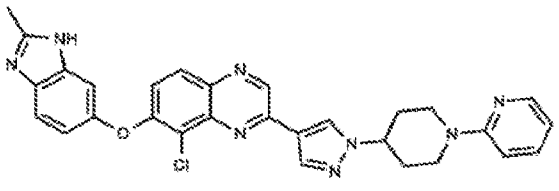
Compound No.	Structure
175	
176	
177	

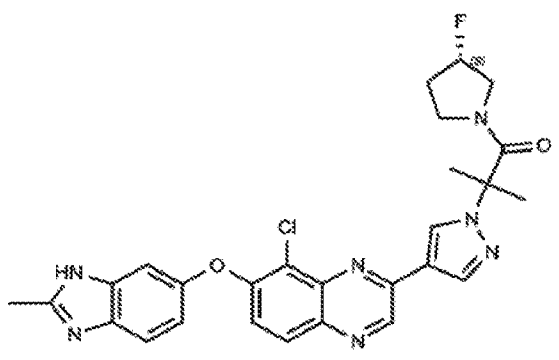
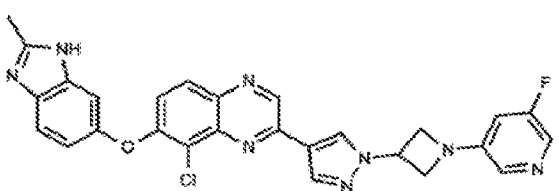
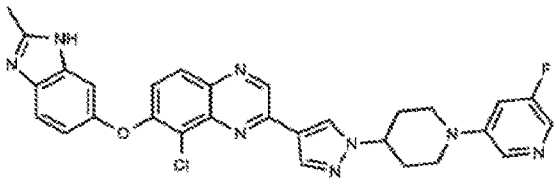
Compound No.	Structure
178	 Chemical structure of compound 178: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-chloro-2-((1H-1,2,4-triazol-4-yl)methyl)quinoline group. The triazole ring is further connected to a cyclobutyl group, which is substituted with a trifluoromethyl group (CF₃) at the 1-position.
179	 Chemical structure of compound 179: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-((1H-1,2,4-triazol-4-yl)methyl)-2-(furan-2-yl)quinoline group. The triazole ring is further connected to a cyclobutyl group, which is substituted with a trifluoromethyl group (CF₃) at the 1-position.
180	 Chemical structure of compound 180: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-chloro-2-((1H-1,2,4-triazol-4-yl)methyl)quinoline group. The triazole ring is further connected to a cyclobutyl group, which is substituted with a hydroxyl group (OH) at the 1-position.
181	 Chemical structure of compound 181: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-chloro-2-((1H-1,2,4-triazol-4-yl)methyl)quinoline group. The triazole ring is further connected to a cyclobutyl group, which is substituted with a hydroxyl group (OH) at the 1-position.

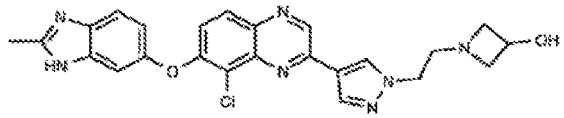
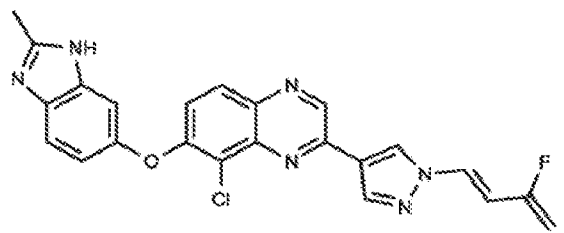
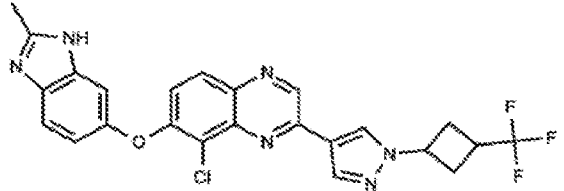
Compound No.	Structure
182	 Chemical structure of compound 182: A 4-methyl-1H-imidazo[5,1-b]pyridine ring is connected via an ether linkage to a 4-chloro-2,6-dimethyl-1H-imidazo[5,1-b]pyridine ring. This second ring is further connected via a pyrimidine ring to a 1-methyl-4-(2,2,2-trifluoroethyl)-1H-imidazole ring.
183	 Chemical structure of compound 183: A 4-methyl-1H-imidazo[5,1-b]pyridine ring is connected via an ether linkage to a 4-chloro-2,6-dimethyl-1H-imidazo[5,1-b]pyridine ring. This second ring is further connected via a pyrimidine ring to a 1-methyl-4-(2-hydroxy-2-methylpropanoyl)-1H-imidazole ring.
184	 Chemical structure of compound 184: A 4-methyl-1H-imidazo[5,1-b]pyridine ring is connected via an ether linkage to a 4-chloro-2,6-dimethyl-1H-imidazo[5,1-b]pyridine ring. This second ring is further connected via a pyrimidine ring to a 1-methyl-4-(2-methylpropanoyl)-1H-imidazole ring.

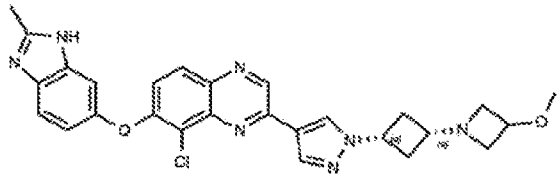
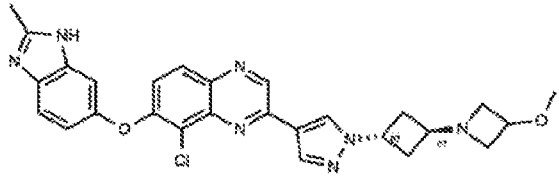
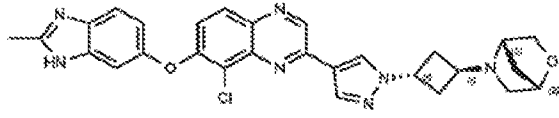
Compound No.	Structure
185	 Chemical structure of compound 185: A molecule featuring a 4-methyl-1H-indazole ring connected via an ether linkage to a 4-chloroquinoline ring. The quinoline ring is further connected via a pyrazole ring to a 4-membered nitrogen-containing ring, which is substituted with a carbonyl group and a 4-membered nitrogen-containing ring.
186	 Chemical structure of compound 186: A molecule featuring a 4-methyl-1H-indazole ring connected via an ether linkage to a 4-chloroquinoline ring. The quinoline ring is further connected via a pyrazole ring to a 4-membered nitrogen-containing ring, which is substituted with a carbonyl group and a 4-membered nitrogen-containing ring.
187	 Chemical structure of compound 187: A molecule featuring a 4-methyl-1H-indazole ring connected via an ether linkage to a 4-chloroquinoline ring. The quinoline ring is further connected via a pyrazole ring to a 4-membered nitrogen-containing ring, which is substituted with a carbonyl group and a 4-membered nitrogen-containing ring.

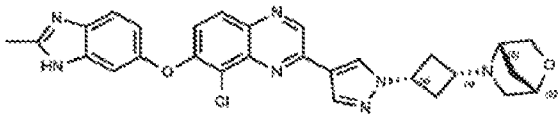
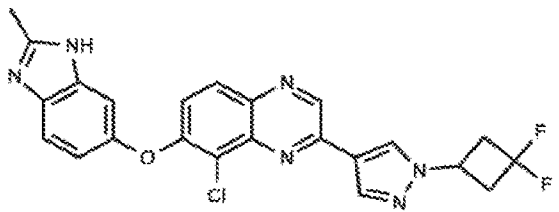
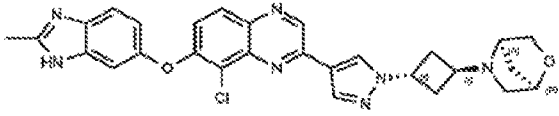
Compound No.	Structure
188	 Chemical structure of compound 188: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 8, and a 1H-imidazol-2-yl group at position 4. The imidazole ring at position 4 is further substituted with a 2-((2S,3S)-2-oxo-3-(4-methyl-1H-imidazol-2-yl)propyl)pyrrolidine-1-carboxamide group.
189	 Chemical structure of compound 189: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 8, and a 1H-imidazol-2-yl group at position 4. The imidazole ring at position 4 is further substituted with a 1-((2S,3S)-2-oxo-3-(4-methyl-1H-imidazol-2-yl)propyl)pyrrolidine-1-carboxamide group.
190	 Chemical structure of compound 190: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 8, and a 1H-imidazol-2-yl group at position 4. The imidazole ring at position 4 is further substituted with a 1-((2S,3S)-2-oxo-3-(4-methyl-1H-imidazol-2-yl)propyl)pyrrolidine-1-carboxamide group.
191	 Chemical structure of compound 191: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 8, and a 1H-imidazol-2-yl group at position 4. The imidazole ring at position 4 is further substituted with a 1-((2S,3S)-2-oxo-3-(4-methyl-1H-imidazol-2-yl)propyl)pyrrolidine-1-carboxamide group.

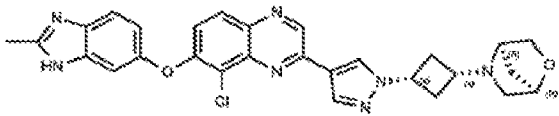
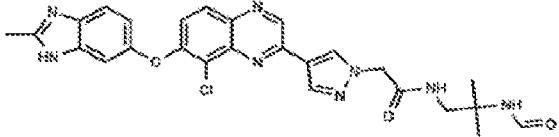
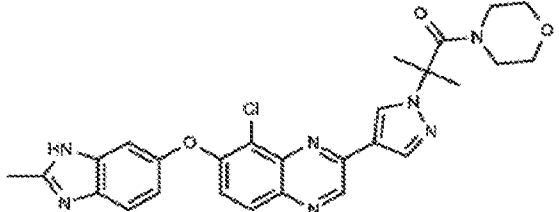
Compound No.	Structure
192	 Chemical structure of compound 192: A 4-(4-chloro-7-(4-methyl-1H-imidazol-2-yl)phenoxy)quinazoline-2-yl group is connected via a 1,2,3-triazole ring to a 4-(4-methyl-1H-imidazol-2-yl)phenyl group. The triazole ring is further connected to a 4-(4-methyl-1H-imidazol-2-yl)phenyl group.
193	 Chemical structure of compound 193: A 4-(4-chloro-7-(4-methyl-1H-imidazol-2-yl)phenoxy)quinazoline-2-yl group is connected via a 1,2,3-triazole ring to a 4-(4-methyl-1H-imidazol-2-yl)phenyl group. The triazole ring is further connected to a 4-(4-methyl-1H-imidazol-2-yl)phenyl group.
194	 Chemical structure of compound 194: A 4-(4-chloro-7-(4-methyl-1H-imidazol-2-yl)phenoxy)quinazoline-2-yl group is connected via a 1,2,3-triazole ring to a 4-(4-methyl-1H-imidazol-2-yl)phenyl group. The triazole ring is further connected to a 4-(4-methyl-1H-imidazol-2-yl)phenyl group.

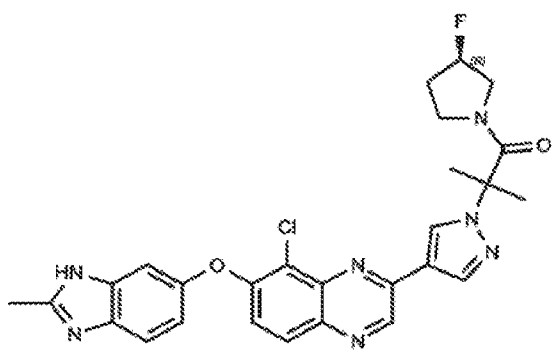
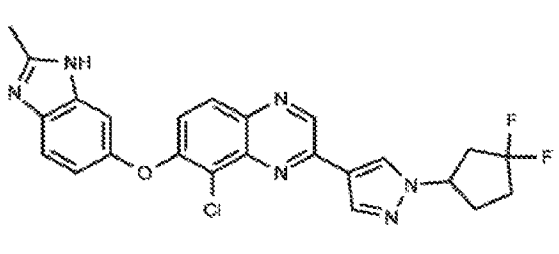
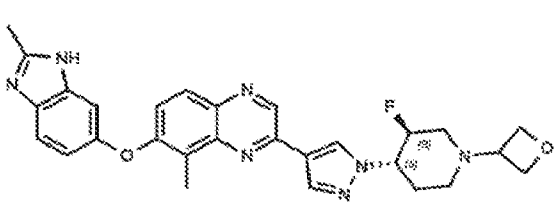
Compound No.	Structure
195	 Chemical structure of compound 195: A quinoline ring system with a chlorine atom at position 6 and a 4-methyl-1H-imidazol-2-yl group at position 8. The quinoline is connected via an ether linkage to a 4-(4-methyl-1H-imidazol-2-yl)-1H-imidazole ring, which is further connected to a 1-(4-fluorophenyl)-4-methyl-1H-imidazole ring.
196	 Chemical structure of compound 196: A quinoline ring system with a chlorine atom at position 6 and a 4-methyl-1H-imidazol-2-yl group at position 8. The quinoline is connected via an ether linkage to a 4-(4-methyl-1H-imidazol-2-yl)-1H-imidazole ring, which is further connected to a 1-(4-fluorophenyl)-1H-imidazole ring.
197	 Chemical structure of compound 197: A quinoline ring system with a chlorine atom at position 6 and a 4-methyl-1H-imidazol-2-yl group at position 8. The quinoline is connected via an ether linkage to a 4-(4-methyl-1H-imidazol-2-yl)-1H-imidazole ring, which is further connected to a 1-(4-fluorophenyl)-1H-imidazole ring.

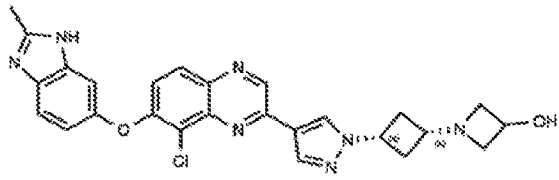
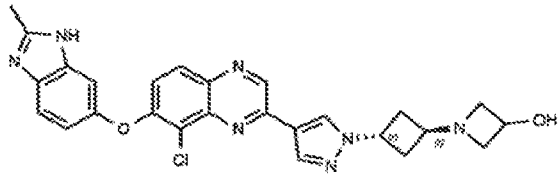
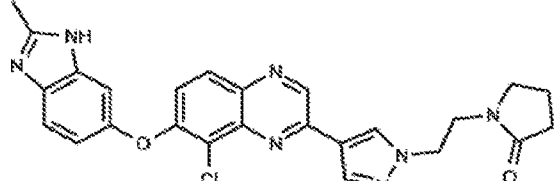
Compound No.	Structure
198	 Chemical structure of compound 198: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 7, and a 1-(4-hydroxy-1H-imidazol-2-yl)ethyl group at position 4.
199	 Chemical structure of compound 199: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 7, and a 1-(2-(2-fluoroethylidene)-1H-imidazol-4-yl)ethyl group at position 4.
200	 Chemical structure of compound 200: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 7, and a 1-(4-(difluoromethyl)-1H-imidazol-2-yl)ethyl group at position 4.

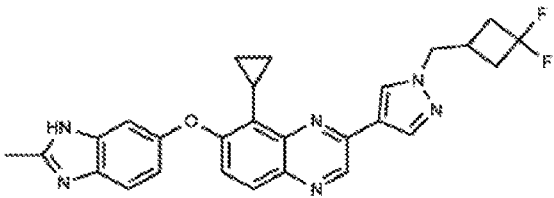
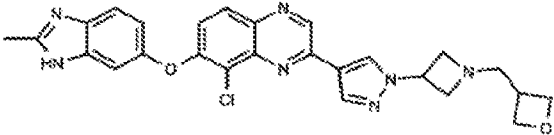
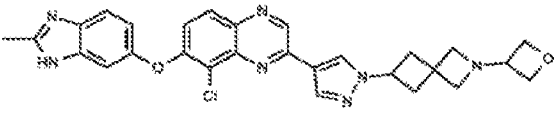
Compound No.	Structure
201	 Chemical structure of compound 201: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 8, and a 1-(4-methoxy-4,5-dihydro-1H-tetrazol-5-yl)pyrrol-2-yl group at position 4. Stereochemistry is indicated with a wedge bond to the pyrrolidine ring and a dashed bond to the tetrazole ring.
202	 Chemical structure of compound 202: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 8, and a 1-(4-methoxy-4,5-dihydro-1H-tetrazol-5-yl)pyrrol-2-yl group at position 4. Stereochemistry is indicated with a wedge bond to the pyrrolidine ring and a dashed bond to the tetrazole ring.
203	 Chemical structure of compound 203: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 8, and a 1-(4-methoxy-4,5-dihydro-1H-tetrazol-5-yl)pyrrol-2-yl group at position 4. Stereochemistry is indicated with a wedge bond to the pyrrolidine ring and a dashed bond to the tetrazole ring.

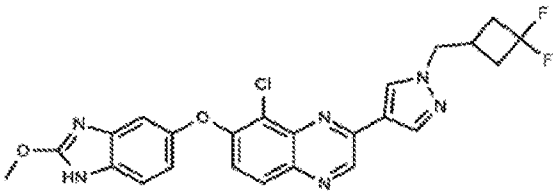
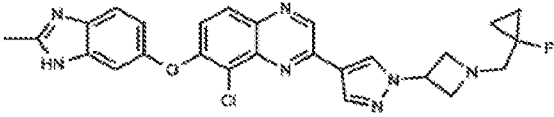
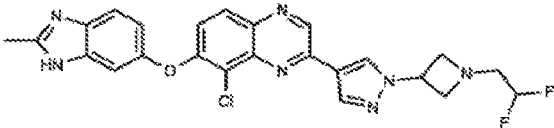
Compound No.	Structure
204	 Chemical structure of compound 204: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 4-chloro-2-((1H-imidazol-2-yl)methyl)quinoline group. This quinoline group is further connected via a 1H-imidazol-2-yl group to a cyclobutyl ring, which is in turn connected to a 2-chloro-1,2,3,4-tetrahydropyridine ring.
205	 Chemical structure of compound 205: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 4-chloro-2-((1H-imidazol-2-yl)methyl)quinoline group. This quinoline group is further connected via a 1H-imidazol-2-yl group to a cyclobutyl ring, which is in turn connected to a 2-chloro-1,2,3,4-tetrahydropyridine ring.
206	 Chemical structure of compound 206: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 4-chloro-2-((1H-imidazol-2-yl)methyl)quinoline group. This quinoline group is further connected via a 1H-imidazol-2-yl group to a cyclobutyl ring, which is in turn connected to a 2-chloro-1,2,3,4-tetrahydropyridine ring.

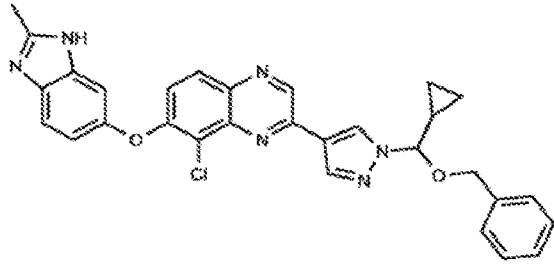
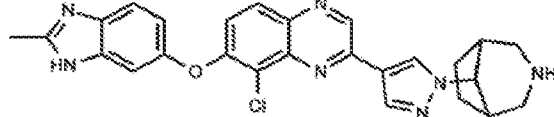
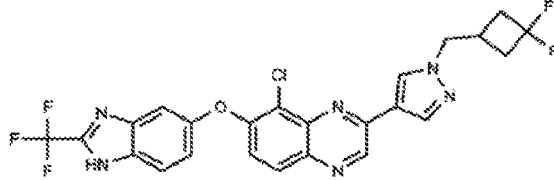
Compound No.	Structure
207	 Chemical structure of compound 207: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 4-chloro-2,3-dihydroquinazolin-2-yl group. This is further connected to a 1,2,4-triazole ring, which is linked to a cyclobutane ring, and finally to a morpholine ring.
208	 Chemical structure of compound 208: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 4-chloro-2,3-dihydroquinazolin-2-yl group. This is further connected to a 1,2,4-triazole ring, which is linked to a carbonyl group, and finally to a morpholine ring.
209	 Chemical structure of compound 209: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 4-chloro-2,3-dihydroquinazolin-2-yl group. This is further connected to a 1,2,4-triazole ring, which is linked to a carbonyl group, and finally to a morpholine ring.

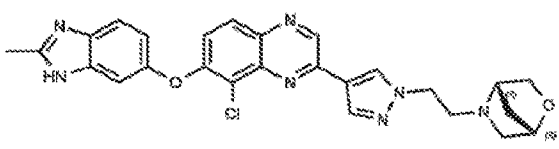
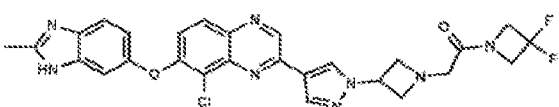
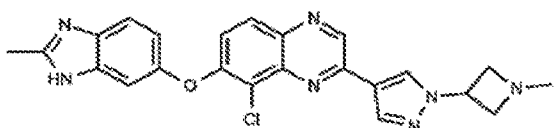
Compound No.	Structure
210	 Chemical structure of compound 210: A quinoline ring system with a chlorine atom at position 6 and a 4-methyl-1H-imidazol-2-yl group at position 3. The quinoline is connected via an ether linkage to a 4-methyl-1H-imidazol-2-yl group, which is further connected to a 4-(2-fluoro-2-methylpropanamido)pyrimidin-5-yl group.
211	 Chemical structure of compound 211: A quinoline ring system with a chlorine atom at position 6 and a 4-methyl-1H-imidazol-2-yl group at position 3. The quinoline is connected via an ether linkage to a 4-methyl-1H-imidazol-2-yl group, which is further connected to a 4-(2,2-difluorocyclopentyl)pyrimidin-5-yl group.
212	 Chemical structure of compound 212: A quinoline ring system with a chlorine atom at position 6 and a 4-methyl-1H-imidazol-2-yl group at position 3. The quinoline is connected via an ether linkage to a 4-methyl-1H-imidazol-2-yl group, which is further connected to a 4-(2-fluoro-2-methylpropanamido)pyrimidin-5-yl group.

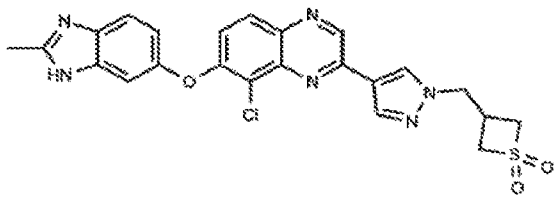
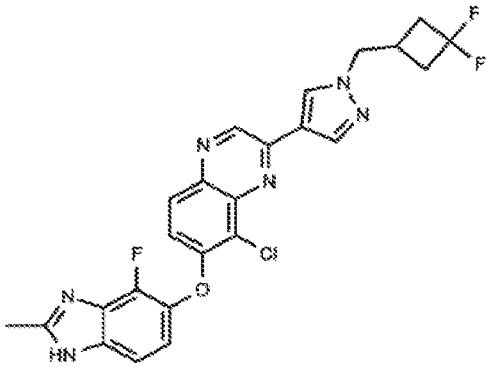
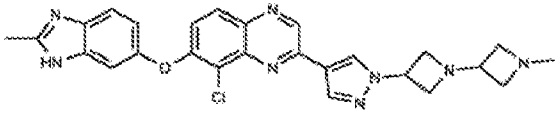
Compound No.	Structure
213	 Chemical structure of compound 213: A 4-(4-methyl-1H-imidazol-2-yl)phenyl group is connected via an ether linkage to a 4-chloro-2-((4-methyl-1H-imidazol-2-yl)phenyl)quinazolin-6-yl group. This quinazolinyl group is further connected via a pyrimidin-2-yl group to a 1,4-bis(methylene)dipiperidine moiety, which is terminated with a hydroxyl group.
214	 Chemical structure of compound 214: A 4-(4-methyl-1H-imidazol-2-yl)phenyl group is connected via an ether linkage to a 4-chloro-2-((4-methyl-1H-imidazol-2-yl)phenyl)quinazolin-6-yl group. This quinazolinyl group is further connected via a pyrimidin-2-yl group to a 1,4-bis(methylene)dipiperidine moiety, which is terminated with a hydroxyl group. The stereochemistry at the chiral center is indicated by a wedge bond.
215	 Chemical structure of compound 215: A 4-(4-methyl-1H-imidazol-2-yl)phenyl group is connected via an ether linkage to a 4-chloro-2-((4-methyl-1H-imidazol-2-yl)phenyl)quinazolin-6-yl group. This quinazolinyl group is further connected via a pyrimidin-2-yl group to a 1,4-bis(methylene)dipiperidine moiety, which is terminated with a carbonyl group.

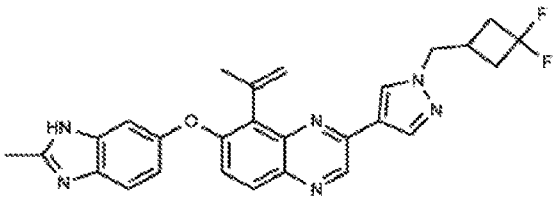
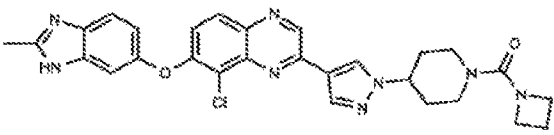
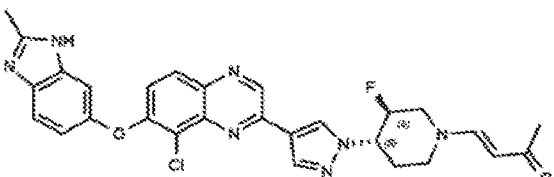
Compound No.	Structure
216	 Chemical structure of compound 216: A quinazoline core substituted with a cyclopropyl group at position 4, a 4-methyl-1H-indol-3-yl group at position 6, and a 1-(2,2-difluorocyclobutyl)methyl group at position 2. The quinazoline is linked at position 7 to a pyrazole ring, which is further linked to the difluorocyclobutyl group.
217	 Chemical structure of compound 217: A quinazoline core substituted with a cyclopropyl group at position 4, a 4-methyl-1H-indol-3-yl group at position 6, and a chlorine atom at position 8. The quinazoline is linked at position 7 to a pyrazole ring, which is further linked to a 1-(oxet-3-yl)methyl group via a 1,3-dioxolane intermediate.
218	 Chemical structure of compound 218: A quinazoline core substituted with a cyclopropyl group at position 4, a 4-methyl-1H-indol-3-yl group at position 6, and a chlorine atom at position 8. The quinazoline is linked at position 7 to a pyrazole ring, which is further linked to a 1-(oxet-3-yl)methyl group via a 1,3-dioxolane intermediate.

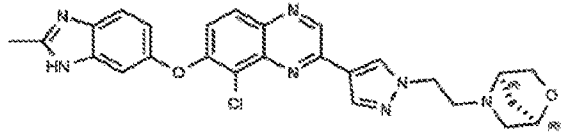
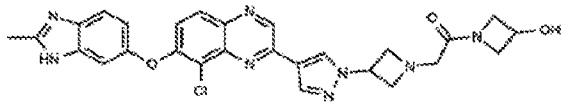
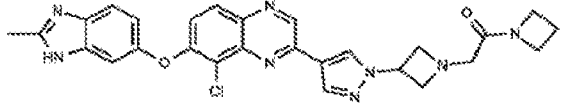
Compound No.	Structure
219	 Chemical structure of compound 219: A 7-methoxy-1H-indolizin-5-yl group is connected via an ether linkage to a 4-chloro-1H-indolizin-5-yl group. This is further connected to a 1H-imidazol-2-yl group, which is linked to a 1-(2,2-difluorocyclobutyl)methyl group.
220	 Chemical structure of compound 220: A 7-methyl-1H-indolizin-5-yl group is connected via an ether linkage to a 4-chloro-1H-indolizin-5-yl group. This is further connected to a 1H-imidazol-2-yl group, which is linked to a 1-(2-(2-fluorocyclopropyl)ethyl)pyrrolidin-4-yl group.
221	 Chemical structure of compound 221: A 7-methyl-1H-indolizin-5-yl group is connected via an ether linkage to a 4-chloro-1H-indolizin-5-yl group. This is further connected to a 1H-imidazol-2-yl group, which is linked to a 1-(2-(2,2-difluoroethyl)ethyl)pyrrolidin-4-yl group.

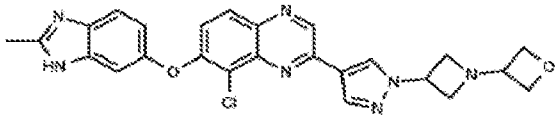
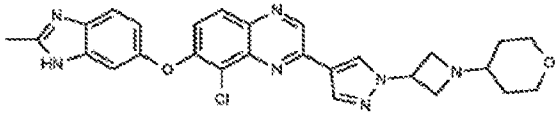
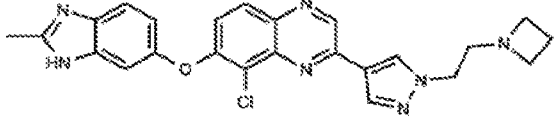
Compound No.	Structure
222	 Chemical structure of compound 222: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 4-chloro-2,3-bis(4-methyl-1H-indol-3-yl)quinazoline core. This core is further substituted with a 1-(benzyloxy)-2-(4-methyl-1H-indol-3-yl)pyrazole group.
223	 Chemical structure of compound 223: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 4-chloro-2,3-bis(4-methyl-1H-indol-3-yl)quinazoline core. This core is further substituted with a 1-(adamantan-1-yl)-2-(4-methyl-1H-indol-3-yl)pyrazole group.
224	 Chemical structure of compound 224: A molecule featuring a 4-(trifluoromethyl)-1H-indol-3-yl group connected via an ether linkage to a 4-chloro-2,3-bis(4-(trifluoromethyl)-1H-indol-3-yl)quinazoline core. This core is further substituted with a 1-(4-(trifluoromethyl)cyclobutyl)-2-(4-(trifluoromethyl)-1H-indol-3-yl)pyrazole group.

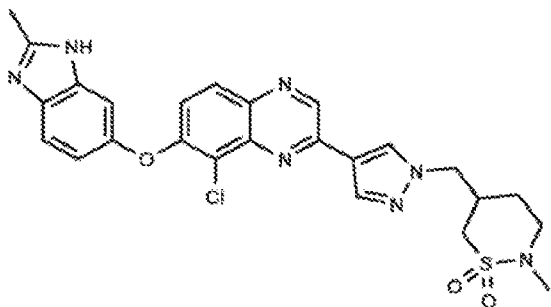
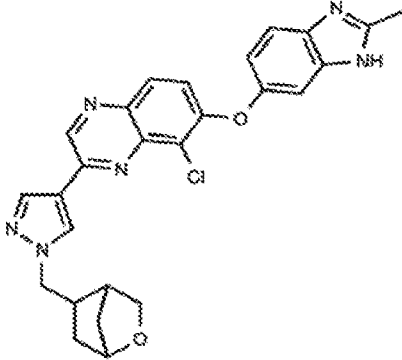
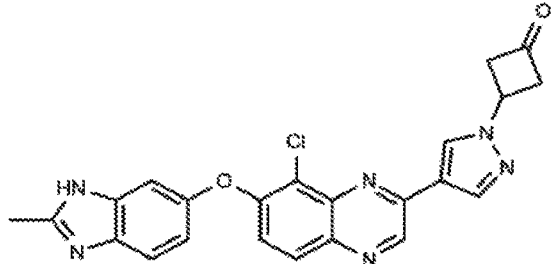
Compound No.	Structure
225	 Chemical structure of compound 225: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 4-chloro-2,6-diazin-3-yl group. This is further connected to a 1H-imidazol-2-yl group, which is linked via a methylene bridge to a 1,4-dioxane ring.
226	 Chemical structure of compound 226: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 4-chloro-2,6-diazin-3-yl group. This is further connected to a 1H-imidazol-2-yl group, which is linked via a methylene bridge to a 1,4-dioxane ring.
227	 Chemical structure of compound 227: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 4-chloro-2,6-diazin-3-yl group. This is further connected to a 1H-imidazol-2-yl group, which is linked via a methylene bridge to a 1,4-dioxane ring.

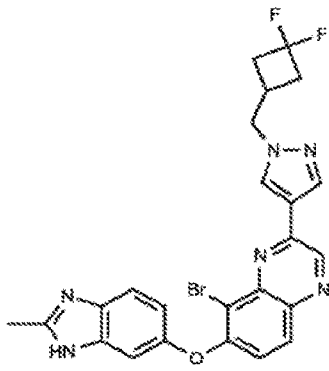
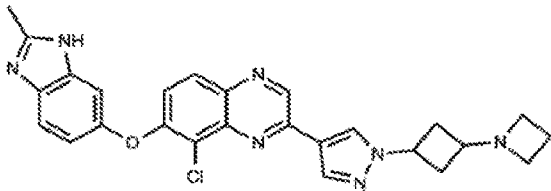
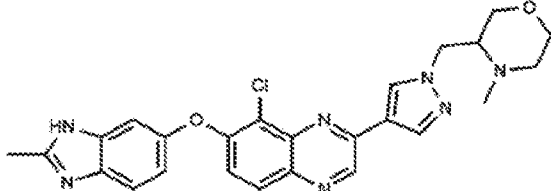
Compound No.	Structure
228	 Chemical structure of compound 228: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-chloro-2-((1H-1,2,4-triazol-4-yl)methyl)phenyl group. The triazole ring is further connected via its 1-position to a 2-sulfonylpropyl chain.
229	 Chemical structure of compound 229: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-chloro-2-((1H-1,2,4-triazol-4-yl)methyl)phenyl group. The triazole ring is further connected via its 1-position to a 2-(2,2-difluorocyclobutyl)methyl chain.
230	 Chemical structure of compound 230: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-chloro-2-((1H-1,2,4-triazol-4-yl)methyl)phenyl group. The triazole ring is further connected via its 1-position to a 2-(2-methylazetidin-1-yl)methyl chain.

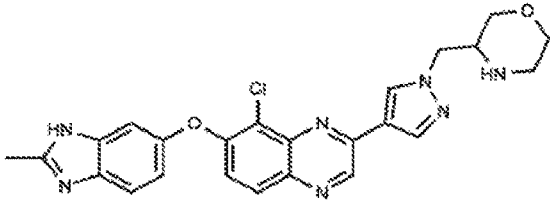
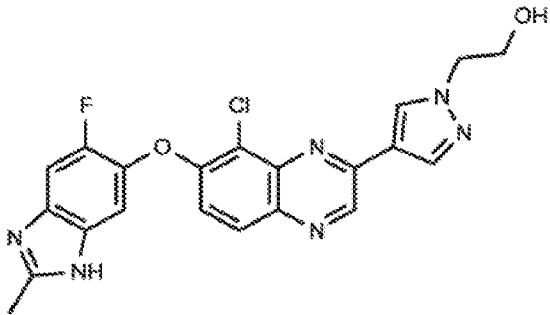
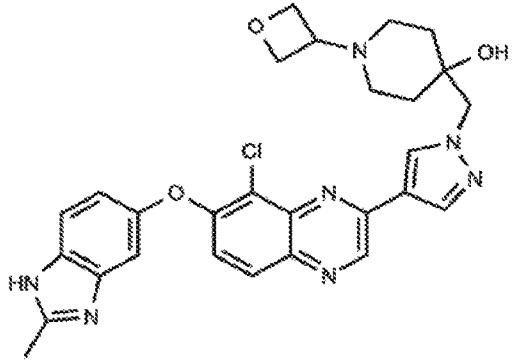
Compound No.	Structure
231	 Chemical structure of compound 231: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 4-(4-methyl-1H-indol-3-yloxy)-6-methyl-2,3-dihydroquinazolin-2-yl group. This is further connected via a pyrimidin-2-yl group to a 4-(2,3-difluorocyclobutyl)pyrimidin-2-yl group.
232	 Chemical structure of compound 232: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 4-(4-methyl-1H-indol-3-yloxy)-6-chloro-2,3-dihydroquinazolin-2-yl group. This is further connected via a pyrimidin-2-yl group to a 4-(4-methyl-1H-indol-3-yloxy)-6-chloro-2,3-dihydroquinazolin-2-yl group, which is then connected via a piperidine ring to a 4-methyl-1H-indol-3-yl group.
233	 Chemical structure of compound 233: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 4-(4-methyl-1H-indol-3-yloxy)-6-chloro-2,3-dihydroquinazolin-2-yl group. This is further connected via a pyrimidin-2-yl group to a 4-(4-methyl-1H-indol-3-yloxy)-6-chloro-2,3-dihydroquinazolin-2-yl group, which is then connected via a piperidine ring to a 4-methyl-1H-indol-3-yl group.

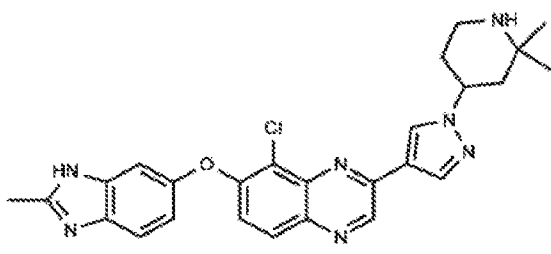
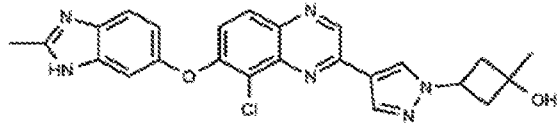
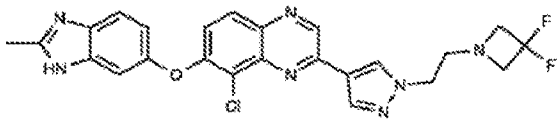
Compound No.	Structure
234	 Chemical structure of compound 234: A 4-methyl-1H-imidazo[5,4-b]pyridine ring is connected via an ether linkage to a 4-chloro-2,6-diazobenzene ring. This is further connected to a 1H-imidazole ring, which is linked via its nitrogen to a 2-(2,2,6,6-tetramethyl-1,3-dioxane-5-yl)ethyl group.
235	 Chemical structure of compound 235: A 4-methyl-1H-imidazo[5,4-b]pyridine ring is connected via an ether linkage to a 4-chloro-2,6-diazobenzene ring. This is further connected to a 1H-imidazole ring, which is linked via its nitrogen to a 2-(2-hydroxy-1,3-dioxol-5-yl)ethyl group.
236	 Chemical structure of compound 236: A 4-methyl-1H-imidazo[5,4-b]pyridine ring is connected via an ether linkage to a 4-chloro-2,6-diazobenzene ring. This is further connected to a 1H-imidazole ring, which is linked via its nitrogen to a 2-(2-oxo-1,3-dioxol-5-yl)ethyl group.

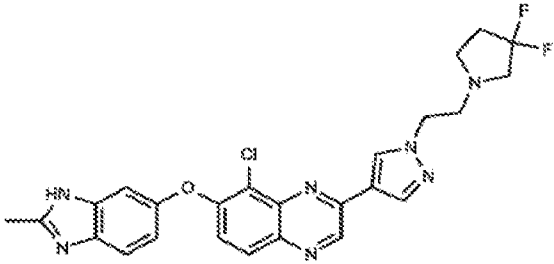
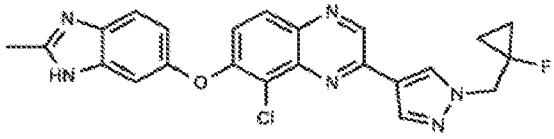
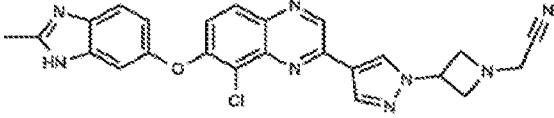
Compound No.	Structure
237	 Chemical structure of compound 237: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-chloro-2-((1-(1,3-dioxolan-2-yl)pyrrolidin-2-yl)methyl)pyrimidin-5-yl group.
238	 Chemical structure of compound 238: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-chloro-2-((1-(1,3-dioxan-2-yl)pyrrolidin-2-yl)methyl)pyrimidin-5-yl group.
239	 Chemical structure of compound 239: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-chloro-2-((1-(azetidin-1-yl)ethyl)methyl)pyrimidin-5-yl group.

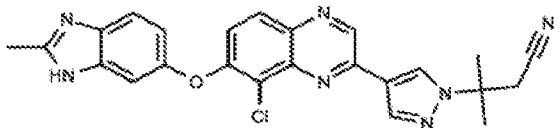
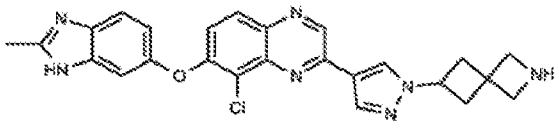
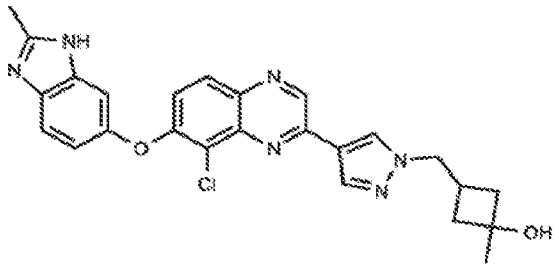
Compound No.	Structure
240	 Chemical structure of compound 240: A 4-(4-chloro-2-((4-methyl-1H-imidazol-2-yl)oxy)phenyl)quinazoline-3-yl group is connected via a 1,2,3-triazole ring to a 4-(methylsulfonyl)pyrrolidine ring.
241	 Chemical structure of compound 241: A 4-(4-chloro-2-((4-methyl-1H-imidazol-2-yl)oxy)phenyl)quinazoline-3-yl group is connected via a 1,2,3-triazole ring to a 4-(adamantan-1-ylmethyl)-1H-imidazole ring.
242	 Chemical structure of compound 242: A 4-(4-chloro-2-((4-methyl-1H-imidazol-2-yl)oxy)phenyl)quinazoline-3-yl group is connected via a 1,2,3-triazole ring to a 4-(adamantan-1-ylmethyl)-1H-imidazole ring.

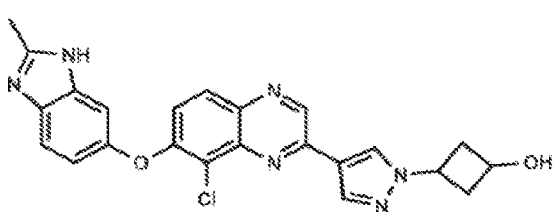
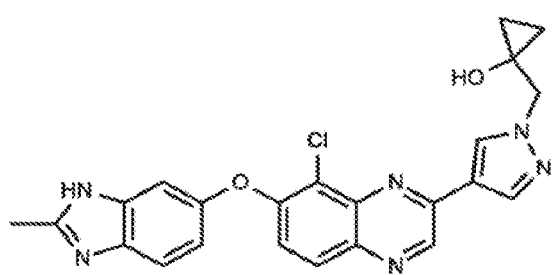
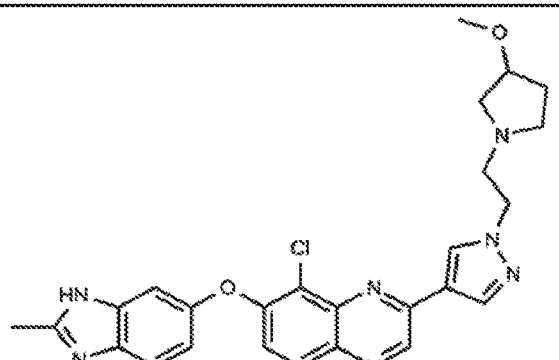
Compound No.	Structure
243	 Chemical structure of compound 243: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 6-bromo-2,4-dihydropyrimidin-5-yl group. This pyrimidine ring is further connected via a 1,2,4-triazole ring to a 1,1-difluoroethyl group.
244	 Chemical structure of compound 244: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 6-chloro-2,4-dihydropyrimidin-5-yl group. This pyrimidine ring is further connected via a 1,2,4-triazole ring to a 1,4-diazabicyclo[2.2.0]hex-6-yl group.
245	 Chemical structure of compound 245: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 6-chloro-2,4-dihydropyrimidin-5-yl group. This pyrimidine ring is further connected via a 1,2,4-triazole ring to a 1,4-diazabicyclo[2.2.0]hex-6-yl group.

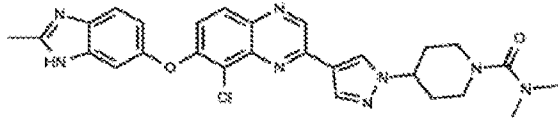
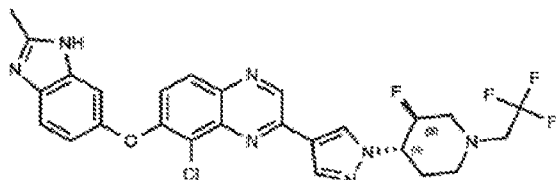
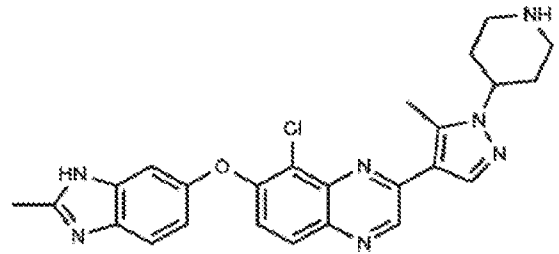
Compound No.	Structure
246	
247	
248	

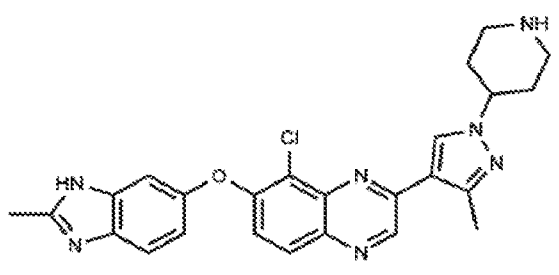
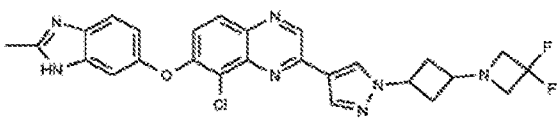
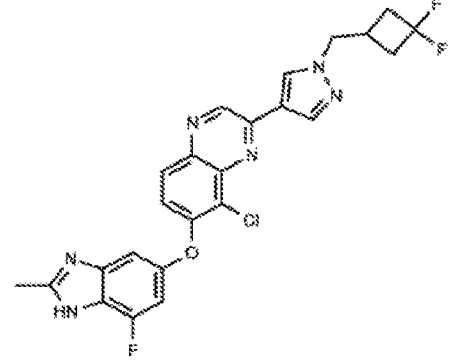
Compound No.	Structure
249	 Chemical structure of compound 249: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 4, a chlorine atom at position 6, and a 1-(4-methyl-1H-imidazol-2-yl)pyrrolidine group at position 2.
250	 Chemical structure of compound 250: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 4, a chlorine atom at position 6, and a 1-(4-methyl-1H-imidazol-2-yl)pyrrolidine group at position 2.
251	 Chemical structure of compound 251: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 4, a chlorine atom at position 6, and a 1-(4-methyl-1H-imidazol-2-yl)pyrrolidine group at position 2.

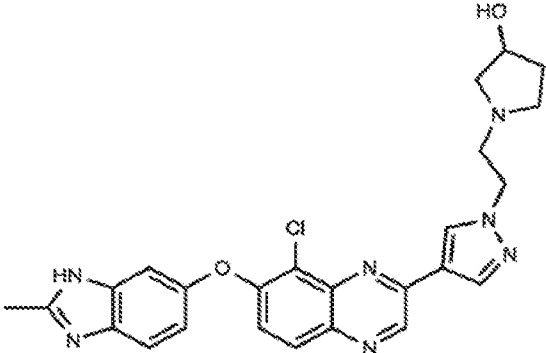
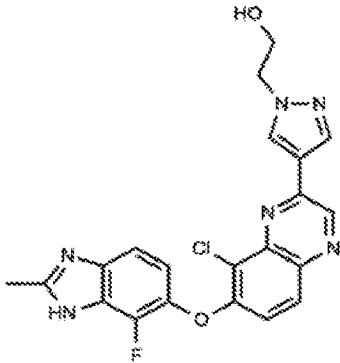
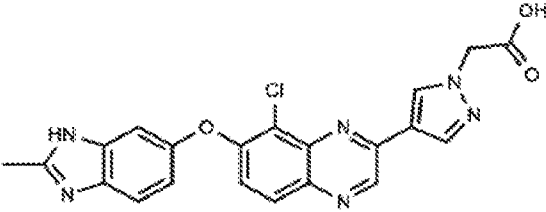
Compound No.	Structure
252	 Chemical structure of compound 252: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-chloroquinoline ring. This quinoline ring is further connected to a 1,2,4-triazole ring, which is linked to a 2,2-difluoroethyl group.
253	 Chemical structure of compound 253: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-chloroquinoline ring. This quinoline ring is further connected to a 1,2,4-triazole ring, which is linked to a 2-fluoroethyl group.
254	 Chemical structure of compound 254: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-chloroquinoline ring. This quinoline ring is further connected to a 1,2,4-triazole ring, which is linked to a 2-cyanoethyl group.

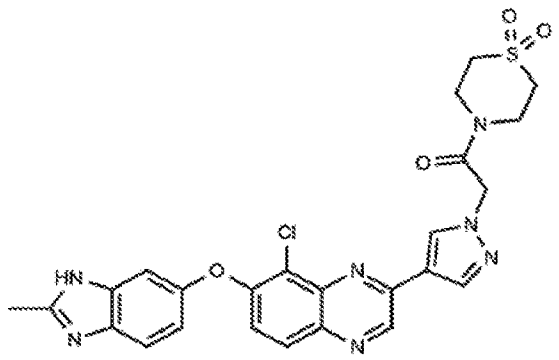
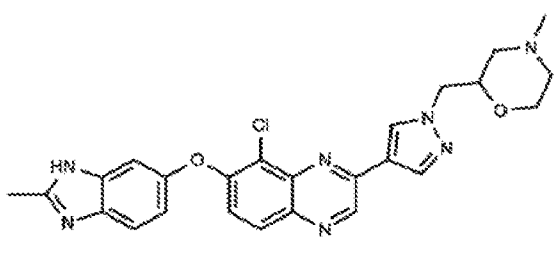
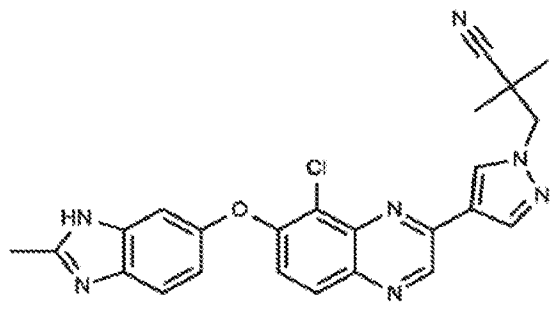
Compound No.	Structure
255	 Chemical structure of compound 255: A 4-(4-methyl-1H-imidazol-2-yl)phenoxy group is linked via an ether bond to a 6-chloro-2-((1-(2-cyano-2-methylpropyl)-1H-imidazol-4-yl)methyl)quinazoline group.
256	 Chemical structure of compound 256: A 4-(4-methyl-1H-imidazol-2-yl)phenoxy group is linked via an ether bond to a 6-chloro-2-((1-(4,5-dihydro-1H-bicyclo[3.1.0]hex-6-yl)-1H-imidazol-4-yl)methyl)quinazoline group.
257	 Chemical structure of compound 257: A 4-(4-methyl-1H-imidazol-2-yl)phenoxy group is linked via an ether bond to a 6-chloro-2-((1-(4-hydroxy-4-methylcyclopropyl)-1H-imidazol-4-yl)methyl)quinazoline group.

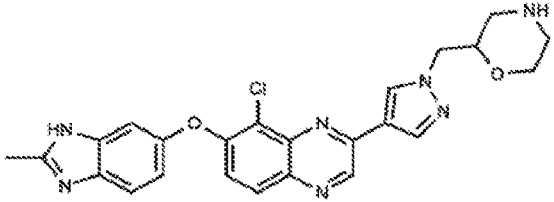
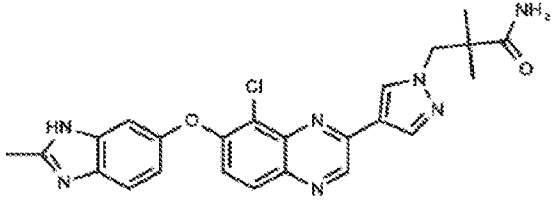
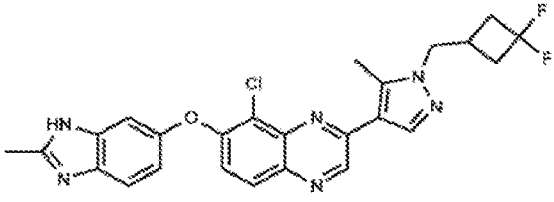
Compound No.	Structure
258	 Chemical structure of compound 258: A 4-methyl-1H-indol-5-yl group is connected via an ether linkage to a 4-chloro-2-((1H-1,2,4-triazol-4-yl)methyl)quinoline group, which is further connected to a 4-hydroxycyclobutyl group.
259	 Chemical structure of compound 259: A 4-methyl-1H-indol-5-yl group is connected via an ether linkage to a 4-chloro-2-((1H-1,2,4-triazol-4-yl)methyl)quinoline group, which is further connected to a 4-((2-hydroxy-2-cyclopropyl)ethyl)-1H-1,2,4-triazol-5-yl group.
260	 Chemical structure of compound 260: A 4-methyl-1H-indol-5-yl group is connected via an ether linkage to a 4-chloro-2-((1H-1,2,4-triazol-4-yl)methyl)quinoline group, which is further connected to a 4-((2-methoxy-2-(propylamino)ethyl)-1H-1,2,4-triazol-5-yl) group.

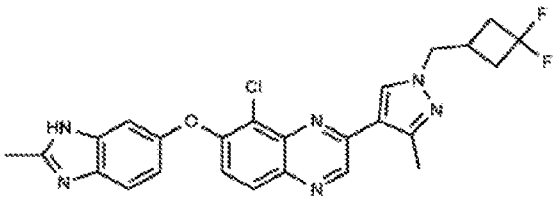
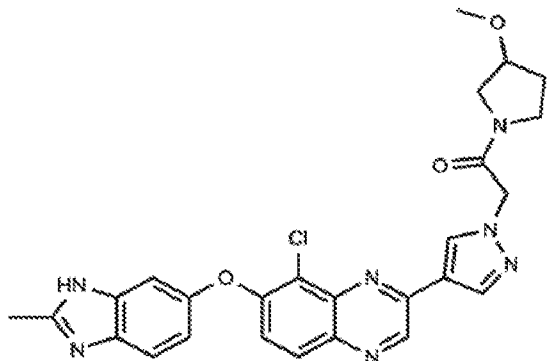
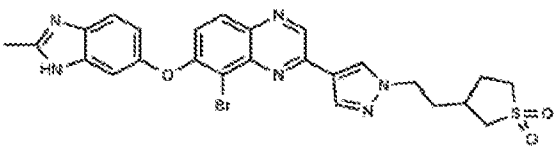
Compound No.	Structure
261	 Chemical structure of compound 261: A quinazoline core substituted with a 4-methyl-1H-indol-3-yl group at position 6, a 4-chlorophenyl group at position 8, and a 1-(4-methyl-1H-indol-3-yl)-4-methyl-1H-pyrazol-5-yl group at position 4. The pyrazole ring is further substituted with a 4-methyl-1H-piperidin-1-yl group.
262	 Chemical structure of compound 262: A quinazoline core substituted with a 4-methyl-1H-indol-3-yl group at position 6, a 4-chlorophenyl group at position 8, and a 1-(4-methyl-1H-indol-3-yl)-4-methyl-1H-pyrazol-5-yl group at position 4. The pyrazole ring is further substituted with a 4-methyl-1H-piperidin-1-yl group, which is in turn substituted with a 4-methyl-1H-piperidin-1-yl group.
263	 Chemical structure of compound 263: A quinazoline core substituted with a 4-methyl-1H-indol-3-yl group at position 6, a 4-chlorophenyl group at position 8, and a 1-(4-methyl-1H-indol-3-yl)-4-methyl-1H-pyrazol-5-yl group at position 4. The pyrazole ring is further substituted with a 4-methyl-1H-piperidin-1-yl group.

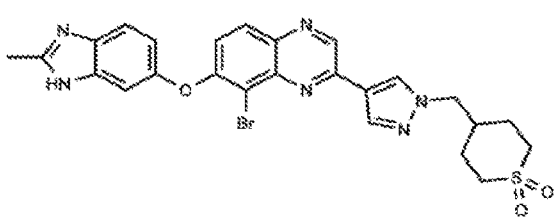
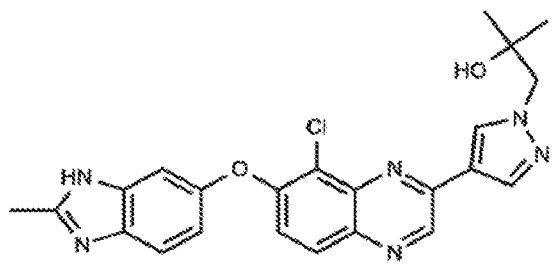
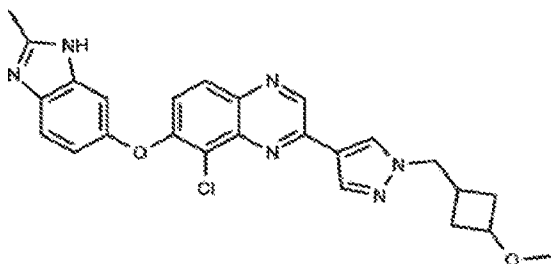
Compound No.	Structure
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265	 <chem>Cc1c[nH]c2ccc(Oc3ccc4nc(C5=CN(C)C5N(C6CCCC6)C6)cnc4c3)cc12</chem>
266	 <chem>Cc1c[nH]c2ccc(Oc3ccc4nc(C5=CN(C)C5N(C6CCCC6)C6)cnc4c3)cc12</chem>

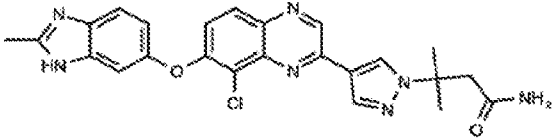
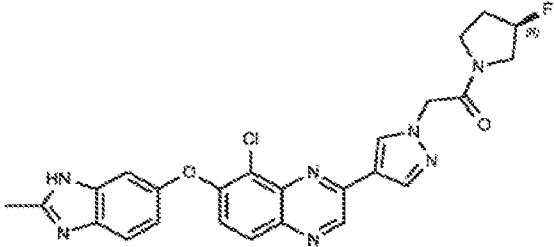
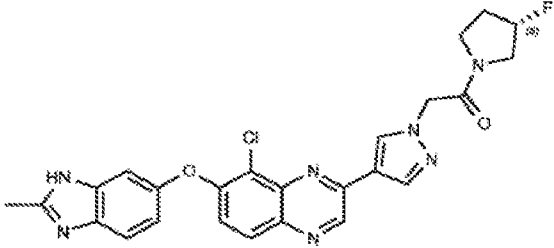
Compound No.	Structure
267	 Chemical structure of compound 267: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 7, and a 1-(1,2,4-triazol-4-yl)propyl group at position 4. The triazole ring is further substituted with a 2-hydroxypropyl group.
268	 Chemical structure of compound 268: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 7, and a 1-(1,2,4-triazol-4-yl)propyl group at position 4. The triazole ring is further substituted with a 2-hydroxypropyl group.
269	 Chemical structure of compound 269: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 7, and a 1-(1,2,4-triazol-4-yl)propyl group at position 4. The triazole ring is further substituted with a 2-hydroxypropyl group.

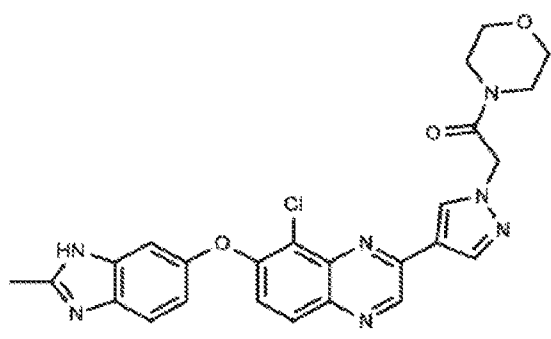
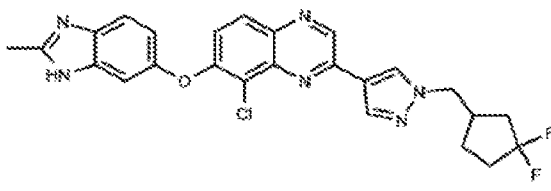
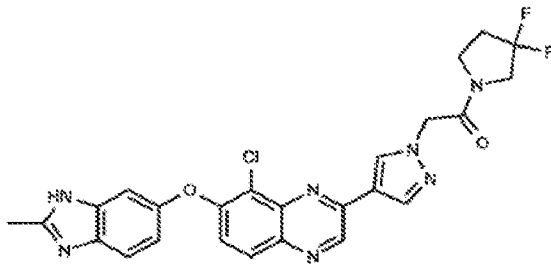
Compound No.	Structure
270	 Chemical structure of compound 270: A 4-methyl-1H-indazole ring is connected via an ether linkage to a 4-chloroquinoline ring. The quinoline ring is further connected to a 1H-imidazole ring, which is substituted with a 2-(methylsulfonyl)ethyl group.
271	 Chemical structure of compound 271: A 4-methyl-1H-indazole ring is connected via an ether linkage to a 4-chloroquinoline ring. The quinoline ring is further connected to a 1H-imidazole ring, which is substituted with a 2-methyl-2-oxazolidinylmethyl group.
272	 Chemical structure of compound 272: A 4-methyl-1H-indazole ring is connected via an ether linkage to a 4-chloroquinoline ring. The quinoline ring is further connected to a 1H-imidazole ring, which is substituted with a 2-cyano-2-methylpropyl group.

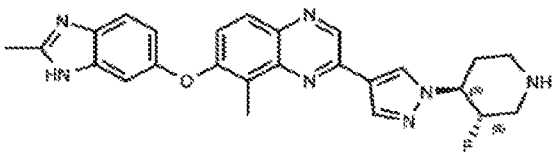
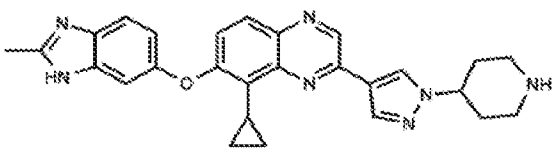
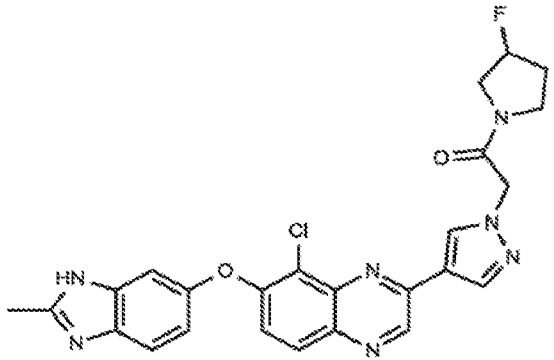
Compound No.	Structure
273	 Chemical structure of compound 273: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 4-chloroquinoline ring. This quinoline ring is further connected to a 1,2,4-triazole ring, which is substituted with a 2-morpholinoethyl group.
274	 Chemical structure of compound 274: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 4-chloroquinoline ring. This quinoline ring is further connected to a 1,2,4-triazole ring, which is substituted with a 2-((2-aminopropan-2-yl)amino)ethyl group.
275	 Chemical structure of compound 275: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 4-chloroquinoline ring. This quinoline ring is further connected to a 1,2,4-triazole ring, which is substituted with a 2-(2,2-difluorocyclopropyl)ethyl group.

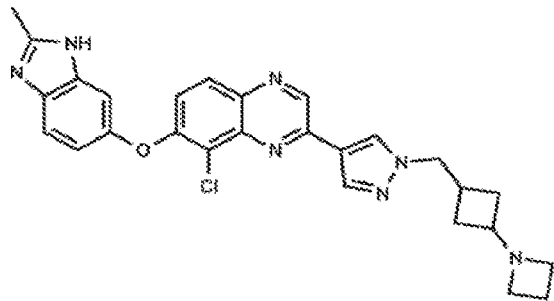
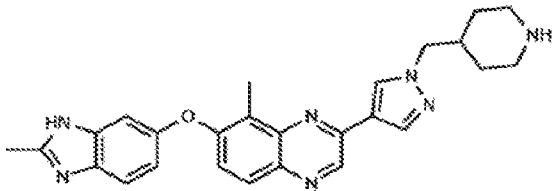
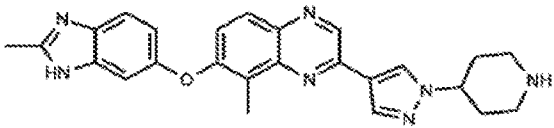
Compound No.	Structure
276	 Chemical structure of compound 276: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 8, and a 1-(4-(difluoromethyl)cyclobutyl)-1H-imidazol-2-yl group at position 4.
277	 Chemical structure of compound 277: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 8, and a 1-(2-((4-methoxypyrrolidin-1-yl)methyl)ethyl)-1H-imidazol-2-yl group at position 4.
278	 Chemical structure of compound 278: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a bromine atom at position 8, and a 1-(2-(4-methyl-1H-imidazol-2-yl)ethyl)-1H-imidazol-2-yl group at position 4.

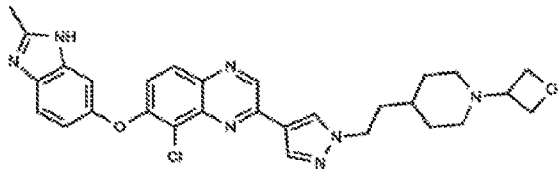
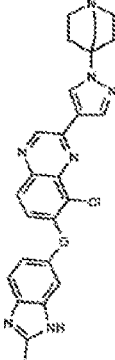
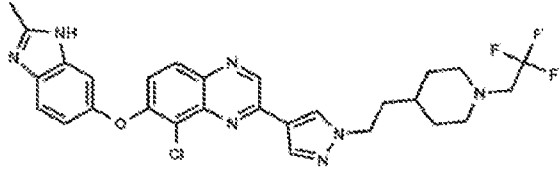
Compound No.	Structure
279	 Chemical structure of compound 279: A 4-methyl-1H-indazole ring is connected via an ether linkage to a 6-bromoquinoline ring. The quinoline ring is further connected via a triazole ring to a cyclohexylmethyl group, which is substituted with a sulfonamide group (-SO₂NH₂).
280	 Chemical structure of compound 280: A 4-methyl-1H-indazole ring is connected via an ether linkage to a 6-chloroquinoline ring. The quinoline ring is further connected via a triazole ring to a 1-(2-hydroxy-2-methylpropyl)-1H-imidazole group.
281	 Chemical structure of compound 281: A 4-methyl-1H-indazole ring is connected via an ether linkage to a 6-chloroquinoline ring. The quinoline ring is further connected via a triazole ring to a cyclobutylmethyl group, which is substituted with a methoxy group (-OCH₃).

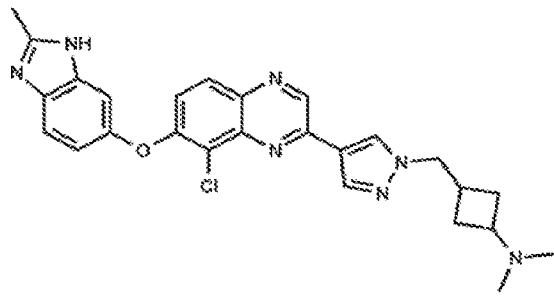
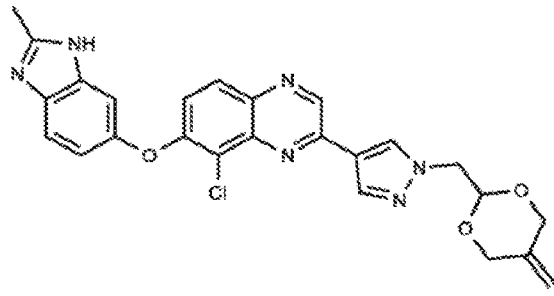
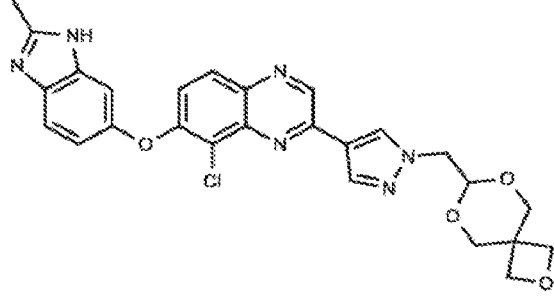
Compound No.	Structure
282	 Chemical structure of compound 282: A molecule featuring a 4-methyl-1H-indol-5-yl group connected via an ether linkage to a 4-chloro-2-(1H-imidazol-2-yl)phenyl group. The imidazole ring is substituted with a 2-amino-2-methylpropanoyl group.
283	 Chemical structure of compound 283: A molecule featuring a 4-methyl-1H-indol-5-yl group connected via a chlorine atom to a 4-chloro-2-(1H-imidazol-2-yl)phenyl group. The imidazole ring is substituted with a 2-(2-fluoropyrrolidin-1-yl)ethyl group.
284	 Chemical structure of compound 284: A molecule featuring a 4-methyl-1H-indol-5-yl group connected via an ether linkage to a 4-chloro-2-(1H-imidazol-2-yl)phenyl group. The imidazole ring is substituted with a 2-(2-fluoropyrrolidin-1-yl)ethyl group. The stereochemistry at the chiral center is indicated with a wedge bond.

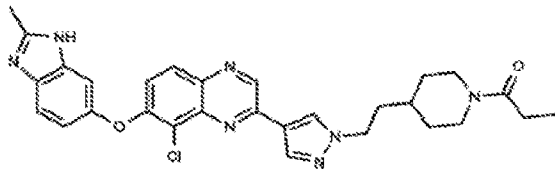
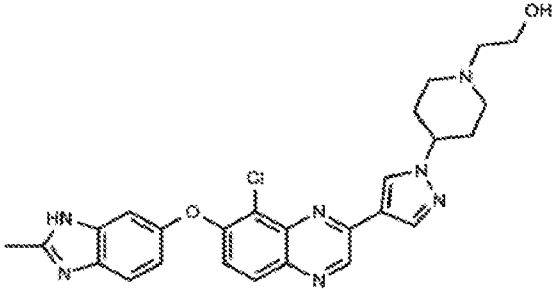
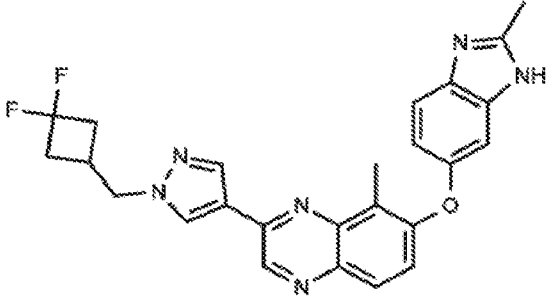
Compound No.	Structure
285	 Chemical structure of compound 285: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 6-chloroquinoline ring. This quinoline ring is further connected to a 1H-imidazole ring, which is linked to a 2-(morpholin-4-yl)ethyl ester group.
286	 Chemical structure of compound 286: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 6-chloroquinoline ring. This quinoline ring is further connected to a 1H-imidazole ring, which is linked to a 2-(2,2-difluorocyclopentyl)ethyl ester group.
287	 Chemical structure of compound 287: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 6-chloroquinoline ring. This quinoline ring is further connected to a 1H-imidazole ring, which is linked to a 2-(2,2-difluoropyrrolidin-1-yl)ethyl ester group.

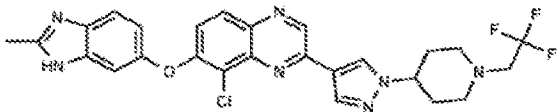
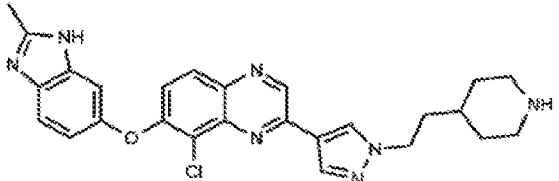
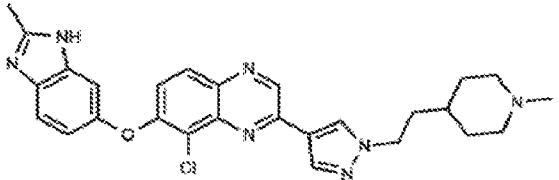
Compound No.	Structure
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289	
290	

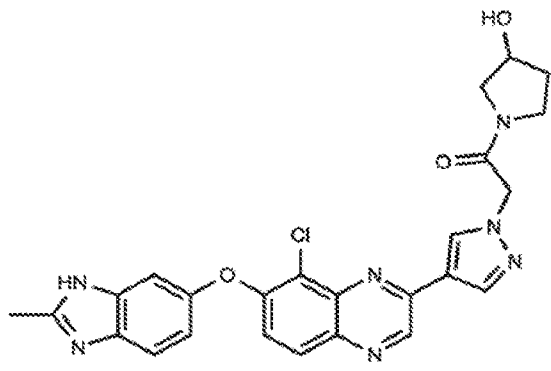
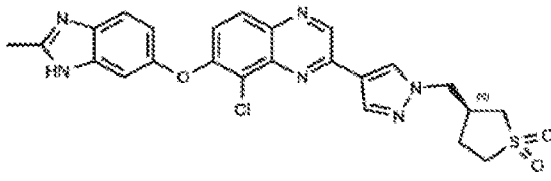
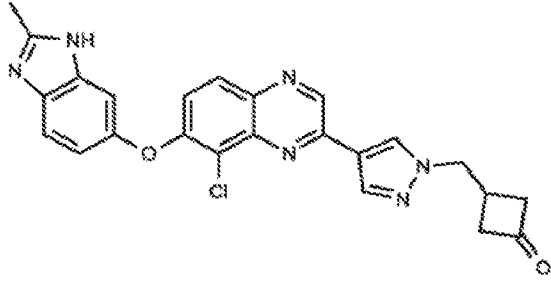
Compound No.	Structure
291	 Chemical structure of compound 291: A 4-methyl-1H-indazole ring is connected via an ether linkage to a 4-chloro-2-methylquinoline ring. This quinoline ring is further connected via a triazole ring to a 4-(azetidin-1-ylmethyl)pyrazole ring.
292	 Chemical structure of compound 292: A 4-methyl-1H-indazole ring is connected via an ether linkage to a 4-methylquinoline ring. This quinoline ring is further connected via a triazole ring to a 4-(piperidin-1-ylmethyl)pyrazole ring.
293	 Chemical structure of compound 293: A 4-methyl-1H-indazole ring is connected via an ether linkage to a 4-methylquinoline ring. This quinoline ring is further connected via a triazole ring to a 4-(piperidin-1-yl)pyrazole ring.

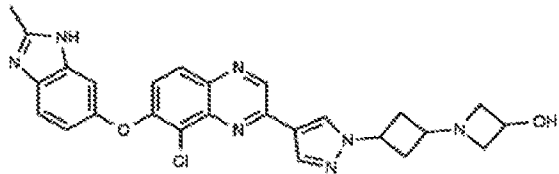
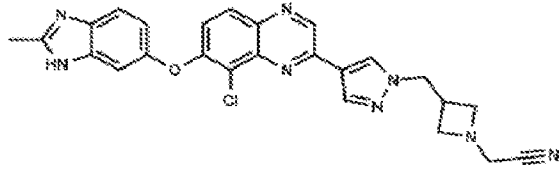
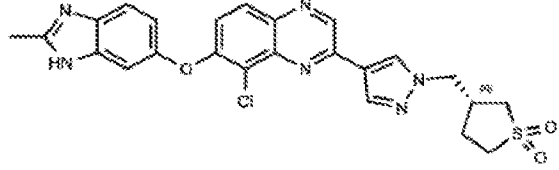
Compound No.	Structure
294	 Chemical structure of compound 294: A 4-methyl-1H-imidazo[5,4-b]pyridine ring is connected via an ether linkage to a 4-chloroquinoline ring. The quinoline ring is further connected via a pyrazole ring to a 4-(4-(chloromethyl)piperidin-1-yl)butyl group.
295	 Chemical structure of compound 295: A 4-methyl-1H-imidazo[5,4-b]pyridine ring is connected via an ether linkage to a 4-chloroquinoline ring. The quinoline ring is further connected via a pyrazole ring to a 4-(4-(chloromethyl)piperidin-1-yl)butyl group.
296	 Chemical structure of compound 296: A 4-methyl-1H-imidazo[5,4-b]pyridine ring is connected via an ether linkage to a 4-chloroquinoline ring. The quinoline ring is further connected via a pyrazole ring to a 4-(4-(trifluoromethyl)piperidin-1-yl)butyl group.

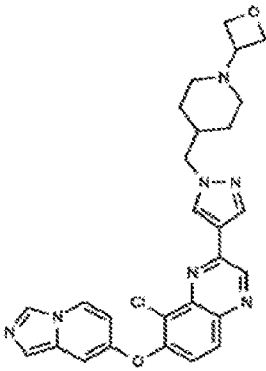
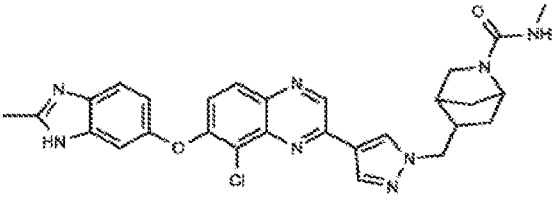
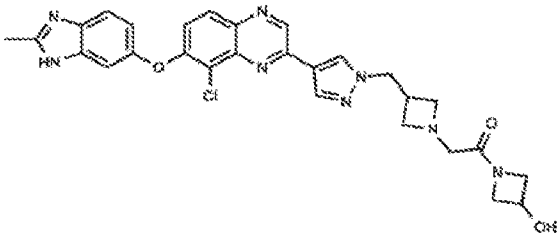
Compound No.	Structure
297	 Chemical structure of compound 297: A 4-methyl-1H-indazol-5-yl group is connected via an ether linkage to a 4-chloro-2-((1-methyl-1,3-dihydroisobenzofuran-2-yl)methyl)quinazolin-6-yl group.
298	 Chemical structure of compound 298: A 4-methyl-1H-indazol-5-yl group is connected via an ether linkage to a 4-chloro-2-((1-methyl-1,3-dihydroisobenzofuran-2-yl)methyl)quinazolin-6-yl group, which is further connected to a 1,3-dioxolane ring.
299	 Chemical structure of compound 299: A 4-methyl-1H-indazol-5-yl group is connected via an ether linkage to a 4-chloro-2-((1-methyl-1,3-dihydroisobenzofuran-2-yl)methyl)quinazolin-6-yl group, which is further connected to a 1,3-dioxane ring.

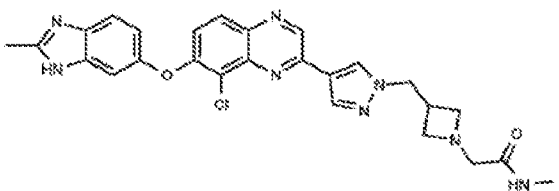
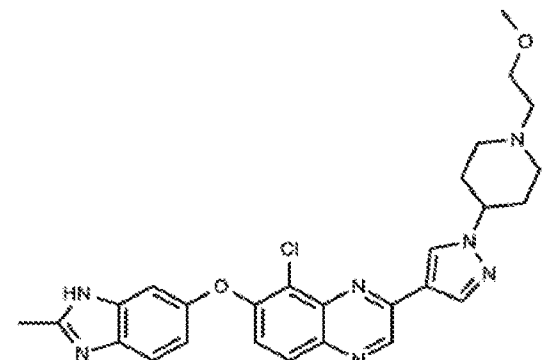
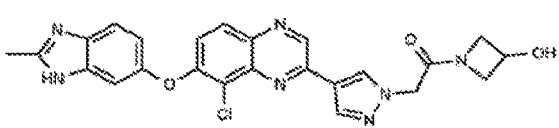
Compound No.	Structure
300	 Chemical structure of compound 300: A quinoline ring system substituted with a chlorine atom at position 8, a 4-methyl-1H-imidazol-2-yl group at position 6, and a 1-((2-(4-methyl-1H-imidazol-2-yl)ethyl)amino)pyrrolidine-3-carbonyl group at position 2. The quinoline ring is connected at position 4 to a 1H-imidazole ring, which is further connected at position 2 to a 1-((2-(4-methyl-1H-imidazol-2-yl)ethyl)amino)pyrrolidine-3-carbonyl group.
301	 Chemical structure of compound 301: A quinoline ring system substituted with a chlorine atom at position 8, a 4-methyl-1H-imidazol-2-yl group at position 6, and a 1-((2-(4-methyl-1H-imidazol-2-yl)ethyl)amino)pyrrolidine-3-carbonyl group at position 2. The quinoline ring is connected at position 4 to a 1H-imidazole ring, which is further connected at position 2 to a 1-((2-(4-methyl-1H-imidazol-2-yl)ethyl)amino)pyrrolidine-3-carbonyl group.
302	 Chemical structure of compound 302: A quinoline ring system substituted with a chlorine atom at position 8, a 4-methyl-1H-imidazol-2-yl group at position 6, and a 1-((2-(4-methyl-1H-imidazol-2-yl)ethyl)amino)pyrrolidine-3-carbonyl group at position 2. The quinoline ring is connected at position 4 to a 1H-imidazole ring, which is further connected at position 2 to a 1-((2-(4-methyl-1H-imidazol-2-yl)ethyl)amino)pyrrolidine-3-carbonyl group.

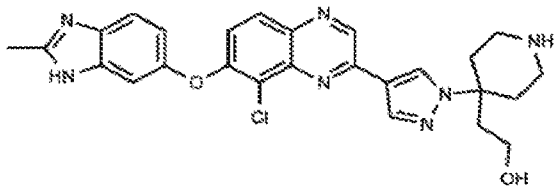
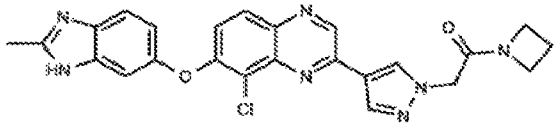
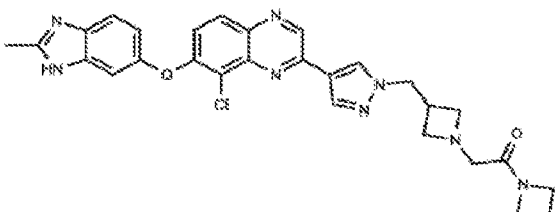
Compound No.	Structure
303	 Chemical structure of compound 303: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 7, and a 1-(2-(2,2,2-trifluoroethyl)piperidin-1-yl)-1H-imidazol-2-yl group at position 4.
304	 Chemical structure of compound 304: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 7, and a 1-(2-(piperidin-4-yl)ethyl)-1H-imidazol-2-yl group at position 4.
305	 Chemical structure of compound 305: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 7, and a 1-(2-(N-methylpiperidin-4-yl)ethyl)-1H-imidazol-2-yl group at position 4.

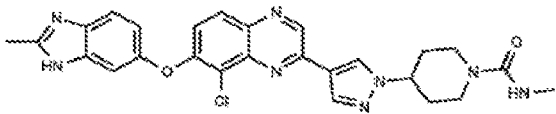
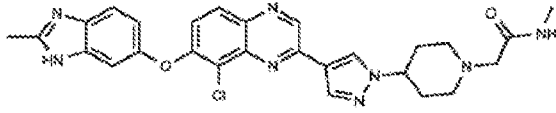
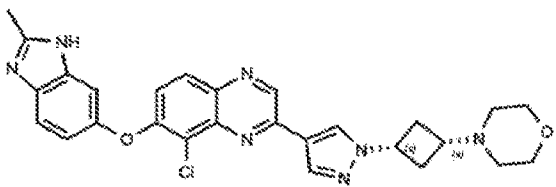
Compound No.	Structure
306	 Chemical structure of compound 306: A 4-methyl-1H-indazole ring is connected via an ether linkage to a 4-chloroquinoline ring. The quinoline ring is further connected to a 1,2,4-triazole ring, which is linked to a 2-hydroxy-1-(2-methyl-1H-indazol-4-yl)ethan-1-one derivative.
307	 Chemical structure of compound 307: A 4-methyl-1H-indazole ring is connected via an ether linkage to a 4-chloroquinoline ring. The quinoline ring is further connected to a 1,2,4-triazole ring, which is linked to a 2-(chloromethyl)-1,3-dioxane derivative.
308	 Chemical structure of compound 308: A 4-methyl-1H-indazole ring is connected via an ether linkage to a 4-chloroquinoline ring. The quinoline ring is further connected to a 1,2,4-triazole ring, which is linked to a 2-(chloromethyl)-1,3-dioxane derivative.

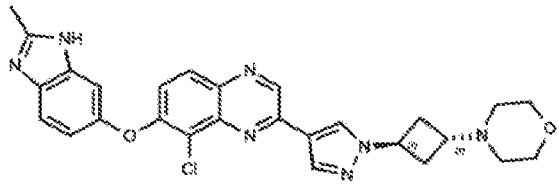
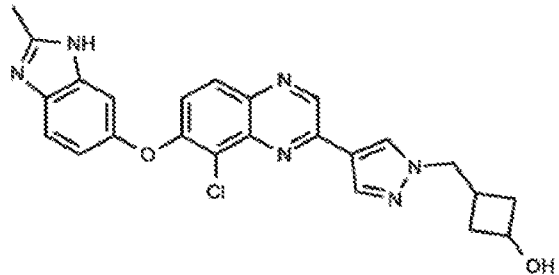
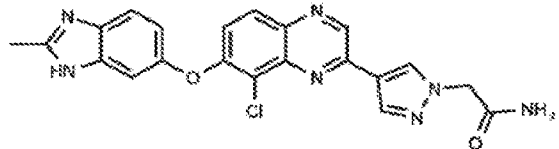
Compound No.	Structure
309	 Chemical structure of compound 309: A 4-methyl-1H-imidazo[5,1-b]pyridine ring is connected via an ether linkage to a 4-chloro-2,6-diazapyrene ring. This is further connected to a 1,2,4-triazole ring, which is linked to a cyclobutane ring, and finally to a 2-hydroxymethylcyclobutane ring.
310	 Chemical structure of compound 310: A 4-methyl-1H-imidazo[5,1-b]pyridine ring is connected via an ether linkage to a 4-chloro-2,6-diazapyrene ring. This is further connected to a 1,2,4-triazole ring, which is linked to a cyclobutane ring, and finally to a 2-cyanoethylcyclobutane ring.
311	 Chemical structure of compound 311: A 4-methyl-1H-imidazo[5,1-b]pyridine ring is connected via an ether linkage to a 4-chloro-2,6-diazapyrene ring. This is further connected to a 1,2,4-triazole ring, which is linked to a cyclobutane ring, and finally to a 2-sulfonylmethylcyclobutane ring.

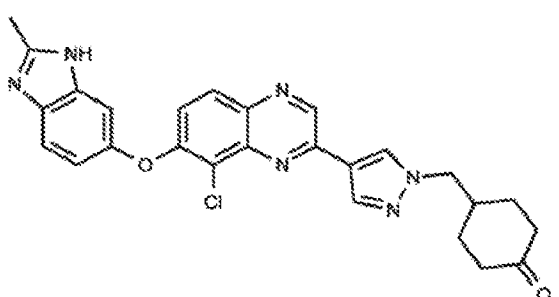
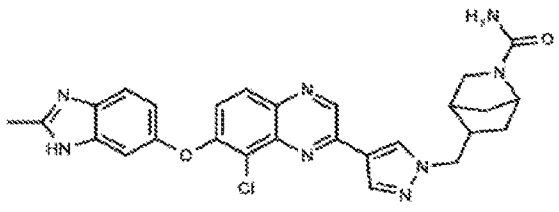
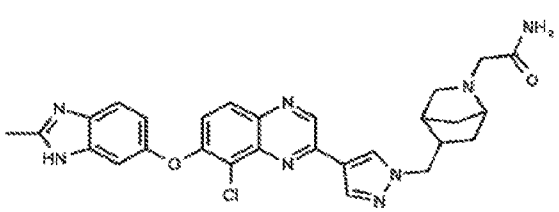
Compound No.	Structure
312	 Chemical structure of compound 312: A 7-chloro-2,3-bis(4-chloroquinolin-2-yl)quinoline core is substituted at the 4-position with a 1-(4-(4-oxo-1,4-dihydro-2H-pyrimidin-2-yl)butyl)piperidine-4-yl group.
313	 Chemical structure of compound 313: A 7-chloro-2,3-bis(4-methyl-1H-indol-5-yl)quinoline core is substituted at the 4-position with a 1-(4-(4-methyl-1H-indol-5-yl)-1H-pyrazol-5-yl)piperidine-4-yl group.
314	 Chemical structure of compound 314: A 7-chloro-2,3-bis(4-methyl-1H-indol-5-yl)quinoline core is substituted at the 4-position with a 1-(4-(4-methyl-1H-indol-5-yl)-1H-pyrazol-5-yl)piperidine-4-yl group.

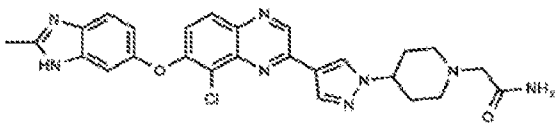
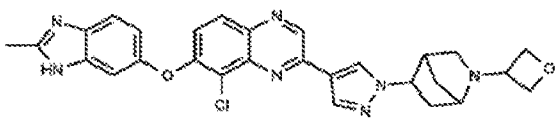
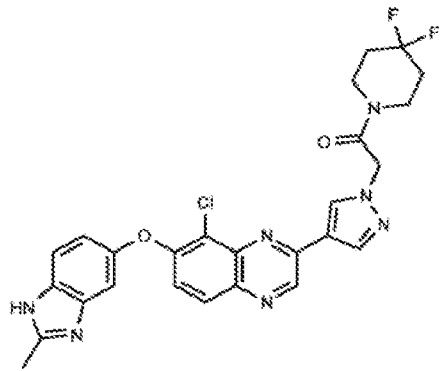
Compound No.	Structure
315	 Chemical structure of compound 315: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 6-chloroquinoline ring. This quinoline ring is further connected to a 1,2,4-triazole ring, which is linked to a 4-membered azetidine ring. The azetidine ring is connected to a carbonyl group, which is further linked to an NH group.
316	 Chemical structure of compound 316: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 6-chloroquinoline ring. This quinoline ring is further connected to a 1,2,4-triazole ring, which is linked to a 4-membered azetidine ring. The azetidine ring is connected to a carbonyl group, which is further linked to an NH group.
317	 Chemical structure of compound 317: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 6-chloroquinoline ring. This quinoline ring is further connected to a 1,2,4-triazole ring, which is linked to a 4-membered azetidine ring. The azetidine ring is connected to a carbonyl group, which is further linked to an NH group.

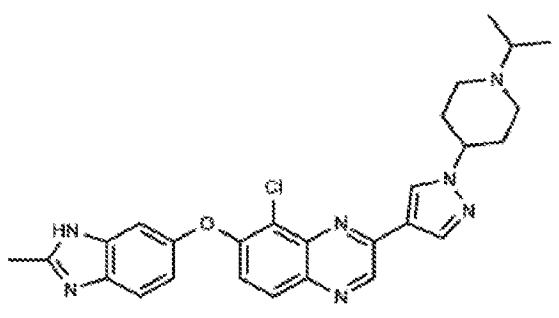
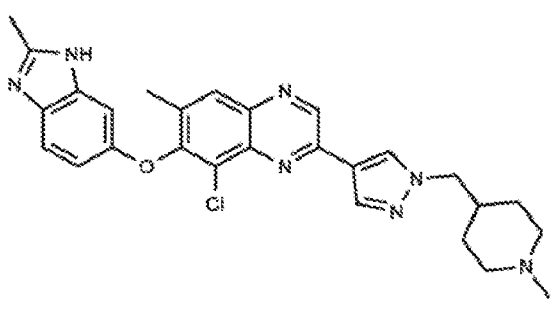
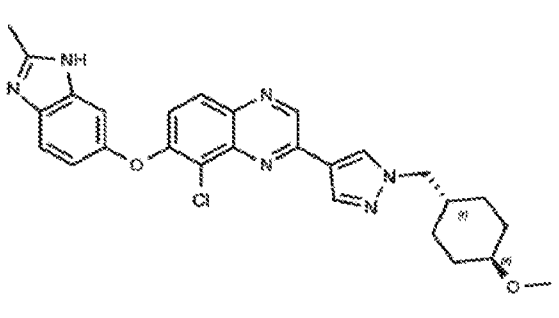
Compound No.	Structure
318	 Chemical structure of compound 318: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-chloro-2,6-diazin-3-yl group. This is further connected to a 1,2,4-triazole ring, which is substituted with a 2-hydroxy-2-(tetrahydro-2H-pyran-2-yl)ethyl group.
319	 Chemical structure of compound 319: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-chloro-2,6-diazin-3-yl group. This is further connected to a 1,2,4-triazole ring, which is substituted with a 2-oxo-2-(azetidin-1-yl)ethyl group.
320	 Chemical structure of compound 320: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-chloro-2,6-diazin-3-yl group. This is further connected to a 1,2,4-triazole ring, which is substituted with a 2-((azetidin-1-yl)methyl)-2-oxoethyl group.

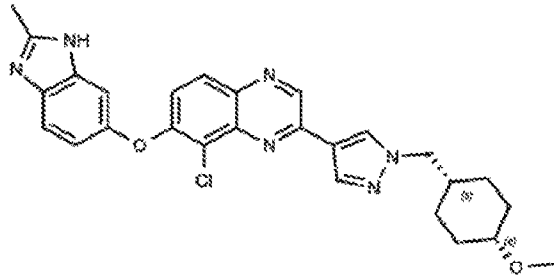
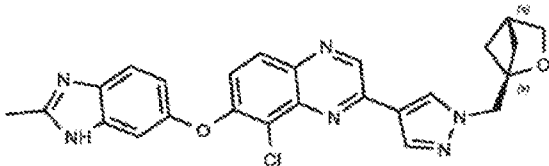
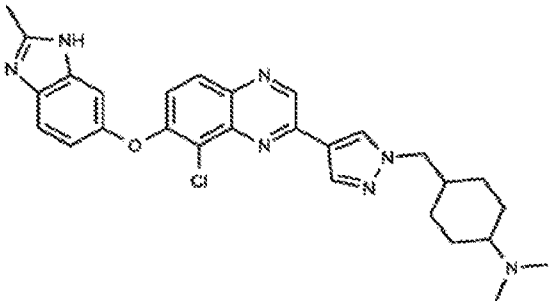
Compound No.	Structure
321	 Chemical structure of compound 321: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 8, and a 1-(1-methyl-4-(methylamino)pyrrolidin-3-yl)pyrazol-4-yl group at position 4.
322	 Chemical structure of compound 322: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 8, and a 1-(1-methyl-4-(methylamino)pyrrolidin-3-yl)pyrazol-4-yl group at position 4.
323	 Chemical structure of compound 323: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 8, and a 1-(1-methyl-4-(methylamino)pyrrolidin-3-yl)pyrazol-4-yl group at position 4.

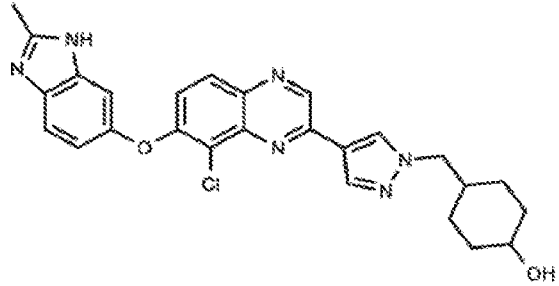
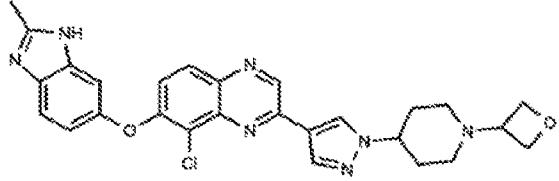
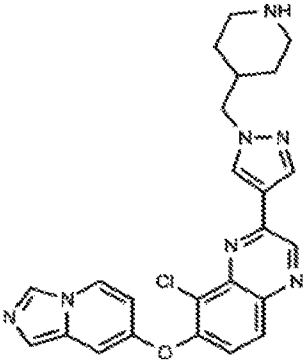
Compound No.	Structure
324	 Chemical structure of compound 324: A molecule featuring a 4-methyl-1H-imidazo[5,1-b]pyridine ring connected via an ether linkage to a 4-chloro-2,6-dimethylquinoline ring. This quinoline ring is further connected via a pyrazole ring to a cyclobutane ring, which is in turn connected to a morpholine ring.
325	 Chemical structure of compound 325: A molecule featuring a 4-methyl-1H-imidazo[5,1-b]pyridine ring connected via an ether linkage to a 4-chloro-2,6-dimethylquinoline ring. This quinoline ring is further connected via a pyrazole ring to a cyclobutane ring, which is in turn connected to a hydroxyl group (OH).
326	 Chemical structure of compound 326: A molecule featuring a 4-methyl-1H-imidazo[5,1-b]pyridine ring connected via an ether linkage to a 4-chloro-2,6-dimethylquinoline ring. This quinoline ring is further connected via a pyrazole ring to a cyclobutane ring, which is in turn connected to an amide group (NH₂).

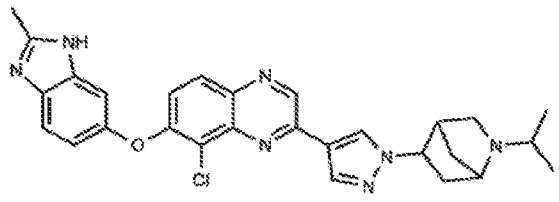
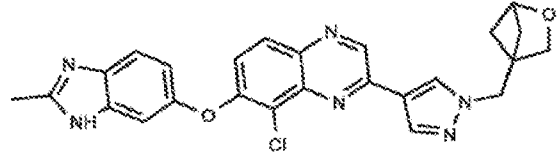
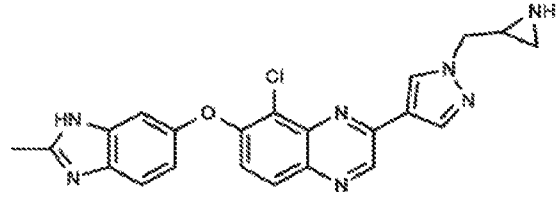
Compound No.	Structure
327	 Chemical structure of compound 327: A 4-(4-methyl-1H-imidazol-2-yl)phenoxy group is linked via an ether bond to a 6-chloroquinoline ring. The quinoline ring is further substituted at the 2-position with a 1-(cyclohexylmethyl)-1H-imidazol-2-yl group.
328	 Chemical structure of compound 328: A 4-(4-methyl-1H-imidazol-2-yl)phenoxy group is linked via an ether bond to a 6-chloroquinoline ring. The quinoline ring is further substituted at the 2-position with a 1-(adamantan-1-ylmethyl)-1H-imidazol-2-yl group. The adamantane moiety is substituted with a primary amide group (-CONH₂).
329	 Chemical structure of compound 329: A 4-(4-methyl-1H-imidazol-2-yl)phenoxy group is linked via an ether bond to a 6-chloroquinoline ring. The quinoline ring is further substituted at the 2-position with a 1-(adamantan-1-ylmethyl)-1H-imidazol-2-yl group. The adamantane moiety is substituted with a primary amide group (-CONH₂).

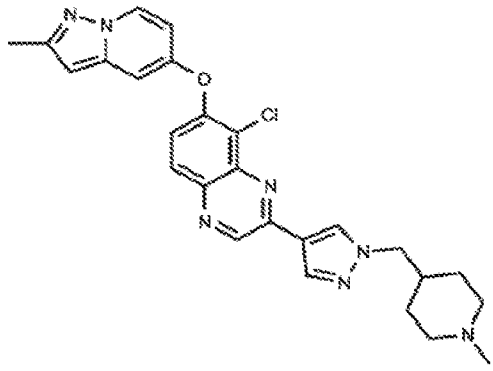
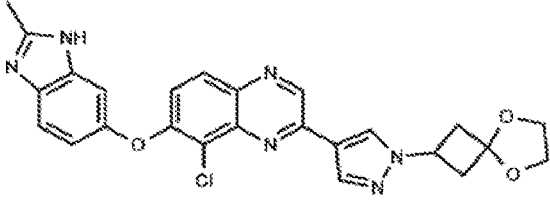
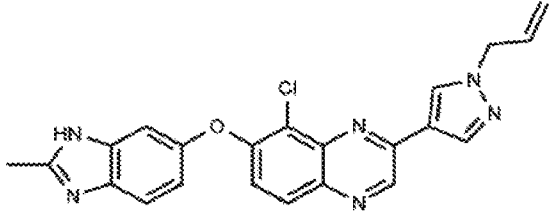
Compound No.	Structure
330	 Chemical structure of compound 330: A quinoline ring system with a chlorine atom at position 8 and a 4-methyl-1H-imidazol-2-yl group at position 6. The quinoline is connected via an ether linkage to a 4-methyl-1H-imidazol-2-yl group. This imidazole is further connected to a 1,4-diazepane ring, which is linked to a 2-aminoacetyl group.
331	 Chemical structure of compound 331: A quinoline ring system with a chlorine atom at position 8 and a 4-methyl-1H-imidazol-2-yl group at position 6. The quinoline is connected via an ether linkage to a 4-methyl-1H-imidazol-2-yl group. This imidazole is further connected to a 1,4-diazepane ring, which is linked to a 2-oxo-2-(oxolan-3-yl)ethyl group.
332	 Chemical structure of compound 332: A quinoline ring system with a chlorine atom at position 8 and a 4-methyl-1H-imidazol-2-yl group at position 6. The quinoline is connected via an ether linkage to a 4-methyl-1H-imidazol-2-yl group. This imidazole is further connected to a 1,4-diazepane ring, which is linked to a 2-oxo-2-(4,4-difluorophenyl)ethyl group.

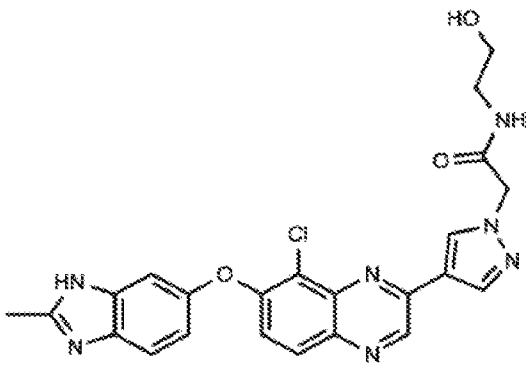
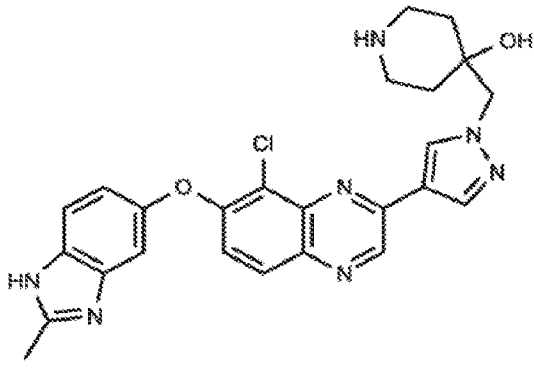
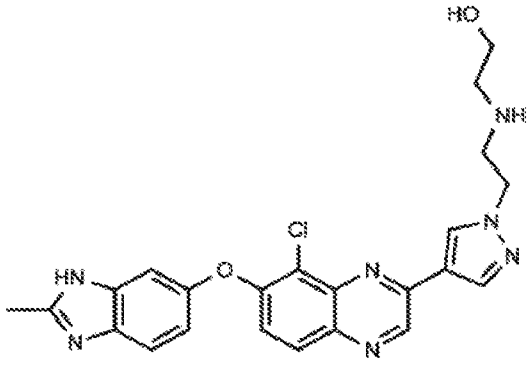
Compound No.	Structure
333	 Chemical structure of compound 333: A 4-methyl-1H-indazole ring is connected via an ether linkage to a 6-chloroquinoline ring. The quinoline ring is further connected to a 1,2,4-triazole ring, which is in turn connected to a 4-(dimethylamino)pyrimidin-2-yl group.
334	 Chemical structure of compound 334: A 4-methyl-1H-indazole ring is connected via an ether linkage to a 6-chloroquinoline ring. The quinoline ring is further connected to a 1,2,4-triazole ring, which is in turn connected to a 4-(dimethylamino)pyrimidin-2-yl group.
335	 Chemical structure of compound 335: A 4-methyl-1H-indazole ring is connected via an ether linkage to a 6-chloroquinoline ring. The quinoline ring is further connected to a 1,2,4-triazole ring, which is in turn connected to a 4-(dimethylamino)pyrimidin-2-yl group.

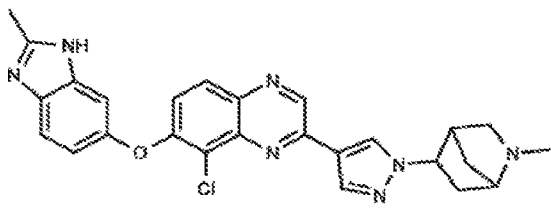
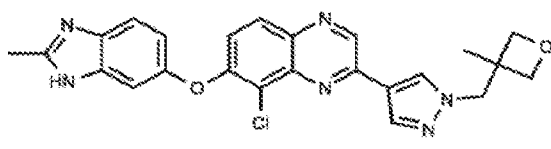
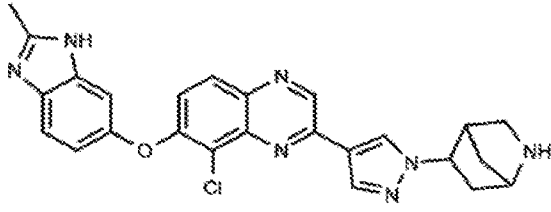
Compound No.	Structure
336	 Chemical structure of compound 336: A 4-methyl-1H-imidazo[5,4-b]pyridine ring is connected via an ether linkage to a 4-chloro-2-((1-methoxy-4-((1-methyl-1H-imidazo[5,4-b]pyridin-4-yl)oxy)-4,5,6,7-tetrahydro-2H-pyran-2-yl)pyrazol-5-yl)quinoline ring.
337	 Chemical structure of compound 337: A 4-methyl-1H-imidazo[5,4-b]pyridine ring is connected via an ether linkage to a 4-chloro-2-((1-((1S,2S,3S,4S)-3,4-epoxycyclohexyl)methyl)-1H-pyrazol-5-yl)quinoline ring.
338	 Chemical structure of compound 338: A 4-methyl-1H-imidazo[5,4-b]pyridine ring is connected via an ether linkage to a 4-chloro-2-((1-((1S,2S,3S,4S)-3,4-epoxycyclohexyl)methyl)-1H-pyrazol-5-yl)quinoline ring.

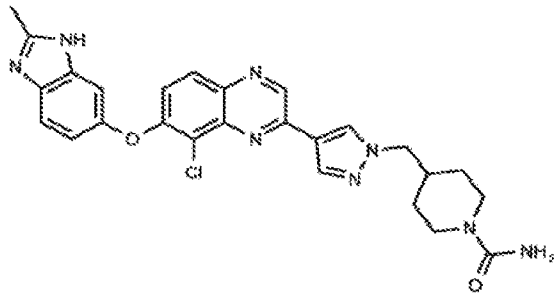
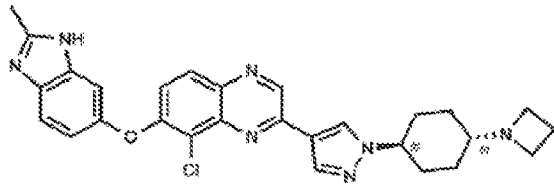
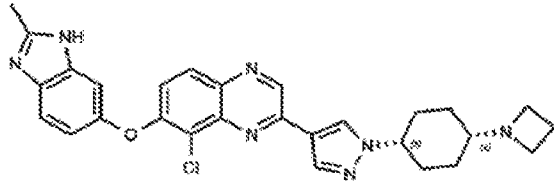
Compound No.	Structure
339	 Chemical structure of compound 339: A 4-(4-methyl-1H-imidazol-2-yl)phenoxy group is linked via an ether bond to a 6-chloro-2,3-bis(4-methyl-1H-imidazol-2-yl)quinazolin-4-yl group. This quinazolinyl group is further linked via a 1,2,4-triazole ring to a 4-(4-hydroxycyclohexyl)methyl group.
340	 Chemical structure of compound 340: A 4-(4-methyl-1H-imidazol-2-yl)phenoxy group is linked via an ether bond to a 6-chloro-2,3-bis(4-methyl-1H-imidazol-2-yl)quinazolin-4-yl group. This quinazolinyl group is further linked via a 1,2,4-triazole ring to a 4-(4-(oxolan-2-yl)piperidin-1-yl)methyl group.
341	 Chemical structure of compound 341: A 4-(4-methyl-1H-imidazol-2-yl)phenoxy group is linked via an ether bond to a 6-chloro-2,3-bis(4-methyl-1H-imidazol-2-yl)quinazolin-4-yl group. This quinazolinyl group is further linked via a 1,2,4-triazole ring to a 4-(4-(piperidin-1-yl)methyl)methyl group.

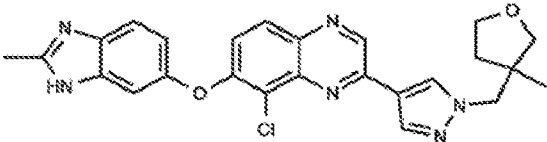
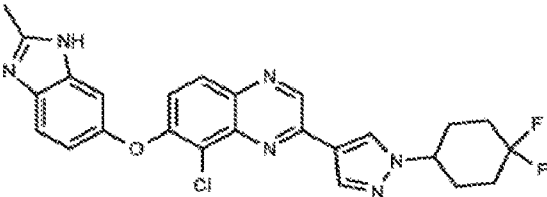
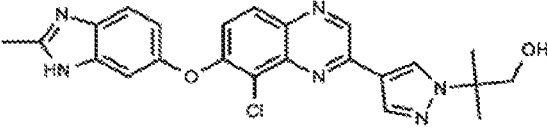
Compound No.	Structure
342	 Chemical structure of compound 342: A 4-methyl-1H-indazole ring is connected via an ether linkage to a 6-chloroquinoline ring. The quinoline ring is further connected to a 1H-imidazole ring, which is substituted with a 2-isopropyl-2-azabicyclo[2.2.1]hept-5-yl group.
343	 Chemical structure of compound 343: A 4-methyl-1H-indazole ring is connected via an ether linkage to a 6-chloroquinoline ring. The quinoline ring is further connected to a 1H-imidazole ring, which is substituted with a 2-oxaspiro[3.3]hept-2-yl group.
344	 Chemical structure of compound 344: A 4-methyl-1H-indazole ring is connected via an ether linkage to a 6-chloroquinoline ring. The quinoline ring is further connected to a 1H-imidazole ring, which is substituted with a 2-aziridin-1-yl group.

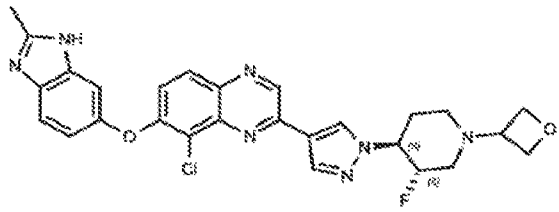
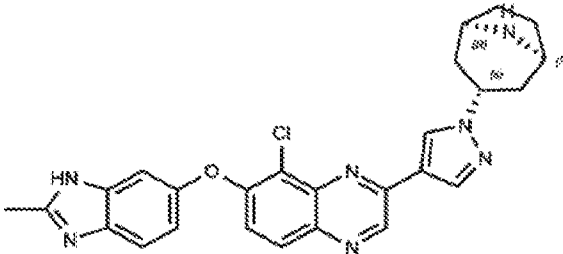
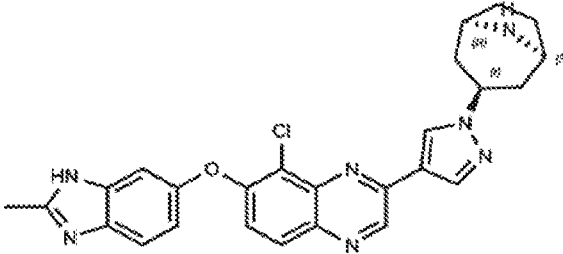
Compound No.	Structure
345	 Chemical structure of compound 345: A 4-methyl-1H-indazole ring is connected via an ether linkage to a 4-chloroquinoline ring. The quinoline ring is further connected via a double bond to a 1-(4-methyl-1H-indazol-5-yl)pyrazole ring, which is then connected via a methylene group to a 4-methyl-1H-indazole ring.
346	 Chemical structure of compound 346: A 4-methyl-1H-indazole ring is connected via an ether linkage to a 4-chloroquinoline ring. The quinoline ring is further connected via a double bond to a 1-(4-methyl-1H-indazol-5-yl)pyrazole ring, which is then connected via a methylene group to a 4-methyl-1H-indazole ring.
347	 Chemical structure of compound 347: A 4-methyl-1H-indazole ring is connected via an ether linkage to a 4-chloroquinoline ring. The quinoline ring is further connected via a double bond to a 1-(4-methyl-1H-indazol-5-yl)pyrazole ring, which is then connected via a methylene group to a 4-methyl-1H-indazole ring.

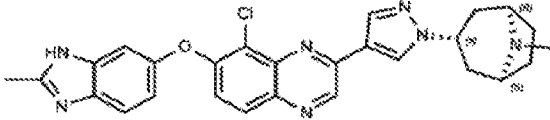
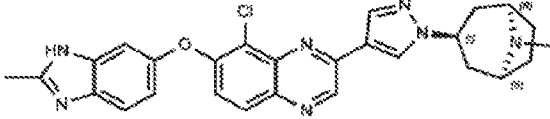
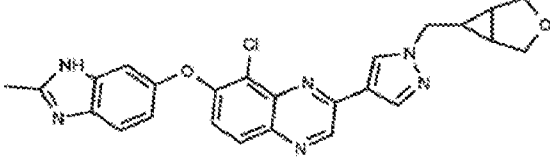
Compound No.	Structure
348	 Chemical structure of compound 348: A 4-(4-methyl-1H-imidazol-2-yl)phenyl group is connected via an ether linkage to a 6-chloro-2-(1H-imidazol-4-yl)quinazolin-4-yl group. The imidazole ring is further substituted with a 2-((2-hydroxyethyl)amino)ethyl carbonyl group.
349	 Chemical structure of compound 349: A 4-(4-methyl-1H-imidazol-2-yl)phenyl group is connected via an ether linkage to a 6-chloro-2-(1H-imidazol-4-yl)quinazolin-4-yl group. The imidazole ring is further substituted with a 2-(4-morpholin-4-yl)ethyl group.
350	 Chemical structure of compound 350: A 4-(4-methyl-1H-imidazol-2-yl)phenyl group is connected via an ether linkage to a 6-chloro-2-(1H-imidazol-4-yl)quinazolin-4-yl group. The imidazole ring is further substituted with a 3-((2-hydroxyethyl)amino)propyl group.

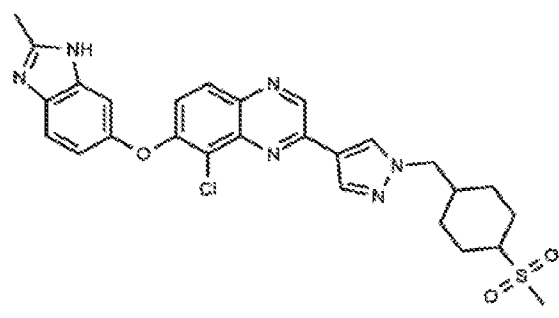
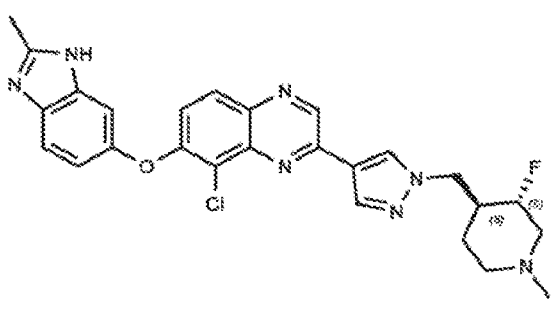
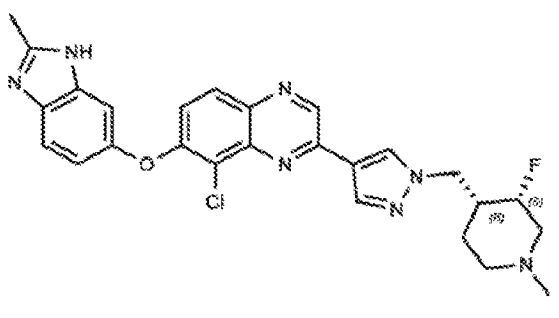
Compound No.	Structure
351	 Chemical structure of compound 351: A molecule featuring a 4-methyl-1H-indazol-5-yl group connected via an ether linkage to a 4-chloro-2-((1-methyl-1,2,3,4-tetrahydrophthalazine-5-yl)methyl)quinazolin-6-yl group.
352	 Chemical structure of compound 352: A molecule featuring a 4-methyl-1H-indazol-5-yl group connected via an ether linkage to a 4-chloro-2-((1-methyl-1,2,3,4-tetrahydrophthalazine-5-yl)methyl)quinazolin-6-yl group.
353	 Chemical structure of compound 353: A molecule featuring a 4-methyl-1H-indazol-5-yl group connected via an ether linkage to a 4-chloro-2-((1-methyl-1,2,3,4-tetrahydrophthalazine-5-yl)methyl)quinazolin-6-yl group.

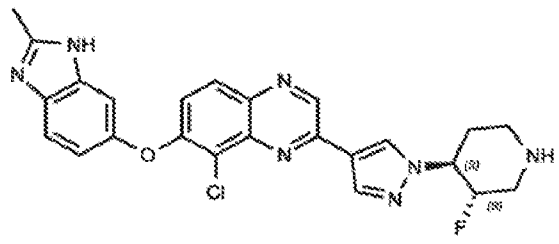
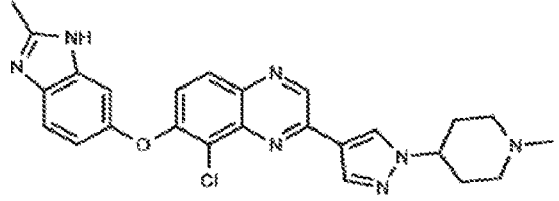
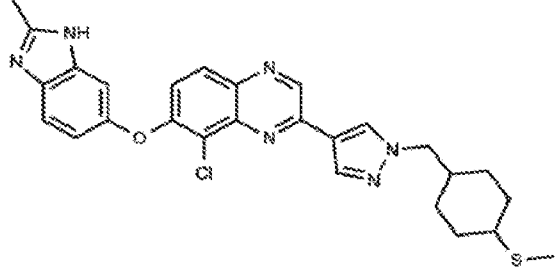
Compound No.	Structure
354	 Chemical structure of compound 354: A molecule featuring a 4-methyl-1H-imidazo[5,4-b]pyridine ring connected via an ether linkage to a 4-chloro-2-((1H-imidazo[5,4-b]pyridin-4-yl)oxy)quinoline ring. This quinoline ring is further connected via a pyrazole ring to a piperidine ring, which is substituted with a primary amide group (-CONH₂).
355	 Chemical structure of compound 355: A molecule featuring a 4-methyl-1H-imidazo[5,4-b]pyridine ring connected via an ether linkage to a 4-chloro-2-((1H-imidazo[5,4-b]pyridin-4-yl)oxy)quinoline ring. This quinoline ring is further connected via a pyrazole ring to a piperidine ring, which is substituted with a cyclobutyl group.
356	 Chemical structure of compound 356: A molecule featuring a 4-methyl-1H-imidazo[5,4-b]pyridine ring connected via an ether linkage to a 4-chloro-2-((1H-imidazo[5,4-b]pyridin-4-yl)oxy)quinoline ring. This quinoline ring is further connected via a pyrazole ring to a piperidine ring, which is substituted with a cyclobutyl group.

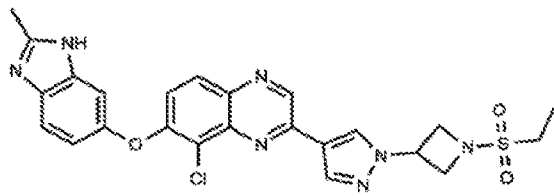
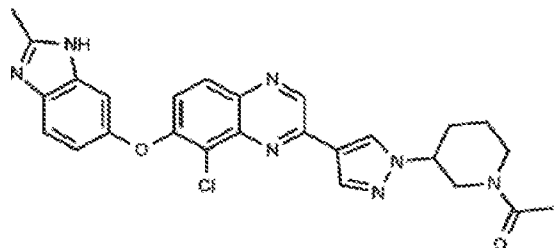
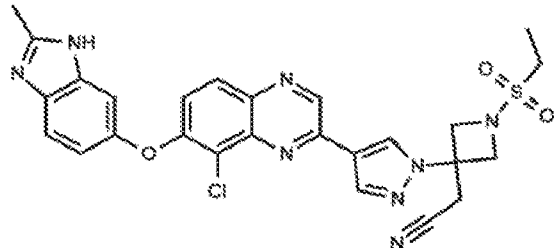
Compound No.	Structure
357	 Chemical structure of compound 357: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-chloroquinoline ring. This quinoline ring is further connected via a 1,2,4-triazole ring to a 4,4-dimethyl-1,3-dioxane ring.
358	 Chemical structure of compound 358: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-chloroquinoline ring. This quinoline ring is further connected via a 1,2,4-triazole ring to a 1,1-difluoro-4,4-dihydrocyclohexyl ring.
359	 Chemical structure of compound 359: A 4-methyl-1H-indol-3-yl group is connected via an ether linkage to a 4-chloroquinoline ring. This quinoline ring is further connected via a 1,2,4-triazole ring to a 2-hydroxy-2-methylpropyl group.

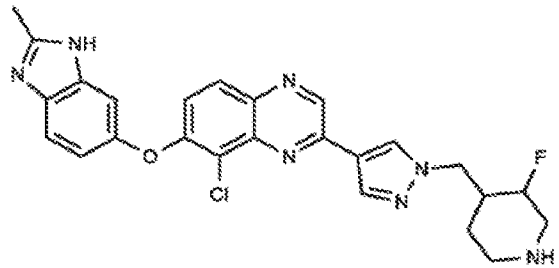
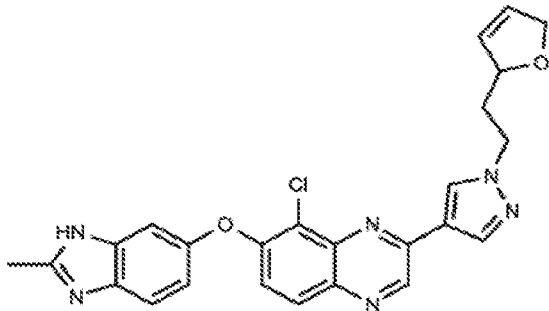
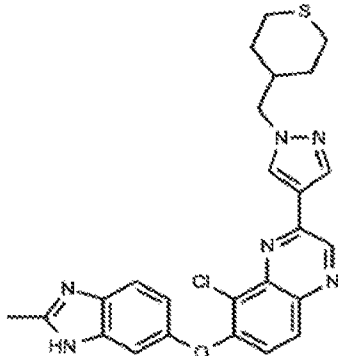
Compound No.	Structure
360	 Chemical structure of compound 360: A 4-methyl-1H-imidazo[5,4-b]pyridine ring is connected via an ether linkage to a 4-chloro-2-((1-((2-oxaspiro[3.3]heptan-2-ylideneamino)ethyl)pyrrolidin-4-yl)pyrazol-4-yl)quinoline ring.
361	 Chemical structure of compound 361: A 4-methyl-1H-imidazo[5,4-b]pyridine ring is connected via an ether linkage to a 4-chloro-2-((1-((2-oxaspiro[3.3]heptan-2-ylideneamino)ethyl)pyrrolidin-4-yl)pyrazol-4-yl)quinoline ring.
362	 Chemical structure of compound 362: A 4-methyl-1H-imidazo[5,4-b]pyridine ring is connected via an ether linkage to a 4-chloro-2-((1-((2-oxaspiro[3.3]heptan-2-ylideneamino)ethyl)pyrrolidin-4-yl)pyrazol-4-yl)quinoline ring.

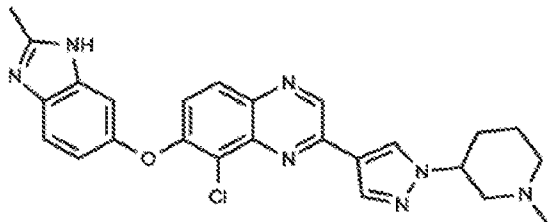
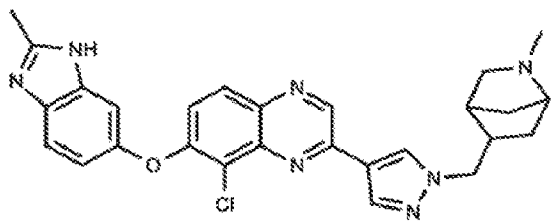
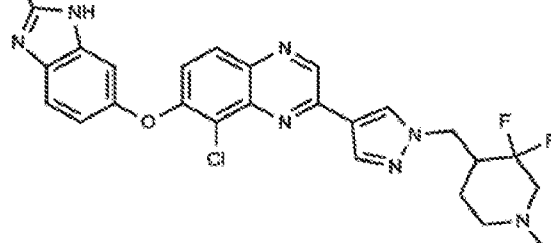
Compound No.	Structure
363	 Chemical structure of compound 363: A 4-methyl-1H-indazole ring is connected via an ether linkage to a 4-chloroquinoline ring. The quinoline ring is further connected via a pyrazole ring to a 7-membered azepane ring.
364	 Chemical structure of compound 364: A 4-methyl-1H-indazole ring is connected via an ether linkage to a 4-chloroquinoline ring. The quinoline ring is further connected via a pyrazole ring to a 7-membered azepane ring.
365	 Chemical structure of compound 365: A 4-methyl-1H-indazole ring is connected via an ether linkage to a 4-chloroquinoline ring. The quinoline ring is further connected via a pyrazole ring to a cyclopropylmethyl group.

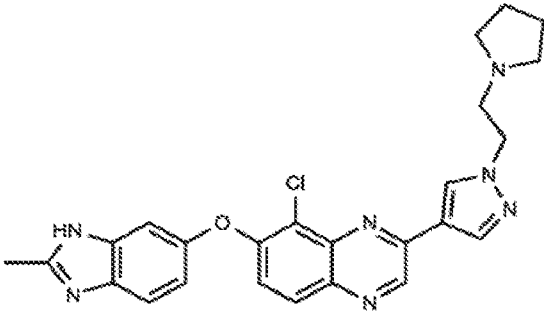
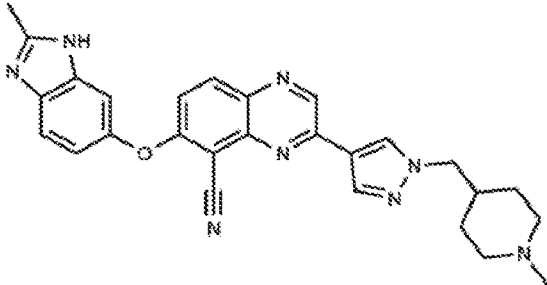
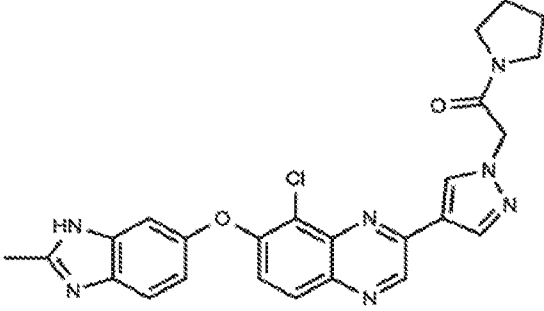
Compound No.	Structure
366	 Chemical structure of compound 366: A molecule featuring a 4-methyl-1H-indazol-5-yl group connected via an ether linkage to a 6-chloroquinoline ring. This quinoline ring is further connected to a 1,2,4-triazole ring, which is linked to a cyclohexyl ring. The cyclohexyl ring is substituted with a methanesulfonyl group (-SO₂CH₃).
367	 Chemical structure of compound 367: A molecule featuring a 4-methyl-1H-indazol-5-yl group connected via an ether linkage to a 6-chloroquinoline ring. This quinoline ring is further connected to a 1,2,4-triazole ring, which is linked to a 1-methyl-2,6-dimethylpiperidine ring. The stereochemistry at the chiral center is indicated with a wedge bond.
368	 Chemical structure of compound 368: A molecule featuring a 4-methyl-1H-indazol-5-yl group connected via an ether linkage to a 6-chloroquinoline ring. This quinoline ring is further connected to a 1,2,4-triazole ring, which is linked to a 1-methyl-2,6-dimethylpiperidine ring. The stereochemistry at the chiral center is indicated with a dashed bond.

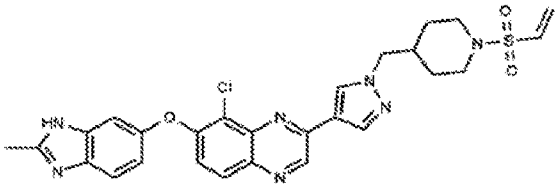
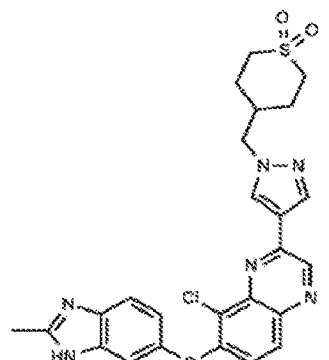
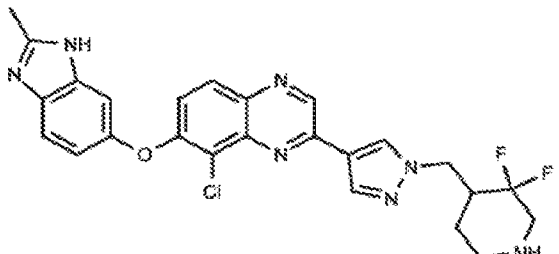
Compound No.	Structure
369	 Chemical structure of compound 369: A 4-(4-chloro-7-((4-methyl-1H-imidazol-2-yl)oxy)quinolin-2-yl)-1H-imidazole connected via an ether linkage to a 4-chloroquinoline ring, which is further connected to a 1,2,4-triazole ring. The triazole ring is substituted with a 4-fluoro-1,4-dihydropyridine ring.
370	 Chemical structure of compound 370: A 4-(4-chloro-7-((4-methyl-1H-imidazol-2-yl)oxy)quinolin-2-yl)-1H-imidazole connected via an ether linkage to a 4-chloroquinoline ring, which is further connected to a 1,2,4-triazole ring. The triazole ring is substituted with a 4-methyl-1,4-dihydropyridine ring.
371	 Chemical structure of compound 371: A 4-(4-chloro-7-((4-methyl-1H-imidazol-2-yl)oxy)quinolin-2-yl)-1H-imidazole connected via an ether linkage to a 4-chloroquinoline ring, which is further connected to a 1,2,4-triazole ring. The triazole ring is substituted with a 4-(methylthio)-1,4-dihydropyridine ring.

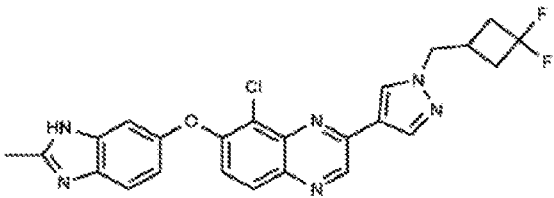
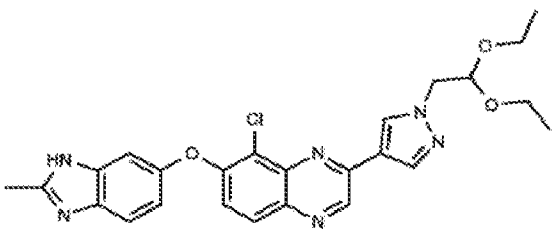
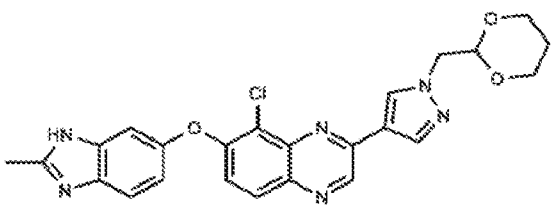
Compound No.	Structure
372	 Chemical structure of compound 372: A 4-methyl-1H-indazol-5-yl group is connected via an ether linkage to a 4-chloro-2-((1-ethylsulfonyl-1H-imidazol-2-yl)methyl)quinoline group.
373	 Chemical structure of compound 373: A 4-methyl-1H-indazol-5-yl group is connected via an ether linkage to a 4-chloro-2-((1-(2-acetyl-2-methylpyrrolidin-1-yl)-1H-imidazol-2-yl)methyl)quinoline group.
374	 Chemical structure of compound 374: A 4-methyl-1H-indazol-5-yl group is connected via an ether linkage to a 4-chloro-2-((1-((2-cyanoethyl)azetidin-1-yl)ethylsulfonyl)-1H-imidazol-2-yl)methyl)quinoline group.

Compound No.	Structure
375	 Chemical structure of compound 375: A 4-methyl-1H-indol-5-yl group is connected via an ether linkage to a 6-chloro-2-((1-(2-fluoro-2,3,4,5-tetrahydro-1H-pyridin-4-yl)pyrazol-4-yl)pyrimidin-4-yl)phenyl group.
376	 Chemical structure of compound 376: A 4-methyl-1H-indol-5-yl group is connected via an ether linkage to a 6-chloro-2-((1-(2-(furan-2-yl)ethyl)pyrazol-4-yl)pyrimidin-4-yl)phenyl group.
377	 Chemical structure of compound 377: A 4-methyl-1H-indol-5-yl group is connected via an ether linkage to a 6-chloro-2-((1-(1,4-dithiane-3-ylmethyl)pyrazol-4-yl)pyrimidin-4-yl)phenyl group.

Compound No.	Structure
378	 Chemical structure of compound 378: A 4-(4-chloro-7-((4-methyl-1H-imidazol-2-yl)oxy)quinazolin-2-yl)-1H-imidazole connected via an ether linkage to a 4-chloro-7-((4-methyl-1H-imidazol-2-yl)oxy)quinazolin-2-yl group, which is further connected via a triazole ring to a 4-methyl-1H-imidazole group.
379	 Chemical structure of compound 379: A 4-(4-chloro-7-((4-methyl-1H-imidazol-2-yl)oxy)quinazolin-2-yl)-1H-imidazole connected via an ether linkage to a 4-chloro-7-((4-methyl-1H-imidazol-2-yl)oxy)quinazolin-2-yl group, which is further connected via a triazole ring to a 4-methyl-1H-imidazole group.
380	 Chemical structure of compound 380: A 4-(4-chloro-7-((4-methyl-1H-imidazol-2-yl)oxy)quinazolin-2-yl)-1H-imidazole connected via an ether linkage to a 4-chloro-7-((4-methyl-1H-imidazol-2-yl)oxy)quinazolin-2-yl group, which is further connected via a triazole ring to a 4-methyl-1H-imidazole group.

Compound No.	Structure
381	 Chemical structure of compound 381: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 8, and a 1-(1H-imidazol-2-yl)propyl group at position 4.
382	 Chemical structure of compound 382: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a nitrile group at position 8, and a 1-(1H-imidazol-2-yl)propyl group at position 4.
383	 Chemical structure of compound 383: A quinazoline core substituted with a 4-(4-methyl-1H-imidazol-2-yl)phenoxy group at position 6, a chlorine atom at position 8, and a 1-(1H-imidazol-2-yl)propyl group at position 4.

Compound No.	Structure
384	 Chemical structure of compound 384: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 4-chloro-2,3-dihydroquinazolin-2-yl group. This is further connected to a 1H-imidazol-2-yl group, which is linked to a 4-(allylsulfamoyl)piperidine ring.
385	 Chemical structure of compound 385: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 4-chloro-2,3-dihydroquinazolin-2-yl group. This is further connected to a 1H-imidazol-2-yl group, which is linked to a 4-(methylsulfonyl)piperidine ring.
386	 Chemical structure of compound 386: A molecule featuring a 4-methyl-1H-indol-3-yl group connected via an ether linkage to a 4-chloro-2,3-dihydroquinazolin-2-yl group. This is further connected to a 1H-imidazol-2-yl group, which is linked to a 4-(difluoromethyl)piperidine ring.

Compound No.	Structure
387	
388	
389	

[0426] In some aspects, the present disclosure provides a compound being an isotopic derivative (e.g., isotopically labeled compound) of any one of the compounds disclosed herein.

[0427] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table I and Table II, or a pharmaceutically acceptable salt thereof.

[0428] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table I and II.

[0429] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table I, or a pharmaceutically acceptable salt thereof.

[0430] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table I.

[0431] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table II, or a pharmaceutically acceptable salt thereof.

[0432] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table II.

[0433] It is understood that the isotopic derivative can be prepared using any of a variety of art-recognized techniques. For example, the isotopic derivative can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples described herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

[0434] In some embodiments, the isotopic derivative is a deuterium labeled compound.

[0435] In some embodiments, the isotopic derivative is a deuterium labeled compound of any one of the compounds of the Formulae disclosed herein.

[0436] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table I and Table II, or a pharmaceutically acceptable salt thereof.

[0437] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table I and Table II.

[0438] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table I, or a pharmaceutically acceptable salt thereof.

[0439] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table I.

[0440] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table II, or a pharmaceutically acceptable salt thereof.

[0441] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table II.

[0442] It is understood that the deuterium labeled compound comprises a deuterium atom having an abundance of deuterium that is substantially greater than the natural abundance of deuterium, which is 0.015%.

[0443] In some embodiments, the deuterium labeled compound has a deuterium enrichment factor

for each deuterium atom of at least 3500 (52.5% deuterium incorporation at each deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation). As used herein, the term “deuterium enrichment factor” means the ratio between the deuterium abundance and the natural abundance of a deuterium.

[0444] It is understood that the deuterium labeled compound can be prepared using any of a variety of art-recognized techniques. For example, the deuterium labeled compound can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples described herein, by substituting a deuterium labeled reagent for a non-deuterium labeled reagent.

[0445] A compound of the invention or a pharmaceutically acceptable salt or solvate thereof that contains the aforementioned deuterium atom(s) is within the scope of the invention. Further, substitution with deuterium (*i.e.*, ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability, *e.g.*, increased *in vivo* half-life or reduced dosage requirements.

[0446] For the avoidance of doubt it is to be understood that, where in this specification a group is qualified by “described herein”, the said group encompasses the first occurring and broadest definition as well as each and all of the particular definitions for that group.

[0447] A suitable pharmaceutically acceptable salt of a compound of the disclosure is, for example, an acid-addition salt of a compound of the disclosure which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, formic, citric methane sulphonate or maleic acid. In addition, a suitable pharmaceutically acceptable salt of a compound of the disclosure which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a pharmaceutically acceptable cation, for example a salt with methylamine, dimethylamine, diethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

[0448] It will be understood that the compounds of the present disclosure and any pharmaceutically acceptable salts thereof, comprise stereoisomers, mixtures of stereoisomers, polymorphs of all isomeric forms of said compounds.

[0449] As used herein, the term “isomerism” means compounds that have identical molecular formulae but differ in the sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers.” Stereoisomers that are not mirror images of one another are termed “diastereoisomers,” and stereoisomers that are non-superimposable mirror images of each other are termed “enantiomers” or sometimes optical isomers. A mixture containing equal amounts of individual enantiomeric forms of opposite chirality is termed a “racemic mixture.”

[0450] As used herein, the term “chiral center” refers to a carbon atom bonded to four nonidentical substituents.

[0451] As used herein, the term “chiral isomer” means a compound with at least one chiral center. Compounds with more than one chiral center may exist either as an individual diastereomer or as a mixture of diastereomers, termed “diastereomeric mixture.” When one chiral center is present, a stereoisomer may be characterized by the absolute configuration (R or S) of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. The substituents attached to the chiral center under consideration are ranked in accordance with the *Sequence Rule* of Cahn, Ingold and Prelog. (Cahn *et al.*, *Angew. Chem. Inter. Edit.* 1966, 5, 385; errata 511; Cahn *et al.*, *Angew. Chem.* 1966, 78, 413; Cahn and Ingold, *J. Chem. Soc.* 1951 (London), 612; Cahn *et al.*, *Experientia* 1956, 12, 81; Cahn, *J. Chem. Educ.* 1964, 41, 116).

[0452] As used herein, the term “geometric isomer” means the diastereomers that owe their existence to hindered rotation about double bonds or a cycloalkyl linker (e.g., 1,3-cyclobutyl). These configurations are differentiated in their names by the prefixes *cis* and *trans*, or *Z* and *E*, which indicate that the groups are on the same or opposite side of the double bond in the molecule according to the Cahn-Ingold-Prelog rules.

[0453] It is to be understood that the compounds of the present disclosure may be depicted as different chiral isomers or geometric isomers. It is also to be understood that when compounds have chiral isomeric or geometric isomeric forms, all isomeric forms are intended to be included in the scope of the present disclosure, and the naming of the compounds does not exclude any isomeric forms, it being understood that not all isomers may have the same level of activity.

[0454] It is to be understood that the structures and other compounds discussed in this disclosure include all atropic isomers thereof. It is also to be understood that not all atropic isomers may have the same level of activity.

[0455] As used herein, the term “atropic isomers” are a type of stereoisomer in which the atoms of two isomers are arranged differently in space. Atropic isomers owe their existence to a restricted rotation caused by hindrance of rotation of large groups about a central bond. Such atropic isomers typically exist as a mixture, however as a result of recent advances in chromatography techniques, it has been possible to separate mixtures of two atropic isomers in select cases.

[0456] As used herein, the term “tautomer” is one of two or more structural isomers that exist in equilibrium and is readily converted from one isomeric form to another. This conversion results in the formal migration of a hydrogen atom accompanied by a switch of adjacent conjugated double bonds. Tautomers exist as a mixture of a tautomeric set in solution. In solutions where tautomerisation is possible, a chemical equilibrium of the tautomers will be reached. The exact ratio of the tautomers depends on several factors, including temperature, solvent and pH. The concept of tautomers that are interconvertible by tautomerisations is called tautomerism. Of the various types of tautomerism that are possible, two are commonly observed. In keto-enol tautomerism a simultaneous shift of electrons and a hydrogen atom occurs. Ring-chain tautomerism arises as a result of the aldehyde group (-CHO) in a sugar chain molecule reacting with one of the hydroxy groups (-OH) in the same molecule to give it a cyclic (ring-shaped) form as exhibited by glucose.

[0457] It is to be understood that the compounds of the present disclosure may be depicted as different tautomers. It should also be understood that when compounds have tautomeric forms, all tautomeric forms are intended to be included in the scope of the present disclosure, and the naming of the compounds does not exclude any tautomer form. It will be understood that certain tautomers may have a higher level of activity than others.

[0458] Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed “isomers”. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers”. Stereoisomers that are not mirror images of one another are termed “diastereomers” and those that are non-superimposable mirror images of each other are termed “enantiomers”. When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarised light and designated as dextrorotatory or

levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a “racemic mixture”.

[0459] The compounds of this disclosure may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)-stereoisomers or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of “Advanced Organic Chemistry”, 4th edition J. March, John Wiley and Sons, New York, 2001), for example by synthesis from optically active starting materials or by resolution of a racemic form. Some of the compounds of the disclosure may have geometric isomeric centers (E- and Z- isomers). It is to be understood that the present disclosure encompasses all optical, diastereoisomers and geometric isomers and mixtures thereof that possess inflammasome inhibitory activity.

[0460] The present disclosure also encompasses compounds of the disclosure as defined herein which comprise one or more isotopic substitutions.

[0461] It is to be understood that the compounds of any Formula described herein include the compounds themselves, as well as their salts, and their solvates, if applicable. A salt, for example, can be formed between an anion and a positively charged group (e.g., amino) on a substituted compound disclosed herein. Suitable anions include chloride, bromide, iodide, sulphate, bisulphate, sulphamate, nitrate, phosphate, citrate, methanesulphonate, trifluoroacetate, glutamate, glucuronate, glutarate, malate, maleate, succinate, fumarate, tartrate, tosylate, salicylate, lactate, naphthalenesulphonate, and acetate (e.g., trifluoroacetate).

[0462] As used herein, the term “pharmaceutically acceptable anion” refers to an anion suitable for forming a pharmaceutically acceptable salt. Likewise, a salt can also be formed between a cation and a negatively charged group (e.g., carboxylate) on a substituted compound disclosed herein. Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion or diethylamine ion. The substituted compounds disclosed herein also include those salts containing quaternary nitrogen atoms.

[0463] It is to be understood that the compounds of the present disclosure, for example, the salts of the compounds, can exist in either hydrated or unhydrated (the anhydrous) form or as solvates

with other solvent molecules. Nonlimiting examples of hydrates include monohydrates, dihydrates, etc. Nonlimiting examples of solvates include ethanol solvates, acetone solvates, etc. [0464] As used herein, the term “solvate” means solvent addition forms that contain either stoichiometric or non-stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate; and if the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one molecule of the substance in which the water retains its molecular state as H₂O.

[0465] As used herein, the term “analog” refers to a chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group, or the replacement of one functional group by another functional group). Thus, an analog is a compound that is similar or comparable in function and appearance, but not in structure or origin to the reference compound.

[0466] As used herein, the term “derivative” refers to compounds that have a common core structure and are substituted with various groups as described herein.

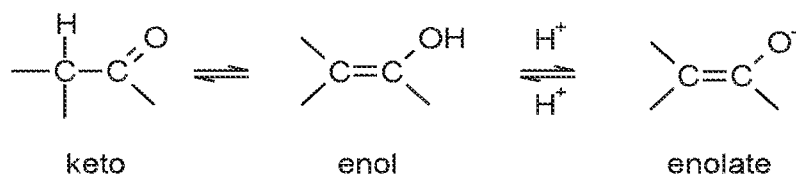
[0467] As used herein, the term “bioisostere” refers to a compound resulting from the exchange of an atom or of a group of atoms with another, broadly similar, atom or group of atoms. The objective of a bioisosteric replacement is to create a new compound with similar biological properties to the parent compound. The bioisosteric replacement may be physicochemically or topologically based. Examples of carboxylic acid bioisosteres include, but are not limited to, acyl sulphonamides, tetrazoles, sulphonates and phosphonates. See, *e.g.*, Patani and LaVoie, *Chem. Rev.* 96, 3147-3176, 1996.

[0468] It is also to be understood that certain compounds of the present disclosure may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. A suitable pharmaceutically acceptable solvate is, for example, a hydrate such as hemi-hydrate, a monohydrate, a di-hydrate or a tri-hydrate. It is to be understood that the disclosure encompasses all such solvated forms that possess inflammasome inhibitory activity.

[0469] It is also to be understood that certain compounds of the present disclosure may exhibit polymorphism, and that the disclosure encompasses all such forms, or mixtures thereof, which possess inflammasome inhibitory activity. It is generally known that crystalline materials may be analysed using conventional techniques such as X-Ray Powder Diffraction analysis, Differential

Scanning Calorimetry, Thermal Gravimetric Analysis, Diffuse Reflectance Infrared Fourier Transform (DRIFT) spectroscopy, Near Infrared (NIR) spectroscopy, solution and/or solid state nuclear magnetic resonance spectroscopy. The water content of such crystalline materials may be determined by Karl Fischer analysis.

[0470] Compounds of the present disclosure may exist in a number of different tautomeric forms and references to compounds of the present disclosure include all such forms. For the avoidance of doubt, where a compound can exist in one of several tautomeric forms, and only one is specifically described or shown, all others are nevertheless embraced by Formula (I). Examples of tautomeric forms include keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, and nitro/aci-nitro.



[0471] Compounds of the present disclosure containing an amine function may also form N-oxides. A reference herein to a compound disclosed herein that contains an amine function also includes the N-oxide. Where a compound contains several amine functions, one or more than one nitrogen atom may be oxidised to form an N-oxide. Particular examples of N-oxides are the N-oxides of a tertiary amine or a nitrogen atom of a nitrogen-containing heterocycle. N-oxides can be formed by treatment of the corresponding amine with an oxidising agent such as hydrogen peroxide or a peracid (e.g. a peroxycarboxylic acid), see for example Advanced Organic Chemistry, by Jerry March, 4th Edition, Wiley Interscience, pages. More particularly, N-oxides can be made by the procedure of L. W. Deady (Syn. Comm. 1977, 7, 509-514) in which the amine compound is reacted with meta-chloroperoxybenzoic acid (mCPBA), for example, in an inert solvent such as dichloromethane.

[0472] The compounds of the present disclosure may be administered in the form of a prodrug which is broken down in the human or animal body to release a compound of the disclosure. A prodrug may be used to alter the physical properties and/or the pharmacokinetic properties of a compound of the disclosure. A prodrug can be formed when the compound of the disclosure contains a suitable group or substituent to which a property-modifying group can be attached.

Examples of prodrugs include derivatives containing *in vivo* cleavable alkyl or acyl substituents at the sulphonylurea group in a compound of the any one of the Formulae disclosed herein.

[0473] Accordingly, the present disclosure includes those compounds of the present disclosure as defined hereinbefore when made available by organic synthesis and when made available within the human or animal body by way of cleavage of a prodrug thereof. Accordingly, the present disclosure includes those compounds of the present disclosure that are produced by organic synthetic means and also such compounds that are produced in the human or animal body by way of metabolism of a precursor compound, that is a compound of the present disclosure may be a synthetically-produced compound or a metabolically-produced compound.

[0474] A suitable pharmaceutically acceptable prodrug of a compound of the present disclosure is one that is based on reasonable medical judgment as being suitable for administration to the human or animal body without undesirable pharmacological activities and without undue toxicity. Various forms of prodrug have been described, for example in the following documents: a) Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985); b) Design of Pro-drugs, edited by H. Bundgaard, (Elsevier, 1985); c) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Pro-drugs", by H. Bundgaard p. 113-191 (1991); d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992); e) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); f) N. Kakeya, et al., Chem. Pharm. Bull., 32, 692 (1984); g) T. Higuchi and V. Stella, "Pro-Drugs as Novel Delivery Systems", A.C.S. Symposium Series, Volume 14; and h) E. Roche (editor), "Bioreversible Carriers in Drug Design", Pergamon Press, 1987.

[0475] A suitable pharmaceutically acceptable prodrug of a compound of the present disclosure that possesses a hydroxy group is, for example, an *in vivo* cleavable ester or ether thereof. An *in vivo* cleavable ester or ether of a compound of the present disclosure containing a hydroxy group is, for example, a pharmaceutically acceptable ester or ether which is cleaved in the human or animal body to produce the parent hydroxy compound. Suitable pharmaceutically acceptable ester forming groups for a hydroxy group include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters). Further suitable pharmaceutically acceptable ester forming groups for a hydroxy group include C₁-C₁₀ alkanoyl groups such as acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups, C₁-C₁₀ alkoxycarbonyl groups such as ethoxycarbonyl, N,N-(C₁-C₆ alkyl)₂carbamoyl, 2-dialkylaminoacetyl and 2-carboxyacetyl groups.

Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, N-alkylaminomethyl, N,N-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-(C₁-C₄ alkyl)piperazin-1-ylmethyl. Suitable pharmaceutically acceptable ether forming groups for a hydroxy group include α -acyloxyalkyl groups such as acetoxymethyl and pivaloyloxymethyl groups.

[0476] A suitable pharmaceutically acceptable prodrug of a compound of the present disclosure that possesses a carboxy group is, for example, an *in vivo* cleavable amide thereof, for example an amide formed with an amine such as ammonia, a C₁-4alkylamine such as methylamine, a (C₁-C₄ alkyl)₂amine such as dimethylamine, N-ethyl-N-methylamine or diethylamine, a C₁-C₄ alkoxy-C₂-C₄ alkylamine such as 2-methoxyethylamine, a phenyl-C₁-C₄ alkylamine such as benzylamine and amino acids such as glycine or an ester thereof.

[0477] A suitable pharmaceutically acceptable prodrug of a compound of the present disclosure that possesses an amino group is, for example, an *in vivo* cleavable amide derivative thereof. Suitable pharmaceutically acceptable amides from an amino group include, for example an amide formed with C₁-C₁₀ alkanoyl groups such as an acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, N-alkylaminomethyl, N,N-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl, and 4-(C₁-C₄ alkyl)piperazin-1-ylmethyl.

[0478] The *in vivo* effects of a compound of the present disclosure may be exerted in part by one or more metabolites that are formed within the human or animal body after administration of a compound of the present disclosure. As stated hereinbefore, the *in vivo* effects of a compound of the present disclosure may also be exerted by way of metabolism of a precursor compound (a prodrug).

Methods of Synthesis

[0479] In some aspects, the present disclosure provides a method of preparing a compound disclosed herein.

[0480] In some aspects, the present disclosure provides a method of preparing a compound, comprising one or more steps as described herein.

[0481] In some aspects, the present disclosure provides a compound obtainable by, or obtained by, or directly obtained by a method for preparing a compound described herein.

[0482] In some aspects, the present disclosure provides an intermediate being suitable for use in a method for preparing a compound described herein.

[0483] The compounds of the present disclosure can be prepared by any suitable technique known in the art. Particular processes for the preparation of these compounds are described further in the accompanying examples.

[0484] In the description of the synthetic methods described herein and in any referenced synthetic methods that are used to prepare the starting materials, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be selected by a person skilled in the art.

[0485] It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reaction conditions utilised.

[0486] It will be appreciated that during the synthesis of the compounds of the disclosure in the processes defined herein, or during the synthesis of certain starting materials, it may be desirable to protect certain substituent groups to prevent their undesired reaction. The skilled chemist will appreciate when such protection is required, and how such protecting groups may be put in place, and later removed. For examples of protecting groups see one of the many general texts on the subject, for example, 'Protective Groups in Organic Synthesis' by Theodora Green (publisher: John Wiley & Sons). Protecting groups may be removed by any convenient method described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with the minimum disturbance of groups elsewhere in the molecule. Thus, if reactants include, for example, groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

[0487] By way of example, a suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl, or t-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed by, for example, hydrolysis with a suitable base such as

an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a tert-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium on carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

[0488] A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium, sodium hydroxide or ammonia. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium on carbon.

[0489] A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a tert-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium on carbon.

[0490] Once a compound of the present disclosure has been synthesized by any one of the processes defined herein, the processes may then further comprise the additional steps of: (i) removing any protecting groups present; (ii) converting the compound of the present disclosure into another compound of the present disclosure; (iii) forming a pharmaceutically acceptable salt, hydrate or solvate thereof; and/or (iv) forming a prodrug thereof.

[0491] The resultant compounds of the present disclosure can be isolated and purified using techniques well known in the art.

[0492] Conveniently, the reaction of the compounds is carried out in the presence of a suitable solvent, which is preferably inert under the respective reaction conditions. Examples of suitable

solvents comprise but are not limited to hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichlorethylene, 1,2-dichloroethane, tetrachloromethane, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF), 2-methyltetrahydrofuran, cyclopentylmethyl ether (CPME), methyl tert-butyl ether (MTBE) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone, methylisobutylketone (MIBK) or butanone; amides, such as acetamide, dimethylacetamide, dimethylformamide (DMF) or N-methylpyrrolidinone (NMP); nitriles, such as acetonitrile; sulphoxides, such as dimethyl sulphoxide (DMSO); nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate or methyl acetate, or mixtures of the said solvents or mixtures with water.

[0493] The reaction temperature is suitably between about -100 °C and 300 °C, depending on the reaction step and the conditions used.

[0494] Reaction times are generally in the range between a fraction of a minute and several days, depending on the reactivity of the respective compounds and the respective reaction conditions. Suitable reaction times are readily determinable by methods known in the art, for example reaction monitoring. Based on the reaction temperatures given above, suitable reaction times generally lie in the range between 10 minutes and 48 hours.

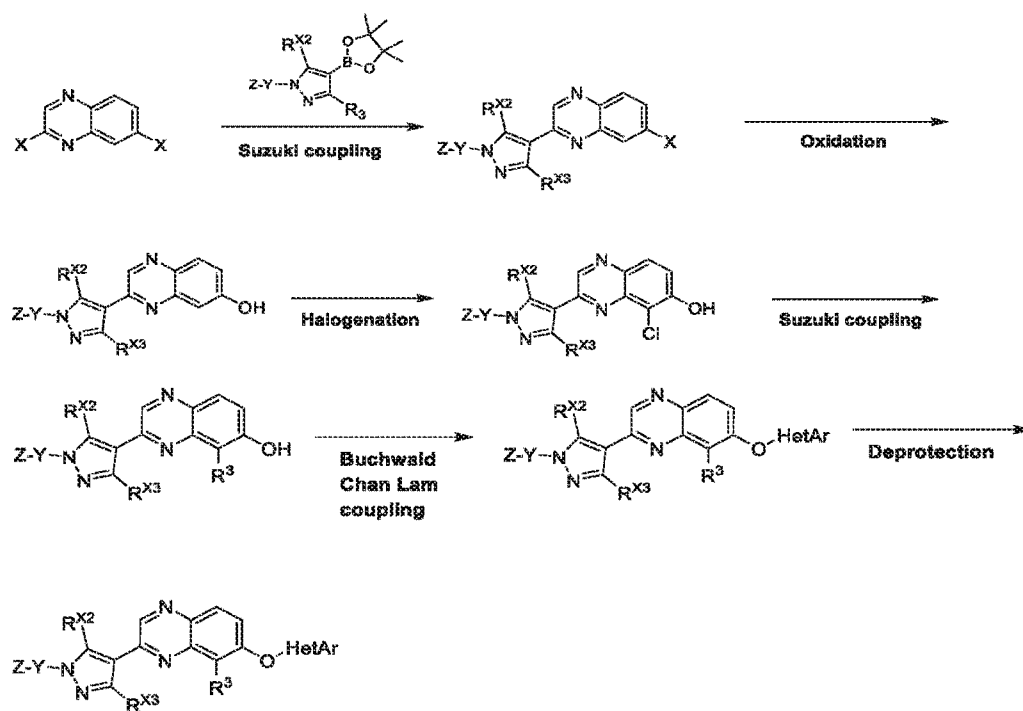
[0495] Moreover, by utilizing the procedures described herein, in conjunction with ordinary skills in the art, additional compounds of the present disclosure can be readily prepared. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

[0496] As will be understood by the person skilled in the art of organic synthesis, compounds of the present disclosure are readily accessible by various synthetic routes, some of which are exemplified in the accompanying examples. The skilled person will easily recognize which kind of reagents and reactions conditions are to be used and how they are to be applied and adapted in any particular instance -- wherever necessary or useful -- in order to obtain the compounds of the present disclosure. Furthermore, some of the compounds of the present disclosure can readily be synthesized by reacting other compounds of the present disclosure under suitable conditions, for instance, by converting one particular functional group being present in a compound of the present disclosure, or a suitable precursor molecule thereof, into another one by applying standard

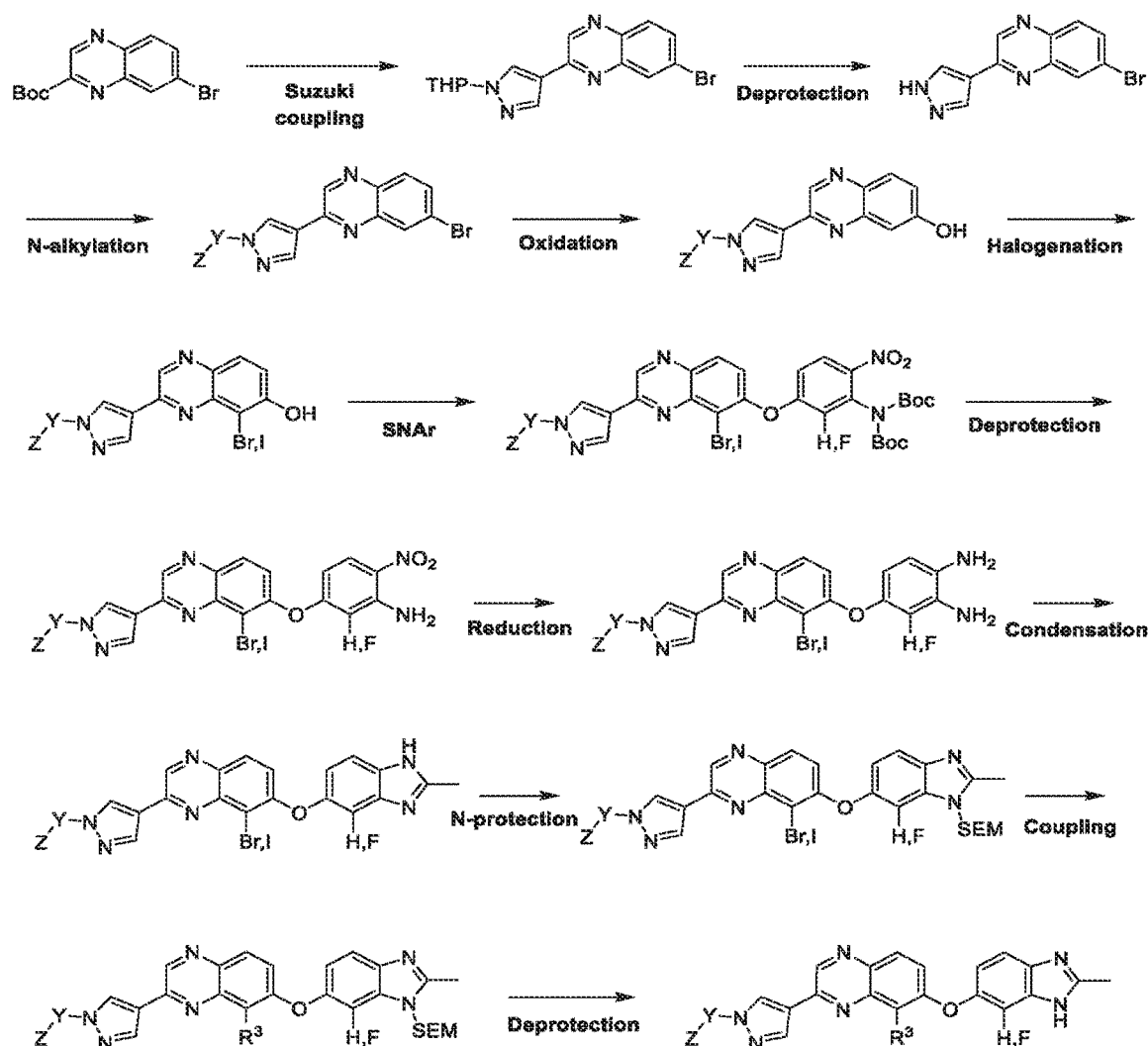
synthetic methods, like reduction, oxidation, addition or substitution reactions; those methods are well known to the skilled person. Likewise, the skilled person will apply – whenever necessary or useful – synthetic protecting (or protective) groups; suitable protecting groups as well as methods for introducing and removing them are well-known to the person skilled in the art of chemical synthesis and are described, in more detail, in, e.g., P.G.M. Wuts, T.W. Greene, “Greene’s Protective Groups in Organic Synthesis”, 4th edition (2006) (John Wiley & Sons).

[0497] General routes for the preparation of a compound of the application are described in Scheme 1 and Scheme 2.

Scheme 1



Scheme 2



Biological Assays

[0498] Compounds designed, selected and/or optimized by methods described above, once produced, can be characterized using a variety of assays known to those skilled in the art to determine whether the compounds have biological activity. For example, the molecules can be characterized by conventional assays, including but not limited to those assays described below, to determine whether they have a predicted activity, binding activity and/or binding specificity.

[0499] Furthermore, high-throughput screening can be used to speed up analysis using such assays. As a result, it can be possible to rapidly screen the molecules described herein for activity, using techniques known in the art. General methodologies for performing high-throughput

screening are described, for example, in Devlin (1998) High Throughput Screening, Marcel Dekker; and U.S. Patent No. 5,763,263. High-throughput assays can use one or more different assay techniques including, but not limited to, those described below.

[0500] Various in vitro or in vivo biological assays are may be suitable for detecting the effect of the compounds of the present disclosure. These in vitro or in vivo biological assays can include, but are not limited to, enzymatic activity assays, electrophoretic mobility shift assays, reporter gene assays, in vitro cell viability assays, and the assays described herein.

[0501] In some embodiments, the biological assay assess the ability of the compounds to inhibit cell proliferation.

[0502] In some embodiments, cells (e.g., SNU-16 (FGFR2-amplification) cells) may be suspended and dispensed in plates. In some embodiments, cells (e.g., UM-UC-14 (FGFR3-S249C) cells) may be suspended and dispensed in plates. In some embodiments, cells (e.g., DMS-114 (FGFR1 overexpression) cells) may by suspended and dispensed in plates. In some embodiments, cells (e.g., RT-112 (FGFR3-Tacc3 fusion) cells) may be suspended and dispensed in plates. In some embodiments, to determine the effect of the compounds of the present disclosure on cell proliferation, cells (e.g., SNU-16, UM-UC-14, DMS-114 and RT112 cells) may be incubated in the presence of vehicle control (e.g., DMSO) or a compound of the present disclosure at varying concentrations and the inhibition of cell growth may be determined by luminescent quantification (e.g., of intracellular ATP content using CellTiterGlo), according to the manufacturers protocol. In some embodiments, to determine the IC₅₀ values, the vehicle-treated cells were normalized as viable cells and the growth was analyzed using a software (e.g., the CDD Vault software (Collaborative Drug Discovery, Burlingame, CA)).

Pharmaceutical Compositions

[0503] In some aspects, the present disclosure provides a pharmaceutical composition comprising a compound of the present disclosure as an active ingredient.

[0504] In some embodiments, the present disclosure provides a pharmaceutical composition comprising a compound described herein and one or more pharmaceutically acceptable carriers or excipients. In some embodiments, the present disclosure provides a pharmaceutical composition comprising at least one compound selected from Table I. In some embodiments, the present disclosure provides a pharmaceutical composition comprising at least one compound selected from

Table II.

[0505] As used herein, the term “composition” is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

[0506] The compounds of present disclosure can be formulated for oral administration in forms such as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups and emulsions. The compounds of present disclosure can also be formulated for intravenous (bolus or infusion), intraperitoneal, topical, subcutaneous, intramuscular or transdermal (e.g., patch) administration, all using forms well known to those of ordinary skill in the pharmaceutical arts.

[0507] The formulation of the present disclosure may be in the form of an aqueous solution comprising an aqueous vehicle. The aqueous vehicle component may comprise water and at least one pharmaceutically acceptable excipient. Suitable acceptable excipients include those selected from the group consisting of a solubility enhancing agent, chelating agent, preservative, tonicity agent, viscosity/suspending agent, buffer, and pH modifying agent, and a mixture thereof.

[0508] Any suitable solubility enhancing agent can be used. Examples of a solubility enhancing agent include cyclodextrin, such as those selected from the group consisting of hydroxypropyl- β -cyclodextrin, methyl- β -cyclodextrin, randomly methylated- β -cyclodextrin, ethylated- β -cyclodextrin, triacetyl- β -cyclodextrin, peracetylated- β -cyclodextrin, carboxymethyl- β -cyclodextrin, hydroxyethyl- β -cyclodextrin, 2-hydroxy-3-(trimethylammonio)propyl- β -cyclodextrin, glucosyl- β -cyclodextrin, sulphated β -cyclodextrin (S- β -CD), maltosyl- β -cyclodextrin, β -cyclodextrin sulphobutyl ether, branched- β -cyclodextrin, hydroxypropyl- γ -cyclodextrin, randomly methylated- γ -cyclodextrin, and trimethyl- γ -cyclodextrin, and mixtures thereof.

[0509] Any suitable chelating agent can be used. Examples of a suitable chelating agent include those selected from the group consisting of ethylenediaminetetraacetic acid and metal salts thereof, disodium edetate, trisodium edetate, and tetrasodium edetate, and mixtures thereof.

[0510] Any suitable preservative can be used. Examples of a preservative include those selected from the group consisting of quaternary ammonium salts such as benzalkonium halides (preferably benzalkonium chloride), chlorhexidine gluconate, benzethonium chloride, cetyl pyridinium chloride, benzyl bromide, phenylmercury nitrate, phenylmercury acetate, phenylmercury

neodecanoate, merthiolate, methylparaben, propylparaben, sorbic acid, potassium sorbate, sodium benzoate, sodium propionate, ethyl p-hydroxybenzoate, propylaminopropyl biguanide, and butyl-p-hydroxybenzoate, and sorbic acid, and mixtures thereof.

[0511] The aqueous vehicle may also include a tonicity agent to adjust the tonicity (osmotic pressure). The tonicity agent can be selected from the group consisting of a glycol (such as propylene glycol, diethylene glycol, triethylene glycol), glycerol, dextrose, glycerin, mannitol, potassium chloride, and sodium chloride, and a mixture thereof.

[0512] The aqueous vehicle may also contain a viscosity/suspending agent. Suitable viscosity/suspending agents include those selected from the group consisting of cellulose derivatives, such as methyl cellulose, ethyl cellulose, hydroxyethylcellulose, polyethylene glycols (such as polyethylene glycol 300, polyethylene glycol 400), carboxymethyl cellulose, hydroxypropylmethyl cellulose, and cross-linked acrylic acid polymers (carbomers), such as polymers of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol (Carbopols - such as Carbopol 934, Carbopol 934P, Carbopol 971, Carbopol 974 and Carbopol 974P), and a mixture thereof.

[0513] In order to adjust the formulation to an acceptable pH (typically a pH range of about 5.0 to about 9.0, more preferably about 5.5 to about 8.5, particularly about 6.0 to about 8.5, about 7.0 to about 8.5, about 7.2 to about 7.7, about 7.1 to about 7.9, or about 7.5 to about 8.0), the formulation may contain a pH modifying agent. The pH modifying agent is typically a mineral acid or metal hydroxide base, selected from the group of potassium hydroxide, sodium hydroxide, and hydrochloric acid, and mixtures thereof, and preferably sodium hydroxide and/or hydrochloric acid. These acidic and/or basic pH modifying agents are added to adjust the formulation to the target acceptable pH range. Hence it may not be necessary to use both acid and base - depending on the formulation, the addition of one of the acid or base may be sufficient to bring the mixture to the desired pH range.

[0514] The aqueous vehicle may also contain a buffering agent to stabilize the pH. When used, the buffer is selected from the group consisting of a phosphate buffer (such as sodium dihydrogen phosphate and disodium hydrogen phosphate), a borate buffer (such as boric acid, or salts thereof including disodium tetraborate), a citrate buffer (such as citric acid, or salts thereof including sodium citrate), and ϵ -aminocaproic acid, and mixtures thereof.

[0515] The formulation may further comprise a wetting agent. Suitable classes of wetting agents

include those selected from the group consisting of polyoxypropylene-polyoxyethylene block copolymers (poloxamers), polyethoxylated ethers of castor oils, polyoxyethylenated sorbitan esters (polysorbates), polymers of oxyethylated octyl phenol (Tyloxapol), polyoxyl 40 stearate, fatty acid glycol esters, fatty acid glyceryl esters, sucrose fatty esters, and polyoxyethylene fatty esters, and mixtures thereof.

[0516] Oral compositions generally include an inert diluent or an edible pharmaceutically acceptable carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0517] According to a further aspect of the disclosure there is provided a pharmaceutical composition which comprises a compound of the disclosure as defined hereinbefore, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in association with a pharmaceutically acceptable diluent or carrier.

[0518] The compositions of the disclosure may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular, intraperitoneal or intramuscular dosing or as a suppository for rectal dosing).

[0519] The compositions of the disclosure may be obtained by conventional procedures using

conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more coloring, sweetening, flavoring and/or preservative agents.

[0520] An effective amount of a compound of the present disclosure for use in therapy is an amount sufficient to treat or prevent an inflammasome related condition referred to herein, slow its progression and/or reduce the symptoms associated with the condition.

[0521] The size of the dose for therapeutic or prophylactic purposes of a compound of the present disclosure will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well-known principles of medicine.

Methods of Use

[0522] In some aspects, the present disclosure provides methods of treating or preventing cancer in a subject, the method comprising administering to the subject a therapeutically effective amount of at least one compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

[0523] In some aspects, the present disclosure provides methods of treating or preventing cancer in a subject, the method comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

[0524] In some aspects, the present disclosure provides methods of treating or preventing cancer in a subject, the method comprising administering to the subject a compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

[0525] In some aspects, the present disclosure provides methods of treating cancer in a subject, the method comprising administering to the subject a therapeutically effective amount of at least one compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

[0526] In some aspects, the present disclosure provides methods of treating cancer in a subject, the method comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

[0527] In some aspects, the present disclosure provides methods of treating cancer in a subject, the method comprising administering to the subject a compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

[0528] In some aspects, the present disclosure provides at least one compound of the present

disclosure, or a pharmaceutically acceptable salt thereof, for treating or preventing cancer in a subject.

[0529] In some aspects, the present disclosure provides a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for treating or preventing cancer in a subject.

[0530] In some aspects, the present disclosure provides at least one compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for treating cancer in a subject.

[0531] In some aspects, the present disclosure provides a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for treating cancer in a subject.

[0532] In some aspects, the present disclosure provides a use of at least one compound of the present disclosure, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing cancer in a subject.

[0533] In some aspects, the present disclosure provides a use of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing cancer in a subject.

[0534] In some aspects, the present disclosure provides a use of at least one compound of the present disclosure, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a subject.

[0535] In some aspects, the present disclosure provides a use of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a subject.

[0536] In some aspects, the present disclosure provides a use of at least one compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for treating or preventing cancer in a subject.

[0537] In some aspects, the present disclosure provides a use of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for treating or preventing cancer in a subject.

[0538] In some aspects, the present disclosure provides a use of at least one compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for treating cancer in a subject.

[0539] In some aspects, the present disclosure provides a use of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for treating cancer in a subject.

[0540] In some aspects, the present disclosure provides methods of treating or preventing cancer

in a subject, the method comprising administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising at least one compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

[0541] In some aspects, the present disclosure provides methods of treating or preventing cancer in a subject, the method comprising administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

[0542] In some aspects, the present disclosure provides methods of treating or preventing cancer in a subject, the method comprising administering to the subject a pharmaceutical composition comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

[0543] In some aspects, the present disclosure provides methods of treating cancer in a subject, the method comprising administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising at least one compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

[0544] In some aspects, the present disclosure provides methods of treating cancer in a subject, the method comprising administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

[0545] In some aspects, the present disclosure provides methods of treating cancer in a subject, the method comprising administering to the subject a pharmaceutical composition comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

[0546] In some aspects, the present disclosure provides a pharmaceutical composition comprising at least one compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for treating or preventing cancer in a subject.

[0547] In some aspects, the present disclosure provides a pharmaceutical composition comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for treating or preventing cancer in a subject.

[0548] In some aspects, the present disclosure provides a pharmaceutical composition comprising at least one compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for treating cancer in a subject.

[0549] In some aspects, the present disclosure provides a pharmaceutical composition comprising

a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for treating cancer in a subject.

[0550] In some aspects, the present disclosure provides a use of a pharmaceutical composition comprising at least one compound of the present disclosure, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing cancer in a subject.

[0551] In some aspects, the present disclosure provides a use of a pharmaceutical composition comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing cancer in a subject.

[0552] In some aspects, the present disclosure provides a use of a pharmaceutical composition comprising at least one compound of the present disclosure, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a subject.

[0553] In some aspects, the present disclosure provides a use of a pharmaceutical composition comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a subject.

[0554] In some aspects, the present disclosure provides a use of a pharmaceutical composition comprising at least one compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for treating or preventing cancer in a subject.

[0555] In some aspects, the present disclosure provides a use of a pharmaceutical composition comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for treating or preventing cancer in a subject.

[0556] In some aspects, the present disclosure provides a use of a pharmaceutical composition comprising at least one compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for treating cancer in a subject.

[0557] In some aspects, the present disclosure provides a use of a pharmaceutical composition comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for treating cancer in a subject.

[0558] In some aspects, the present disclosure provides methods of treating or preventing cancer in a subject, the method comprising administering to the subject a therapeutically effective amount of a pharmaceutical kit comprising at least one compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

[0559] In some aspects, the present disclosure provides methods of treating or preventing cancer

in a subject, the method comprising administering to the subject a therapeutically effective amount of a pharmaceutical kit comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

[0560] In some aspects, the present disclosure provides methods of treating or preventing cancer in a subject, the method comprising administering to the subject a pharmaceutical kit comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

[0561] In some aspects, the present disclosure provides methods of treating cancer in a subject, the method comprising administering to the subject a therapeutically effective amount of a pharmaceutical kit comprising at least one compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

[0562] In some aspects, the present disclosure provides methods of treating cancer in a subject, the method comprising administering to the subject a therapeutically effective amount of a pharmaceutical kit comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

[0563] In some aspects, the present disclosure provides methods of treating cancer in a subject, the method comprising administering to the subject a pharmaceutical kit comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

[0564] In some aspects, the present disclosure provides a pharmaceutical kit comprising at least one compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for treating or preventing cancer in a subject.

[0565] In some aspects, the present disclosure provides a pharmaceutical kit comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for treating or preventing cancer in a subject.

[0566] In some aspects, the present disclosure provides a pharmaceutical kit comprising at least one compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for treating cancer in a subject.

[0567] In some aspects, the present disclosure provides a pharmaceutical kit comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for treating cancer in a subject.

[0568] In some aspects, the present disclosure provides a use of a pharmaceutical kit comprising at least one compound of the present disclosure, or a pharmaceutically acceptable salt thereof, in

the manufacture of a medicament for treating or preventing cancer in a subject.

[0569] In some aspects, the present disclosure provides a use of a pharmaceutical kit comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing cancer in a subject.

[0570] In some aspects, the present disclosure provides a use of a pharmaceutical kit comprising at least one compound of the present disclosure, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a subject.

[0571] In some aspects, the present disclosure provides a use of a pharmaceutical kit comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a subject.

[0572] In some aspects, the present disclosure provides a use of a pharmaceutical kit comprising at least one compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for treating or preventing cancer in a subject.

[0573] In some aspects, the present disclosure provides a use of a pharmaceutical kit comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for treating or preventing cancer in a subject.

[0574] In some aspects, the present disclosure provides a use of a pharmaceutical kit comprising at least one compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for treating cancer in a subject.

[0575] In some aspects, the present disclosure provides a use of a pharmaceutical kit comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for treating cancer in a subject.

[0576] *FGFR2* is a human gene located on chromosome 10 that encodes for a protein known as FGFR2. *FGFR3* is a human gene located on chromosome 4 that encodes for a protein known as FGFR3. Both FGFR2 and FGFR3 are produced in a variety of different isoforms through alternative splicing. The "b isoforms" are primarily expressed in epithelial tissues while the "c isoforms" are primarily expressed mesenchymal tissues.

[0577] FGFR2 and FGFR3 are members of the fibroblast growth factor receptor family. Members of the fibroblast growth factor receptor family are proteins that are located on the cellular surface and bind to various members of the fibroblast growth factor (FGF) family of proteins. FGFR2 and FGFR3 have an extracellular ligand domain, composed of three immunoglobulin-like domains, a

single transmembrane helix domain, and an intracellular tyrosine kinase domain. Upon binding of an FGF ligand to extracellular ligand domains, the receptors dimerize, and the intracellular tyrosine kinase domains within the dimer cross-phosphorylate each other, thereby activating the kinases domains, allowing them to subsequently bind to adaptor proteins and phosphorylate other intracellular signaling molecules. Members of the fibroblast growth factor receptor family are known to regulate various cellular process including, but not limited to, proliferation and differentiation, particularly within the context of development and tissue repair.

[0578] Overexpression of *FGFR2* has been implicated in a variety of different cancers, including, but not limited to, gastric cancer and triple negative breast cancer.

[0579] Overexpression of *FGFR3* has been implicated in a variety of different cancers, including, but not limited to, lung cancer and bladder cancer.

[0580] Mutations in the *FGFR2* gene, which produce mutant *FGFR2* proteins, have been implicated in a variety of different cancers, including, but not limited to, endometrial carcinoma and lung cancer.

[0581] Mutations in the *FGFR3* gene, which produce mutant *FGFR3* proteins, have been implicated in a variety of different cancers, including, but not limited to, bladder cancer.

[0582] Fusions of the *FGFR2* gene, which produce fusions of *FGFR2* proteins, have been implicated in a variety of different cancers, including, but not limited to, bladder cancer and intrahepatic cholangiocarcinoma.

[0583] Fusions of the *FGFR3* gene, which produce fusions of *FGFR3* proteins, have been implicated in a variety of different cancers, including, but not limited to, bladder cancer and glioblastoma.

[0584] In some embodiments, the subject is a mammal.

[0585] In some embodiments, the subject is a human.

[0586] In some embodiments, the subject has previously undergone at least one round of anti-cancer therapy. In some embodiments, the subject has previously undergone at least one round of anti-cancer therapy and has acquired resistance to treatment with the anti-cancer therapy. In some embodiments, the anti-cancer therapy can comprise the administration of at least one of futibatinib, pemigatinib, erdafitinib, infigratinib, Debio-1347.

[0587] In some embodiments, the cancer is characterized by at least one oncogenic mutation in the *FGFR2* gene.

[0588] In some embodiments, the cancer is characterized by at least one oncogenic mutation in the *FGFR3* gene.

[0589] It is understood that a cancer that is characterized by at least one oncogenic mutation in the *FGFR2* gene and/or *FGFR3* gene is a cancer that is typically associated with at least one oncogenic mutation in the *FGFR2* gene and/or *FGFR3* gene, including, but not limited to, cancers whose primary oncogenic activity is thought to be driven by the at least one oncogenic mutation in the *FGFR2* gene and/or *FGFR3* gene.

[0590] In some embodiments, the cancer is characterized by overexpression of the *FGFR2* gene.

[0591] In some embodiments, the cancer is characterized by overexpression of the *FGFR3* gene.

[0592] It is understood that a cancer that is characterized by overexpression of the *FGFR2* gene and/or *FGFR3* gene is a cancer that is typically associated with the overexpression of the *FGFR2* gene and/or *FGFR3* gene, including, but not limited to, cancers whose primary oncogenic activity is thought to be driven by the overexpression of the *FGFR2* gene and/or *FGFR3* gene.

[0593] In some embodiments, the cancer is characterized by at least one oncogenic variant of *FGFR2*.

[0594] In some embodiments, the cancer is characterized by at least one oncogenic variant of *FGFR3*.

[0595] It is understood that a cancer that is characterized by at least one oncogenic variant of *FGFR2* and/or *FGFR3* is a cancer that is typically associated with at least one oncogenic variant of *FGFR2* and/or *FGFR3*, including, but not limited to, cancers whose primary oncogenic activity is thought to be driven by the at least one oncogenic variant of *FGFR2* and/or *FGFR3*.

[0596] In some embodiments, the cancer is characterized by overexpression of *FGFR2*.

[0597] In some embodiments, the cancer is characterized by overexpression of *FGFR3*.

[0598] It is understood that a cancer that is characterized by overexpression of *FGFR2* and/or *FGFR3* is a cancer that is typically associated with overexpression of *FGFR2* and/or *FGFR3*, including, but not limited to, cancers whose primary oncogenic activity is thought to be driven by overexpression of *FGFR2* and/or *FGFR3*.

[0599] It is understood that an oncogenic variant of *FGFR2* is an *FGFR2* protein that comprises at least one oncogenic mutation and that is produced as the result of the expression of a *FGFR2* gene that comprises at least one oncogenic mutation.

[0600] It is understood that an oncogenic variant of *FGFR3* is an *FGFR3* protein that comprises

at least one oncogenic mutation and that is produced as the result of the expression of a *FGFR3* gene that comprises at least one oncogenic mutation.

[0601] In some embodiments, the subject has at least one oncogenic mutation in the *FGFR2* gene.

[0602] In some embodiments, the subject has at least one oncogenic mutation in the *FGFR3* gene.

[0603] In some embodiments, the subject has at least one tumor and/or cancerous cell that expresses an oncogenic variant of *FGFR2*.

[0604] In some embodiments, the subject has at least one tumor and/or cancerous cell that expresses an oncogenic variant of *FGFR3*.

[0605] In some embodiments, the subject has at least one tumor and/or cancerous cell that overexpresses *FGFR2*.

[0606] In some embodiments, the subject has at least one tumor and/or cancerous cell that overexpresses *FGFR3*.

[0607] As would be appreciated by the skilled artisan, in the context of a gene (*e.g.* *FGFR2* and/or *FGFR3*), an oncogenic mutation can include, but is not limited to a mutation that results in the substitution of one amino acid for another at a specific position within *FGFR2* and/or *FGFR3*, a mutation that results in the substitution of one or more amino acids for one or more amino acids between two specific positions within *FGFR2* and/or *FGFR3*, a mutation that results in an insertion of one or more amino acids between two positions within *FGFR2* and/or *FGFR3*, a mutation that results in the deletion of one or more amino acids between two positions within *FGFR2* and/or *FGFR3*, and mutation that results in a fusion of *FGFR2* and/or *FGFR3*, or portion thereof, with another protein, or portion thereof, or any combination thereof. As would be appreciated by the skilled artisan, in the context of a gene, an oncogenic mutation can include, but is not limited to, a missense mutation, a nonsynonymous mutation, an insertion of one or more nucleotides, a deletion of one or more nucleotides, an inversion and a deletion-insertion. As would be appreciated by the skilled artisan, in the context of a gene (*e.g.* *FGFR2* and/or *FGFR3*), the gene can have one or more of the aforementioned types of oncogenic mutations, including combinations of different types of oncogenic mutations.

[0608] As would be appreciated by the skilled artisan, in the context of a protein (*e.g.* *FGFR2* and/or *FGFR3*), an oncogenic mutation, but is not limited to, the substitution of one amino acid for another at a specific position within *FGFR2* and/or *FGFR3*, the substitution of one or more amino acids for one or more amino acids between two specific positions within *FGFR2* and/or

FGFR3, an insertion of one or more amino acids between two positions within FGFR2 and/or FGFR3, a deletion of one more amino acids between two positions within FGFR2 and/or FGFR3, and a fusion of FGFR2 and/or FGFR3, or portion thereof, with another protein, or portion thereof, or any combination thereof. As would be appreciated by the skilled artisan, in the context of a protein (e.g. FGFR2 and/or FGFR3), the protein can have one or more of the aforementioned types of oncogenic mutations, including combinations of different types of oncogenic mutations.

[0609] In some embodiments, an oncogenic mutation of FGFR2 can be any of the FGFR2 mutations put forth in Table 1a. In some embodiments, an oncogenic mutation of FGFR2 can be a gatekeeper mutation that results in resistance to the existing inhibitors, wherein the gatekeeper mutation is V565I or V565F.

Table 1a. FGFR2 mutations

S252W	V565F	V565I
V565I	N550K	

[0610] In some embodiments, an oncogenic mutation of FGFR3 can be any of the FGFR3 mutations put forth in Table 1b. In some embodiments, an oncogenic mutation of FGFR3 can be a gatekeeper mutation that results in resistance to the existing inhibitors, wherein the gatekeeper mutation is V555M, V555L, or V555F.

Table 1b. FGFR3 mutations

S249C	Tacc3 fusion	V555L
V555F	V555M	

[0611] In some embodiments, an oncogenic variant of FGFR2 can be any of the FGFR2 variants put forth in Table 1c.

Table 1c. FGFR2 oncogenic variants

FGFR2-S252W	FGFR2-V565F	FGFR2-S252W+V565F
FGFR2-V565I	FGFR2-N550K	FGFR2-S252W+V565I
FGFR2-V565I		

[0612] In some embodiments, an oncogenic variant of FGFR3 can be any of the FGFR3 variants put forth in Table 1d.

Table 1d. FGFR3 oncogenic variants

FGFR3-S249C	FGFR3-Tacc3 fusion	FGFR3-S249C+V555M
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FGFR3-V555F	FGFR3-S249C+V555F	FGFR3-S249C+V555L
FGFR3-V555L	FGFR3-V555M	

[0613] In some embodiments, an oncogenic variant of FGFR2 can comprise a gatekeeper mutation that results in resistance to the existing inhibitors, wherein the gatekeeper mutation is V565I or V565F.

[0614] In some embodiments, an oncogenic variant of FGFR3 can comprise a gatekeeper mutation that results in resistance to the existing inhibitors, wherein the gatekeeper mutation is V555M, V555L or V555F.

[0615] As used herein, the term "activating mutation" refers to any oncogenic mutation that results in at least one of: a) increased ligand binding of FGFR2 and/or FGFR3; b) ligand-independent dimerization and activation of FGFR2 and/or FGFR3; and c) increased kinase activity of FGFR2 and/or FGFR3.

[0616] In some embodiments, the cancer is a carcinoma, a lymphoma, a blastoma, a sarcoma, a leukemia, a brain cancer, a breast cancer, a blood cancer, a bone cancer, a lung cancer, a skin cancer, a liver cancer, an ovarian cancer, a bladder cancer, a renal cancer, a kidney cancer, a gastric cancer, a thyroid cancer, a pancreatic cancer, an esophageal cancer, a prostate cancer, a cervical cancer, a uterine cancer, a stomach cancer, a soft tissue cancer, a laryngeal cancer, a small intestine cancer, a testicular cancer, an anal cancer, a vulvar cancer, a joint cancer, an oral cancer, a pharynx cancer or a colorectal cancer.

[0617] In some embodiments, the cancer is adrenocortical carcinoma, bladder urothelial carcinoma, breast invasive carcinoma, cervical squamous cell carcinoma, endocervical adenocarcinoma, cholangiocarcinoma, colon adenocarcinoma, lymphoid neoplasm diffuse large B-cell lymphoma, esophageal carcinoma, glioblastoma multiforme, head and neck squamous cell carcinoma, kidney chromophobe, kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma, acute myeloid leukemia, brain lower grade glioma, liver hepatocellular carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, mesothelioma, ovarian serous cystadenocarcinoma, pancreatic adenocarcinoma, pheochromocytoma, paraganglioma, prostate adenocarcinoma, rectum adenocarcinoma, sarcoma, skin cutaneous melanoma, stomach adenocarcinoma, testicular germ cell tumors, thyroid carcinoma, thymoma, uterine carcinosarcoma, uveal melanoma. Other examples include breast cancer, lung cancer, lymphoma, melanoma, liver cancer, colorectal cancer, ovarian cancer, bladder cancer, renal cancer or gastric

cancer. Further examples of cancer include neuroendocrine cancer, non-small cell lung cancer (NSCLC), small cell lung cancer, thyroid cancer, endometrial cancer, biliary cancer, esophageal cancer, anal cancer, salivary, cancer, vulvar cancer, cervical cancer, Acute lymphoblastic leukemia (ALL), Acute myeloid leukemia (AML), Adrenal gland tumors, Anal cancer, Bile duct cancer, Bladder cancer, Bone cancer, Bowel cancer, Brain tumors, Breast cancer, Cancer of unknown primary (CUP), Cancer spread to bone, Cancer spread to brain, Cancer spread to liver, Cancer spread to lung, Carcinoid, Cervical cancer, Children's cancers, Chronic lymphocytic leukemia (CLL), Chrome myeloid leukemia (CML), Colorectal cancer, Ear cancer, Endometrial cancer, Eye cancer, Follicular dendritic cell sarcoma, Gallbladder cancer, Gastric cancer, Gastro esophageal junction cancers, Germ cell tumors, Gestational trophoblastic disease (GIT)), Hairy cell leukemia, Head and neck cancer, Hodgkin lymphoma, Kaposi's sarcoma, Kidney cancer, Laryngeal cancer, Leukemia, Gastric linitis plastica, Liver cancer, Lung cancer, Lymphoma, Malignant schwannoma, Mediastinal germ cell tumors, Melanoma skin cancer, Men's cancer, Merkel cell skin cancer, Mesothelioma, Molar pregnancy, Mouth and oropharyngeal cancer, Myeloma, Nasal and paranasal sinus cancer, Nasopharyngeal cancer, Neuroblastoma, Neuroendocrine tumors, Non-Hodgkin lymphoma (NHL), Esophageal cancer, Ovarian cancer, Pancreatic cancer, Penile cancer, Persistent trophoblastic disease and choriocarcinoma, Pheochromocytoma, Prostate cancer, Pseudomyxoma peritonei, Rectal cancer, Retinoblastoma, Salivary gland cancer, Secondary' cancer, Signet cell cancer, Skin cancer, Small bowel cancer, Soft tissue sarcoma, Stomach cancer, T cell childhood non Hodgkin lymphoma (NHL), Testicular cancer, Thymus gland cancer, Thyroid cancer, Tongue cancer, Tonsil cancer, Tumors of the adrenal gland, Uterine cancer, Vaginal cancer, Vulval cancer, Wilms' tumor, Womb cancer and Gynaecological cancer. Examples of cancer also include, but are not limited to, Hematologic malignancies, Lymphoma, Cutaneous T-cell lymphoma, Peripheral T-cell lymphoma, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, Multiple myeloma, Chrome lymphocytic leukemia, chronic myeloid leukemia, acute myeloid leukemia, Myelodysplastic syndromes, Myelofibrosis, Biliary tract cancer, Hepatocellular cancer, Colorectal cancer, Breast cancer, Lung cancer, Non-small cell lung cancer, Ovarian cancer, Thyroid Carcinoma, Renal Cell Carcinoma, Pancreatic cancer, Bladder cancer, skin cancer, malignant melanoma, merkel cell carcinoma, Uveal Melanoma or Glioblastoma multiforme.

[0618] In some embodiments, the cancer is gastric cancer, triple negative breast cancer,

melanoma, hepatobiliary cancer, cancer of unknown primary, esophagogastric cancer, cervical cancer, head and neck cancer, CNS cancer, brain cancer, NSCLC, ovarian cancer, breast cancer, soft tissue sarcoma, pancreatic cancer, prostate cancer, renal cell carcinoma, thyroid cancer, lung cancer, bladder cancer, endometrial carcinoma, intrahepatic cholangiocarcinoma or glioblastoma.

Definitions

[0619] Unless otherwise stated, the following terms used in the specification and claims have the following meanings set out below.

[0620] Without wishing to be limited by this statement, it is understood that, while various options for variables are described herein, the disclosure intends to encompass operable embodiments having combinations of the options. The disclosure may be interpreted as excluding the non-operable embodiments caused by certain combinations of the options.

[0621] It is to be understood that a compound of the present disclosure may be depicted in a neutral form, a cationic form (e.g., carrying one or more positive charges), or an anionic form (e.g., carrying one or more negative charges), all of which are intended to be included in the scope of the present disclosure. For example, when a compound of the present disclosure is depicted in an anionic form, it should be understood that such depiction also refers to the various neutral forms, cationic forms, and anionic forms of the compound. For another example, when a compound the present disclosure is depicted in an anionic form, it should be understood that such depiction also refers to various salts (e.g., sodium salt) of the anionic form of the compound.

[0622] A “therapeutically effective amount” means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The “therapeutically effective amount” will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

[0623] As used herein, “alkyl”, “C₁, C₂, C₃, C₄, C₅ or C₆ alkyl” or “C₁-C₆ alkyl” is intended to include C₁, C₂, C₃, C₄, C₅ or C₆ straight chain (linear) saturated aliphatic hydrocarbon groups and C₃, C₄, C₅ or C₆ branched saturated aliphatic hydrocarbon groups. For example, C₁-C₆ alkyl is intends to include C₁, C₂, C₃, C₄, C₅ and C₆ alkyl groups. Examples of alkyl include, moieties having from one to six carbon atoms, such as, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl or n-hexyl. In some embodiments, a straight chain or branched alkyl has six or fewer carbon atoms (e.g., C₁-C₆ for straight chain, C₃-C₆ for branched

chain), and in another embodiment, a straight chain or branched alkyl has four or fewer carbon atoms.

[0624] As used herein, the term “optionally substituted alkyl” refers to unsubstituted alkyl or alkyl having designated substituents replacing one or more hydrogen atoms on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphhydryl, alkylthio, arylthio, thiocarboxylate, sulphates, alkylsulphinyl, sulphonato, sulphamoyl, sulphonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0625] As used herein, the term “alkenyl” includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond. For example, the term “alkenyl” includes straight chain alkenyl groups (*e.g.*, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl), and branched alkenyl groups. In certain embodiments, a straight chain or branched alkenyl group has six or fewer carbon atoms in its backbone (*e.g.*, C₂-C₆ for straight chain, C₃-C₆ for branched chain). The term “C₂-C₆” includes alkenyl groups containing two to six carbon atoms. The term “C₃-C₆” includes alkenyl groups containing three to six carbon atoms.

[0626] As used herein, the term “optionally substituted alkenyl” refers to unsubstituted alkenyl or alkenyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphhydryl, alkylthio, arylthio, thiocarboxylate, sulphates, alkylsulphinyl, sulphonato, sulphamoyl, sulphonamido, nitro, trifluoromethyl, cyano,

heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0627] As used herein, the term “alkynyl” includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond. For example, “alkynyl” includes straight chain alkynyl groups (*e.g.*, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl), and branched alkynyl groups. In certain embodiments, a straight chain or branched alkynyl group has six or fewer carbon atoms in its backbone (*e.g.*, C₂-C₆ for straight chain, C₃-C₆ for branched chain). The term “C₂-C₆” includes alkynyl groups containing two to six carbon atoms. The term “C₃-C₆” includes alkynyl groups containing three to six carbon atoms. As used herein, “C₂-C₆ alkenylene linker” or “C₂-C₆ alkenylene linker” is intended to include C₂, C₃, C₄, C₅ or C₆ chain (linear or branched) divalent unsaturated aliphatic hydrocarbon groups. For example, C₂-C₆ alkenylene linker is intended to include C₂, C₃, C₄, C₅ and C₆ alkenylene linker groups.

[0628] As used herein, the term “optionally substituted alkynyl” refers to unsubstituted alkynyl or alkynyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphhydryl, alkylthio, arylthio, thiocarboxylate, alkylsulphinyl, sulphonato, sulphamoyl, sulphonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0629] Other optionally substituted moieties (such as optionally substituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl) include both the unsubstituted moieties and the moieties having one or more of the designated substituents. For example, substituted heterocycloalkyl includes those substituted with one or more alkyl groups, such as 2,2,6,6-tetramethyl-piperidiny and 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridiny.

[0630] As used herein, the term “cycloalkyl” refers to a saturated or partially unsaturated hydrocarbon monocyclic or polycyclic (*e.g.*, fused, bridged, or spiro rings) system having 3 to 30 carbon atoms (*e.g.*, C₃-C₁₂, C₃-C₁₀, or C₃-C₈). Examples of cycloalkyl include, but are not limited

to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, 1,2,3,4-tetrahydronaphthalenyl, and adamantyl. In the case of polycyclic cycloalkyl, only one of the rings in the cycloalkyl needs to be non-aromatic.

[0631] As used herein, the term “heterocycloalkyl” refers to a saturated or partially unsaturated 3-8 membered monocyclic, 7-12 membered bicyclic (fused, bridged, or spiro rings), or 11-14 membered tricyclic ring system (fused, bridged, or spiro rings) having one or more heteroatoms (such as O, N, S, P, or Se), e.g., 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, or *e.g.*, 1, 2, 3, 4, 5, or 6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen and sulphur, unless specified otherwise. Examples of heterocycloalkyl groups include, but are not limited to, piperidinyl, piperazinyl, pyrrolidinyl, dioxanyl, tetrahydrofuranyl, isoindolinyl, indolinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, oxiranyl, azetidiny, oxetanyl, thietanyl, 1,2,3,6-tetrahydropyridinyl, tetrahydropyranyl, dihydropyranyl, pyranal, morpholinyl, tetrahydrothiopyranal, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 1,4-dioxaspiro[4.5]decanyl, 1-oxaspiro[4.5]decanyl, 1-azaspiro[4.5]decanyl, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-yl, 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-yl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[3.1.0]hexan-3-yl, 1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazolyl, 3,4,5,6,7,8-hexahydropyrido[4,3-d]pyrimidinyl, 4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridinyl, 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidinyl, 2-azaspiro[3.3]heptanyl, 2-methyl-2-azaspiro[3.3]heptanyl, 2-azaspiro[3.5]nonanyl, 2-methyl-2-azaspiro[3.5]nonanyl, 2-azaspiro[4.5]decanyl, 2-methyl-2-azaspiro[4.5]decanyl, 2-oxa-azaspiro[3.4]octanyl, 2-oxa-azaspiro[3.4]octan-6-yl, and the like. In the case of multicyclic heterocycloalkyl, only one of the rings in the heterocycloalkyl needs to be non-aromatic (*e.g.*, 4,5,6,7-tetrahydrobenzo[c]isoxazolyl).

[0632] As used herein, the term “aryl” includes groups with aromaticity, including “conjugated,” or multicyclic systems with one or more aromatic rings and do not contain any heteroatom in the ring structure. The term aryl includes both monovalent species and divalent species. Examples of aryl groups include, but are not limited to, phenyl, biphenyl, naphthyl and the like. Conveniently, an aryl is phenyl.

[0633] As used herein, the term “heteroaryl” is intended to include a stable 5-, 6-, or 7-membered

monocyclic or 7-, 8-, 9-, 10-, 11- or 12-membered bicyclic aromatic heterocyclic ring which consists of carbon atoms and one or more heteroatoms, *e.g.*, 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, or *e.g.*, 1, 2, 3, 4, 5, or 6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen and sulphur. The nitrogen atom may be substituted or unsubstituted (*i.e.*, N or NR wherein R is H or other substituents, as defined). The nitrogen and sulphur heteroatoms may optionally be oxidised (*i.e.*, N→O and S(O)_p, where p = 1 or 2). It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1. Examples of heteroaryl groups include pyrrole, furan, thiophene, thiazole, isothiazole, imidazole, triazole, tetrazole, pyrazole, oxazole, isoxazole, pyridine, pyrazine, pyridazine, pyrimidine, and the like. Heteroaryl groups can also be fused or bridged with alicyclic or heterocyclic rings, which are not aromatic so as to form a multicyclic system (*e.g.*, 4,5,6,7-tetrahydrobenzo[c]isoxazolyl).

[0634] Furthermore, the terms “aryl” and “heteroaryl” include multicyclic aryl and heteroaryl groups, *e.g.*, tricyclic, bicyclic, *e.g.*, naphthalene, benzoxazole, benzodioxazole, benzothiazole, benzoimidazole, benzothiophene, quinoline, isoquinoline, naphthyridine, indole, benzofuran, purine, deazapurine, indolizine.

[0635] The cycloalkyl, heterocycloalkyl, aryl, or heteroaryl ring can be substituted at one or more ring positions (*e.g.*, the ring-forming carbon or heteroatom such as N) with such substituents as described above, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, alkylaminocarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylaryl amino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphhydryl, alkylthio, arylthio, thiocarboxylate, sulphates, alkylsulphinyl, sulphonato, sulphamoyl, sulphonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl and heteroaryl groups can also be fused or bridged with alicyclic or heterocyclic rings, which are not aromatic so as to form a multicyclic system (*e.g.*, tetralin, methylenedioxyphenyl such as benzo[d][1,3]dioxole-5-yl).

[0636] As used herein, the term “substituted,” means that any one or more hydrogen atoms on the designated atom is replaced with a selection from the indicated groups, provided that the

designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is oxo or keto (*i.e.*, =O), then 2 hydrogen atoms on the atom are replaced. Keto substituents are not present on aromatic moieties. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N or N=N). "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[0637] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom in the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such formula. Combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[0638] When any variable (*e.g.*, R) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R moieties, then the group may optionally be substituted with up to two R moieties and R at each occurrence is selected independently from the definition of R. Also, combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[0639] As used herein, the term "hydroxy" or "hydroxyl" includes groups with an -OH or -O[•].

[0640] As used herein, the term "halo" or "halogen" refers to fluoro, chloro, bromo and iodo.

[0641] The term "haloalkyl" or "haloalkoxyl" refers to an alkyl or alkoxy substituted with one or more halogen atoms.

[0642] As used herein, the term "optionally substituted haloalkyl" refers to unsubstituted haloalkyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino,

sulphhydryl, alkylthio, arylthio, thiocarboxylate, sulphates, alkylsulphinyl, sulphonato, sulphamoyl, sulphonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0643] As used herein, the term “alkoxy” or “alkoxyl” includes substituted and unsubstituted alkyl, alkenyl and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups or alkoxyl radicals include, but are not limited to, methoxy, ethoxy, isopropoxy, propoxy, butoxy and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphhydryl, alkylthio, arylthio, thiocarboxylate, sulphates, alkylsulphinyl, sulphonato, sulphamoyl, sulphonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy and trichloromethoxy.

[0644] As used herein, the expressions “one or more of A, B, or C,” “one or more A, B, or C,” “one or more of A, B, and C,” “one or more A, B, and C,” “selected from the group consisting of A, B, and C”, “selected from A, B, and C”, and the like are used interchangeably and all refer to a selection from a group consisting of A, B, and/or C, i.e., one or more As, one or more Bs, one or more Cs, or any combination thereof, unless indicated otherwise.

[0645] It is to be understood that the present disclosure provides methods for the synthesis of the compounds of any of the Formulae described herein. The present disclosure also provides detailed methods for the synthesis of various disclosed compounds of the present disclosure according to the following schemes as well as those shown in the Examples.

[0646] It is to be understood that, throughout the description, where compositions are described as having, including, or comprising specific components, it is contemplated that compositions also consist essentially of, or consist of, the recited components. Similarly, where methods or processes are described as having, including, or comprising specific process steps, the processes also consist

essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps or order for performing certain actions is immaterial so long as the invention remains operable. Moreover, two or more steps or actions can be conducted simultaneously.

[0647] It is to be understood that the synthetic processes of the disclosure can tolerate a wide variety of functional groups, therefore various substituted starting materials can be used. The processes generally provide the desired final compound at or near the end of the overall process, although it may be desirable in certain instances to further convert the compound to a pharmaceutically acceptable salt thereof.

[0648] It is to be understood that compounds of the present disclosure can be prepared in a variety of ways using commercially available starting materials, compounds known in the literature, or from readily prepared intermediates, by employing standard synthetic methods and procedures either known to those skilled in the art, or which will be apparent to the skilled artisan in light of the teachings herein. Standard synthetic methods and procedures for the preparation of organic molecules and functional group transformations and manipulations can be obtained from the relevant scientific literature or from standard textbooks in the field. Although not limited to any one or several sources, classic texts such as Smith, M. B., March, J., *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th edition, John Wiley & Sons: New York, 2001; Greene, T.W., Wuts, P.G. M., *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons: New York, 1999; R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995), incorporated by reference herein, are useful and recognized reference textbooks of organic synthesis known to those in the art

[0649] One of ordinary skill in the art will note that, during the reaction sequences and synthetic schemes described herein, the order of certain steps may be changed, such as the introduction and removal of protecting groups. One of ordinary skill in the art will recognize that certain groups may require protection from the reaction conditions via the use of protecting groups. Protecting groups may also be used to differentiate similar functional groups in molecules. A list of protecting groups and how to introduce and remove these groups can be found in Greene, T.W., Wuts, P.G. M., *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons: New York, 1999.

[0650] It is to be understood that, unless otherwise stated, any description of a method of treatment

includes use of the compounds to provide such treatment or prophylaxis as is described herein, as well as use of the compounds to prepare a medicament to treat or prevent such condition. The treatment includes treatment of human or non-human animals including rodents and other disease models.

[0651] As used herein, the term “subject” includes human and non-human animals, as well as cell lines, cell cultures, tissues, and organs. In some embodiments, the subject is a mammal. The mammal can be *e.g.*, a human or appropriate non-human mammal, such as primate, mouse, rat, dog, cat, cow, horse, goat, camel, sheep or a pig. The subject can also be a bird or fowl. In some embodiments, the subject is a human.

[0652] As used herein, the term “subject in need thereof” refers to a subject having a disease or having an increased risk of developing the disease. A subject in need thereof can be one who has been previously diagnosed or identified as having a disease or disorder disclosed herein. A subject in need thereof can also be one who is suffering from a disease or disorder disclosed herein. Alternatively, a subject in need thereof can be one who has an increased risk of developing such disease or disorder relative to the population at large (*i.e.*, a subject who is predisposed to developing such disorder relative to the population at large). A subject in need thereof can have a refractory or resistant a disease or disorder disclosed herein (*i.e.*, a disease or disorder disclosed herein that does not respond or has not yet responded to treatment). The subject may be resistant at start of treatment or may become resistant during treatment. In some embodiments, the subject in need thereof received and failed all known effective therapies for a disease or disorder disclosed herein. In some embodiments, the subject in need thereof received at least one prior therapy.

[0653] As used herein, the term “treating” or “treat” describes the management and care of a patient for the purpose of combating a disease, condition, or disorder and includes the administration of a compound of the present disclosure, or a pharmaceutically acceptable salt, polymorph or solvate thereof, to alleviate the symptoms or complications of a disease, condition or disorder, or to eliminate the disease, condition or disorder. The term “treat” can also include treatment of a cell *in vitro* or an animal model.

[0654] It is to be understood that a compound of the present disclosure, or a pharmaceutically acceptable salt, polymorph or solvate thereof, can or may also be used to prevent a relevant disease, condition, or disorder, or used to identify suitable candidates for such purposes.

[0655] As used herein, the term “preventing,” “prevent,” or “protecting against” describes reducing or eliminating the onset of the symptoms or complications of such disease, condition or disorder.

[0656] All percentages and ratios used herein, unless otherwise indicated, are by weight. Other features and advantages of the present disclosure are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the present disclosure. The examples do not limit the claimed disclosure. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present disclosure.

[0657] In the synthetic schemes described herein, compounds may be drawn with one particular configuration for simplicity. Such particular configurations are not to be construed as limiting the disclosure to one or another isomer, tautomer, regioisomer or stereoisomer, nor does it exclude mixtures of isomers, tautomers, regioisomers or stereoisomers; however, it will be understood that a given isomer, tautomer, regioisomer or stereoisomer may have a higher level of activity than another isomer, tautomer, regioisomer or stereoisomer.

[0658] It is to be understood that one skilled in the art may refer to general reference texts for detailed descriptions of known techniques discussed herein or equivalent techniques. These texts include Ausubel *et al.*, *Current Protocols in Molecular Biology*, John Wiley and Sons, Inc. (2005); Sambrook *et al.*, *Molecular Cloning, A Laboratory Manual* (3rd edition), Cold Spring Harbor Press, Cold Spring Harbor, New York (2000); Coligan *et al.*, *Current Protocols in Immunology*, John Wiley & Sons, N.Y.; Enna *et al.*, *Current Protocols in Pharmacology*, John Wiley & Sons, N.Y.; Fingl *et al.*, *The Pharmacological Basis of Therapeutics* (1975), *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, PA, 18th edition (1990). These texts can, of course, also be referred to in making or using an aspect of the disclosure.

[0659] It is to be understood that the present disclosure also provides pharmaceutical compositions comprising any compound described herein in combination with at least one pharmaceutically acceptable excipient or carrier.

[0660] As used herein, the term “pharmaceutical composition” is a formulation containing the compounds of the present disclosure in a form suitable for administration to a subject. In one embodiment, the pharmaceutical composition is in bulk or in unit dosage form. The unit dosage form is any of a variety of forms, including, for example, a capsule, an IV bag, a tablet, a single

pump on an aerosol inhaler or a vial. The quantity of active ingredient (*e.g.*, a formulation of the disclosed compound or salt, hydrate, solvate or isomer thereof) in a unit dose of composition is an effective amount and is varied according to the particular treatment involved. One skilled in the art will appreciate that it is sometimes necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. A variety of routes are contemplated, including oral, pulmonary, rectal, parenteral, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, inhalational, buccal, sublingual, intrapleural, intrathecal, intranasal, and the like. Dosage forms for the topical or transdermal administration of a compound of this disclosure include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. In one embodiment, the active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that are required.

[0661] As used herein, the term “pharmaceutically acceptable” refers to those compounds, anions, cations, materials, compositions, carriers, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0662] As used herein, the term “pharmaceutically acceptable excipient” means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A “pharmaceutically acceptable excipient” as used in the specification and claims includes both one and more than one such excipient.

[0663] It is to be understood that a pharmaceutical composition of the disclosure is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, ingestion), inhalation, transdermal (topical), and transmucosal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulphite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates, and agents for

the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0664] It is to be understood that a compound or pharmaceutical composition of the disclosure can be administered to a subject in many of the well-known methods currently used for chemotherapeutic treatment. For example, a compound of the disclosure may be injected into the blood stream or body cavities or taken orally or applied through the skin with patches. The dose chosen should be sufficient to constitute effective treatment but not so high as to cause unacceptable side effects. The state of the disease condition (*e.g.*, a disease or disorder disclosed herein) and the health of the patient should preferably be closely monitored during and for a reasonable period after treatment.

[0665] As used herein, the term “therapeutically effective amount”, refers to an amount of a pharmaceutical agent to treat, ameliorate, or prevent an identified disease or condition, or to exhibit a detectable therapeutic or inhibitory effect. The effect can be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject’s body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Therapeutically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician.

[0666] It is to be understood that, for any compound, the therapeutically effective amount can be estimated initially either in cell culture assays, *e.g.*, of neoplastic cells, or in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. Therapeutic/prophylactic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, ED₅₀ (the dose therapeutically effective in 50% of the population) and LD₅₀ (the dose lethal to 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD₅₀/ED₅₀. Pharmaceutical compositions that exhibit large therapeutic indices are preferred. The dosage may vary within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

[0667] Dosage and administration are adjusted to provide sufficient levels of the active agent(s)

or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

[0668] The pharmaceutical compositions containing active compounds of the present disclosure may be manufactured in a manner that is generally known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilising processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and/or auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Of course, the appropriate formulation is dependent upon the route of administration chosen.

[0669] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol and sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum

monostearate and gelatin.

[0670] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilisation. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0671] Oral compositions generally include an inert diluent or an edible pharmaceutically acceptable carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0672] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser, which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebuliser.

[0673] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels,

or creams as generally known in the art.

[0674] The active compounds can be prepared with pharmaceutically acceptable carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[0675] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the disclosure are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved.

[0676] In therapeutic applications, the dosages of the pharmaceutical compositions used in accordance with the disclosure vary depending on the agent, the age, weight, and clinical condition of the recipient patient, and the experience and judgment of the clinician or practitioner administering the therapy, among other factors affecting the selected dosage. Generally, the dose should be sufficient to result in slowing, and preferably regressing, the symptoms of the disease or disorder disclosed herein and also preferably causing complete regression of the disease or disorder. Dosages can range from about 0.01 mg/kg per day to about 5000 mg/kg per day. In preferred aspects, dosages can range from about 1 mg/kg per day to about 1000 mg/kg per day. In an aspect, the dose will be in the range of about 0.1 mg/day to about 50 g/day; about 0.1 mg/day to about 25 g/day; about 0.1 mg/day to about 10 g/day; about 0.1 mg to about 3 g/day; or about 0.1 mg to about 1 g/day, in single, divided, or continuous doses (which dose may be adjusted for the patient's weight in kg, body surface area in m², and age in years). An effective amount of a pharmaceutical agent is that which provides an objectively identifiable improvement as noted by

the clinician or other qualified observer. Improvement in survival and growth indicates regression. As used herein, the term “dosage effective manner” refers to amount of an active compound to produce the desired biological effect in a subject or cell.

[0677] It is to be understood that the pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[0678] It is to be understood that, for the compounds of the present disclosure being capable of further forming salts, all of these forms are also contemplated within the scope of the claimed disclosure.

[0679] As used herein, the term “pharmaceutically acceptable salts” refer to derivatives of the compounds of the present disclosure wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulphonc, acetic, ascorbic, benzene sulphonc, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulphonc, 1,2-ethane sulphonc, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulphonc, maleic, malic, mandelic, methane sulphonc, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulphamic, sulphanilic, sulphuric, tannic, tartaric, toluene sulphonc, and the commonly occurring amine acids, *e.g.*, glycine, alanine, phenylalanine, arginine, etc.

[0680] In some embodiments, the pharmaceutically acceptable salt is a sodium salt, a potassium salt, a calcium salt, a magnesium salt, a diethylamine salt, a choline salt, a meglumine salt, a benzathine salt, a tromethamine salt, an ammonia salt, an arginine salt, or a lysine salt.

[0681] Other examples of pharmaceutically acceptable salts include hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulphonc acid, 2-naphthalenesulphonc acid, 4-toluenesulphonc acid, camphorsulphonc acid, 4-methylbicyclo-[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic

acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. The present disclosure also encompasses salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. In the salt form, it is understood that the ratio of the compound to the cation or anion of the salt can be 1:1, or any ratio other than 1:1, *e.g.*, 3:1, 2:1, 1:2, or 1:3.

[0682] It is to be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same salt.

[0683] The compounds, or pharmaceutically acceptable salts thereof, are administered orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperitoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally and parenterally. In one embodiment, the compound is administered orally. One skilled in the art will recognize the advantages of certain routes of administration.

[0684] The dosage regimen utilising the compounds is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

[0685] Techniques for formulation and administration of the disclosed compounds of the disclosure can be found in *Remington: the Science and Practice of Pharmacy*, 19th edition, Mack Publishing Co., Easton, PA (1995). In an embodiment, the compounds described herein, and the pharmaceutically acceptable salts thereof, are used in pharmaceutical preparations in combination with a pharmaceutically acceptable carrier or diluent. Suitable pharmaceutically acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The compounds will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein.

[0686] All percentages and ratios used herein, unless otherwise indicated, are by weight. Other features and advantages of the present disclosure are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the

present disclosure. The examples do not limit the claimed disclosure. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present disclosure.

[0687] In the synthetic schemes described herein, compounds may be drawn with one particular configuration for simplicity. Such particular configurations are not to be construed as limiting the disclosure to one or another isomer, tautomer, regioisomer or stereoisomer, nor does it exclude mixtures of isomers, tautomers, regioisomers or stereoisomers; however, it will be understood that a given isomer, tautomer, regioisomer or stereoisomer may have a higher level of activity than another isomer, tautomer, regioisomer or stereoisomer.

[0688] As would be appreciated by the skilled artisan, the *FGFR2* gene is commonly referred to as one of *FGFR2*, *fibroblast growth factor receptor 2*, *BEK*, *JWS*, *BBDS*, *CEK3*, *CFD1*, *ECT1*, *KGFR*, *TK14*, *TK25*, *BFR-1*, *CD332*, *cluster of differentiation 332* and *K-SAM*. Thus, these terms are used herein interchangeably to refer to the *FGFR2* gene.

[0689] As would be appreciated by the skilled artisan, the FGFR2 protein, encoded by the *FGFR2* gene, is commonly referred to as one of FGFR2, fibroblast growth factor receptor 2, BEK, JWS, BBDS, CEK3, CFD1, ECT1, KGFR, TK14, TK25, BFR-1, CD332, cluster of differentiation 332 and K-SAM. Thus, these terms are used herein interchangeably to refer to the FGFR2 protein.

[0690] As used herein, the term FGFR2 can refer to any isoform of the FGFR2 protein, including, but not limited to, FGFR2-IIIB and FGFR2-IIIC.

[0691] As would be appreciated by the skilled artisan, the *FGFR3* gene is commonly referred to as one of *FGFR3*, *fibroblast growth factor receptor 3*, *ACH*, *CD333*, *cluster of differentiation 333*, *CEK2*, *HSFGFR3EX* and *JTK4*. Thus, these terms are used herein interchangeably to refer to the *BRAF* gene.

[0692] As would be appreciated by the skilled artisan, the FGFR3 protein, encoded by the *FGFR3* gene, is commonly referred to as one of FGFR3, fibroblast growth factor receptor 3, ACH, CD333, cluster of differentiation 333, CEK2, HSFGFR3EX and JTK4. Thus, these terms are used herein interchangeably to refer to the FGFR3 protein.

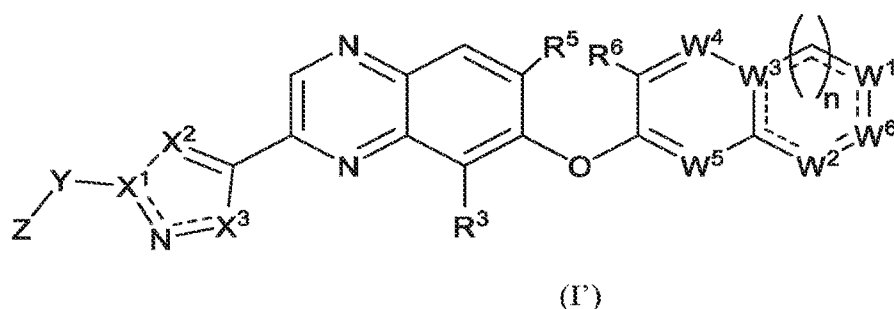
[0693] As used herein, the term FGFR2 can refer to any isoform of the FGFR2 protein, including, but not limited to, FGFR2-IIIB and FGFR2-IIIC.

[0694] All publications and patent documents cited herein are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated

herein by reference. Citation of publications and patent documents is not intended as an admission that any is pertinent prior art, nor does it constitute any admission as to the contents or date of the same. The invention having now been described by way of written description, those of skill in the art will recognize that the invention can be practiced in a variety of embodiments and that the foregoing description and examples below are for purposes of illustration and not limitation of the claims that follow.

Exemplary Embodiments

[0695] Embodiment 1. A compound of Formula (I):



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

each $\equiv$ independently represents a single bond or a double bond;

n is 0 or 1;

W^1 is $C(R^{W1})$ when connected to one double bond and one single bond, $N(R^{W1})$ when connected to two single bonds, or N when connected to one double bond and one single bond;

R^{W1} is H, C_1 - C_6 alkyl, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^2 is $C(R^{W2})$ when connected to one double bond and one single bond, $N(R^{W2})$ or O when connected to two single bonds, or N when connected to one double bond and one single bond;

R^{W2} is H, C_1 - C_6 alkyl, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^3 is C or N;

W^4 is $C(R^{W4})$ or N;

R^{W4} is H, halogen, cyano, C_1 - C_6 alkyl, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^5 is $C(R^{W5})$ or N;

R^{W5} is H, halogen, cyano, C_1 - C_6 alkyl, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^6 is $C(R^{W6})$ when connected to one double bond and one single bond, $N(R^{W6})$ when connected to two single bonds, or N when connected to one double bond and one single bond;

R^{W6} is H, halogen, cyano, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl, or $-S(=O)_2-(C_1-C_6$ alkyl);

X^1 is C or N;

X^2 is N, O, or $C(R^{X2})$;

R^{X2} is H or C_1 - C_6 alkyl;

X^3 is N, O, or $C(R^{X3})$;

R^{X3} is H or C_1 - C_6 alkyl;

R^3 is H, halogen, cyano, NH_2 , $-NH(C_1-C_6$ alkyl), $-NHC(=O)(C_1-C_6$ haloalkyl), $-NHC(=O)O(C_1-C_6$ alkyl), $N(C_1-C_6$ alkyl) $_2$, $-S(=O)_2-(C_1-C_6$ alkyl), $-C(=O)H$, $-C(=O)(C_1-C_6$ alkyl), $-C(=O)O(C_1-C_6$ alkyl), C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_3 - C_{12} cycloalkyl, C_3 - C_{12} cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C_6 - C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the $-NH(C_1-C_6$ alkyl), $-NHC(=O)(C_1-C_6$ haloalkyl), $-NHC(=O)O(C_1-C_6$ alkyl), $N(C_1-C_6$ alkyl) $_2$, $-S(=O)_2-(C_1-C_6$ alkyl), $-C(=O)H$, $-C(=O)(C_1-C_6$ alkyl), $-C(=O)O(C_1-C_6$ alkyl), C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_3 - C_{12} cycloalkyl, C_3 - C_{12} cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C_6 - C_{10} aryl, or 5- to 10-membered heteroaryl, is optionally substituted with one or more R^{3a} ;

each R^{3a} independently is halogen, cyano, oxo, $-OH$, NH_2 , $-NH(C_1-C_6$ alkyl), $-NHC(=O)O(C_1-C_6$ alkyl), $N(C_1-C_6$ alkyl) $_2$, $-S(=O)_2-(C_1-C_6$ alkyl), $-C(=O)(C_1-C_6$ alkyl), $-C(=O)O(C_1-C_6$ alkyl), C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_3 - C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6 - C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the $-NHC(=O)O(C_1-C_6$ alkyl) is optionally substituted with one or more halogen;

R^5 is H, halogen, cyano, or C_1 - C_6 alkyl;

R^6 is H, halogen, cyano, or C_1 - C_6 alkyl;

Y is absent, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, or C_1 - C_6 alkoxy, wherein the C_1 - C_6 alkyl, C_2 - C_6 alkenyl, or C_1 - C_6 alkoxy is optionally substituted with one or more halogen, oxo, cyano, $-OH$, NH_2 , $-NH(C_1-C_6$ alkyl)- OH , C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_1 - C_6 alkoxy optionally substituted with $-(C_1-C_6$ alkyl)(C_6 - C_{10} aryl), or C_3 - C_{12} cycloalkyl;

Z is absent, H, C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl or 5- to 10-membered heteroaryl, is optionally substituted with one or more R^Z;

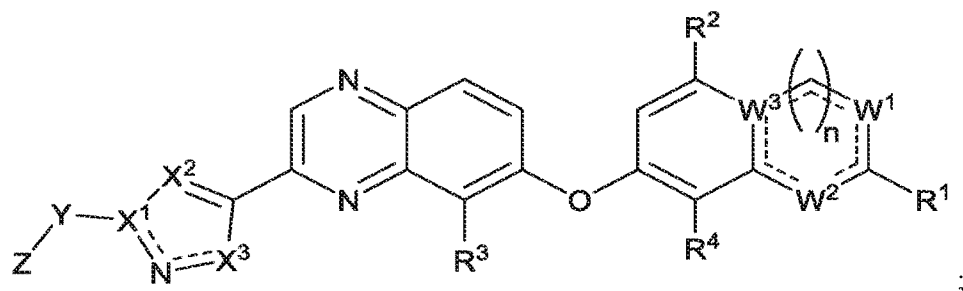
each R^Z independently is oxo, halogen, cyano, -OH, =NR^{Za}, NH₂, NHR^{Za}, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(C₁-C₆ alkyl), -S(=O)(=NR^{Za})-(C₁-C₆ alkyl), -S(=O)₂-(C₁-C₆ alkyl), -S(=O)₂-(C₂-C₆ alkenyl), -C(=O)(3- to 12-membered heterocycloalkyl), -C(=O)NH(C₁-C₆ alkyl), -C(=O)NR^{Za}, -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), -C(=O)-(C₁-C₆ alkoxy), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, or 5- to 10-membered heteroaryl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{Za};

each R^{Za} independently is H, oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, or 3- to 12-membered heterocycloalkyl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, or 3- to 12-membered heterocycloalkyl is optionally substituted with one or more R^{Zb};

and

each R^{Zb} independently is oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, or C₁-C₆ alkoxy.

[0696] Embodiment 2. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

each $\equiv$ independently represents a single bond or a double bond;

n is 0 or 1;

W^1 is $C(R^{W1})$ or $N(R^{W1})$ when connected to two single bonds, or C or N when connected to one double bond and one single bond;

R^{W1} is H, C_1 - C_6 alkyl, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^2 is $C(R^{W2})$ or $N(R^{W2})$ when connected to two single bonds, or C or N when connected to one double bond and one single bond;

R^{W2} is H, C_1 - C_6 alkyl, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^3 is C or N;

X^1 is C or N;

X^2 is N, O, or $C(R^{X2})$;

R^{X2} is H or C_1 - C_6 alkyl;

X^3 is N, O, or $C(R^{X3})$;

R^{X3} is H or C_1 - C_6 alkyl;

R^1 is H, halogen, cyano, or C_1 - C_6 alkyl;

R^2 is H, halogen, cyano, or C_1 - C_6 alkyl;

R^3 is H, halogen, cyano, or C_1 - C_6 alkyl;

R^4 is H, halogen, cyano, or C_1 - C_6 alkyl;

Y is absent or C_1 - C_6 alkyl optionally substituted with one or more oxo or -OH;

Z is H, C_3 - C_8 cycloalkyl, or 3- to 8-membered heterocycloalkyl, wherein the C_3 - C_8 cycloalkyl or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^Z ;

each R^Z independently is oxo, halogen, cyano, -OH, NH_2 , $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, $C_1-C_6 \text{ alkoxyl}$, $C_3-C_8 \text{ cycloalkyl}$, or 3- to 8-membered heterocycloalkyl, wherein the $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, $C_1-C_6 \text{ alkoxyl}$, $C_3-C_8 \text{ cycloalkyl}$, or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{Za} ;

each R^{Za} independently is oxo, halogen, cyano, -OH, NH_2 , $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, $C_1-C_6 \text{ alkyl}$, C_2-C_6

alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{Zb}; and

each R^{Zb} independently is oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, or C₁-C₆ alkoxy.

[0697] Embodiment 3. The compound of any one of the preceding embodiments, wherein:

each $\equiv$ independently represents a single bond or a double bond;

n is 0 or 1;

W¹ is C(R^{W1}) or N(R^{W1}) when connected to two single bonds, or C or N when connected to one double bond and one single bond;

R^{W1} is H, C₁-C₆ alkyl, or -S(=O)₂-(C₁-C₆ alkyl);

W² is C(R^{W2}) or N(R^{W2}) when connected to two single bonds, or C or N when connected to one double bond and one single bond;

R^{W2} is H, C₁-C₆ alkyl, or -S(=O)₂-(C₁-C₆ alkyl);

W³ is C or N;

X¹ is C or N;

X² is N, O, or C(R^{X2});

R^{X2} is H or C₁-C₆ alkyl;

X³ is N, O, or C(R^{X3});

R^{X3} is H or C₁-C₆ alkyl;

R¹ is H, halogen, cyano, or C₁-C₆ alkyl;

R² is H, halogen, cyano, or C₁-C₆ alkyl;

R³ is H, halogen, cyano, or C₁-C₆ alkyl;

R⁴ is H, halogen, cyano, or C₁-C₆ alkyl;

Y is absent or C₁-C₆ alkyl optionally substituted with one or more oxo or -OH;

Z is C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl, wherein the C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^Z;

each R^Z independently is oxo, halogen, cyano, -OH, NH_2 , $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, $C_1-C_6 \text{ alkoxyl}$, $C_3-C_8 \text{ cycloalkyl}$, or 3- to 8-membered heterocycloalkyl, wherein the $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, $C_1-C_6 \text{ alkoxyl}$, $C_3-C_8 \text{ cycloalkyl}$, or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{Za} ;

each R^{Za} independently is oxo, halogen, cyano, -OH, NH_2 , $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, $C_1-C_6 \text{ alkoxyl}$, $C_3-C_8 \text{ cycloalkyl}$, or 3- to 8-membered heterocycloalkyl, wherein the $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, $C_1-C_6 \text{ alkoxyl}$, $C_3-C_8 \text{ cycloalkyl}$, or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{Zb} ; and

each R^{Zb} independently is oxo, halogen, cyano, -OH, NH_2 , $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, or $C_1-C_6 \text{ alkoxyl}$.

[0698] Embodiment 4. The compound of any one of the preceding embodiments, wherein:

each $==$ independently represents a single bond or a double bond;

n is 0 or 1;

W^1 is $C(R^{W1})$ or $N(R^{W1})$ when connected to two single bonds, or C or N when connected to one double bond and one single bond;

R^{W1} is H, $C_1-C_6 \text{ alkyl}$, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^2 is $C(R^{W2})$ or $N(R^{W2})$ when connected to two single bonds, or C or N when connected to one double bond and one single bond;

R^{W2} is H, $C_1-C_6 \text{ alkyl}$, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^3 is C or N;

X^1 is C or N;

X^2 is N, O, or $C(R^{X2})$;

R^{X2} is H or $C_1-C_6 \text{ alkyl}$;

X^3 is N, O, or $C(R^{X3})$;

R^{X3} is H or $C_1-C_6 \text{ alkyl}$;

R^1 is H, halogen, cyano, or C₁-C₆ alkyl;

R^2 is H, halogen, cyano, or C₁-C₆ alkyl;

R^3 is H, halogen, cyano, or C₁-C₆ alkyl;

R^4 is H, halogen, cyano, or C₁-C₆ alkyl;

Y is C₁-C₆ alkyl optionally substituted with one or more oxo or -OH;

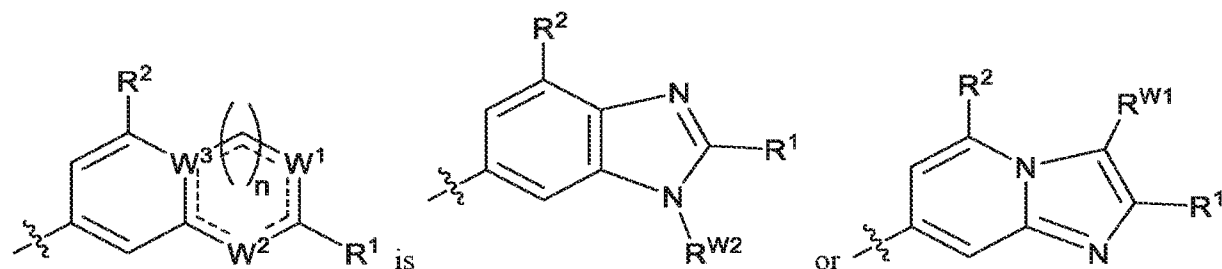
Z is C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl, wherein the C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^Z ;

each R^Z independently is oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{Za} ;

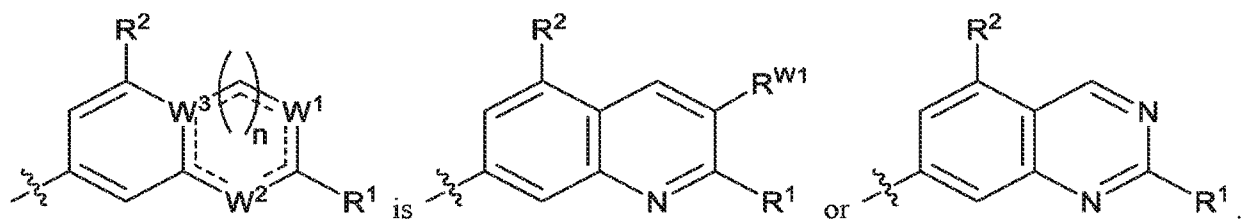
each R^{Za} independently is oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{Zb} ; and

each R^{Zb} independently is oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, or C₁-C₆ alkoxy.

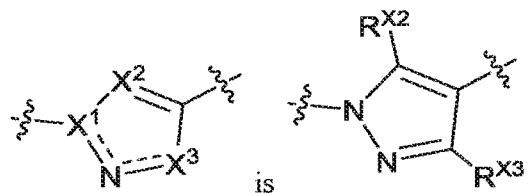
[0699] Embodiment 5. The compound of any one of the preceding embodiments, wherein



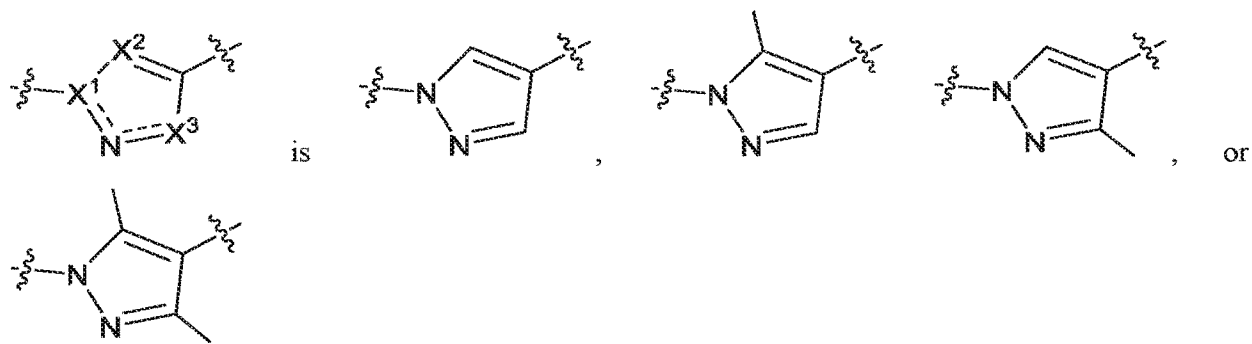
[0700] Embodiment 6. The compound of any one of the preceding embodiments, wherein



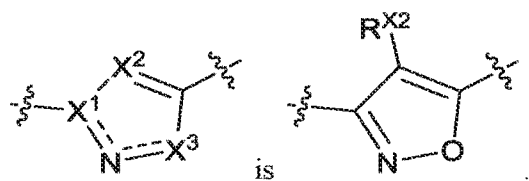
[0701] Embodiment 7. The compound of any one of the preceding embodiments, wherein



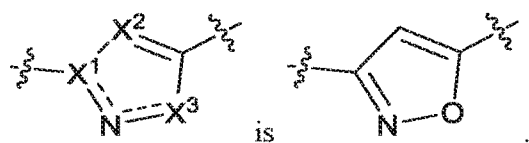
[0702] Embodiment 8. The compound of any one of the preceding embodiments, wherein



[0703] Embodiment 9. The compound of any one of the preceding embodiments, wherein



[0704] Embodiment 10. The compound of any one of the preceding embodiments, wherein



[0705] Embodiment 11. The compound of any one of the preceding embodiments, wherein R¹ is H.

[0706] Embodiment 12. The compound of any one of the preceding embodiments, wherein R¹ is halogen, cyano, or C₁-C₆ alkyl.

[0707] Embodiment 13. The compound of any one of the preceding embodiments, wherein R^1 is C_1 - C_6 alkyl.

[0708] Embodiment 14. The compound of any one of the preceding embodiments, wherein R^1 is CH_3 .

[0709] Embodiment 15. The compound of any one of the preceding embodiments, wherein R^2 is H.

[0710] Embodiment 16. The compound of any one of the preceding embodiments, wherein R^2 is halogen, cyano, or C_1 - C_6 alkyl.

[0711] Embodiment 17. The compound of any one of the preceding embodiments, wherein R^3 is H.

[0712] Embodiment 18. The compound of any one of the preceding embodiments, wherein R^3 is halogen, cyano, or C_1 - C_6 alkyl.

[0713] Embodiment 19. The compound of any one of the preceding embodiments, wherein R^3 is halogen.

[0714] Embodiment 20. The compound of any one of the preceding embodiments, wherein R^3 is Cl.

[0715] Embodiment 21. The compound of any one of the preceding embodiments, wherein R^3 is C_1 - C_6 alkyl.

[0716] Embodiment 22. The compound of any one of the preceding embodiments, wherein R^3 is CH_3 .

[0717] Embodiment 23. The compound of any one of the preceding embodiments, wherein R^4 is H.

[0718] Embodiment 24. The compound of any one of the preceding embodiments, wherein R^4 is halogen, cyano, or C_1 - C_6 alkyl.

[0719] Embodiment 25. The compound of any one of the preceding embodiments, wherein R^4 is halogen.

[0720] Embodiment 26. The compound of any one of the preceding embodiments, wherein R^4 is Cl.

[0721] Embodiment 27. The compound of any one of the preceding embodiments, wherein R^4 is C_1 - C_6 alkyl.

[0722] Embodiment 28. The compound of any one of the preceding embodiments, wherein R^4 is

CH₃.

[0723] Embodiment 29. The compound of any one of the preceding embodiments, wherein Y is absent.

[0724] Embodiment 30. The compound of any one of the preceding embodiments, wherein Y is C₁-C₆ alkyl optionally substituted with one or more oxo or -OH.

[0725] Embodiment 31. The compound of any one of the preceding embodiments, wherein Y is C₁-C₆ alkyl.

[0726] Embodiment 32. The compound of any one of the preceding embodiments, wherein Y is -CH₂-.

[0727] Embodiment 33. The compound of any one of the preceding embodiments, wherein Y is C₁-C₆ alkyl substituted with one or more -OH.

[0728] Embodiment 34. The compound of any one of the preceding embodiments, wherein Z is H.

[0729] Embodiment 35. The compound of any one of the preceding embodiments, wherein Z is C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl, wherein the C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^Z.

[0730] Embodiment 36. The compound of any one of the preceding embodiments, wherein Z is azetidinyI or oxetanyI, wherein the azetidinyI or oxetanyI is optionally substituted with one or more R^Z.

[0731] Embodiment 37. The compound of any one of the preceding embodiments, wherein Z is azetidinyI or oxetanyI.

[0732] Embodiment 38. The compound of any one of the preceding embodiments, wherein Z is pyrrolidinyl or tetrahydrofuranyl, wherein the pyrrolidinyl or tetrahydrofuranyl is optionally substituted with one or more R^Z.

[0733] Embodiment 39. The compound of any one of the preceding embodiments, wherein Z is pyrrolidinyl or tetrahydrofuranyl.

[0734] Embodiment 40. The compound of any one of the preceding embodiments, wherein Z is piperidinyl or tetrahydropyranyl, wherein the piperidinyl or tetrahydropyranyl is optionally substituted with one or more R^Z.

[0735] Embodiment 41. The compound of any one of the preceding embodiments, wherein Z is piperidinyl or tetrahydropyranyl.

[0736] Embodiment 42. The compound of any one of the preceding embodiments, wherein at least one R^Z is oxo, halogen, cyano, -OH.

[0737] Embodiment 43. The compound of any one of the preceding embodiments, wherein at least one R^Z is NH_2 , $NH(C_1-C_6 \text{ alkyl})$, or $N(C_1-C_6 \text{ alkyl})_2$, wherein the $NH(C_1-C_6 \text{ alkyl})$ or $N(C_1-C_6 \text{ alkyl})_2$ is optionally substituted with one or more R^{Za} .

[0738] Embodiment 44. The compound of any one of the preceding embodiments, wherein at least one R^Z is $-S(=O)_2-(C_1-C_6 \text{ alkyl})$ optionally substituted with one or more R^{Za} .

[0739] Embodiment 45. The compound of any one of the preceding embodiments, wherein at least one R^Z is $-C(=O)-(C_1-C_6 \text{ alkyl})$ or $-C(=O)-(C_2-C_6 \text{ alkenyl})$, wherein the $-C(=O)-(C_1-C_6 \text{ alkyl})$ or $-C(=O)-(C_2-C_6 \text{ alkenyl})$ is optionally substituted with one or more R^{Za} .

[0740] Embodiment 46. The compound of any one of the preceding embodiments, wherein at least one R^Z is $-C(=O)-CH=CH_2$.

[0741] Embodiment 47. The compound of any one of the preceding embodiments, wherein at least one R^Z is $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, or $C_1-C_6 \text{ alkoxyl}$, wherein the $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, or $C_1-C_6 \text{ alkoxyl}$ is optionally substituted with one or more R^{Za} .

[0742] Embodiment 48. The compound of any one of the preceding embodiments, wherein at least one R^Z is $C_1-C_6 \text{ alkyl}$ optionally substituted with one or more R^{Za} .

[0743] Embodiment 49. The compound of any one of the preceding embodiments, wherein at least one R^Z is $C_3-C_8 \text{ cycloalkyl}$ or 3- to 8-membered heterocycloalkyl, wherein the $C_3-C_8 \text{ cycloalkyl}$ or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{Za} .

[0744] Embodiment 50. The compound of any one of the preceding embodiments, wherein at least one R^{Za} is oxo, halogen, cyano, or -OH.

[0745] Embodiment 51. The compound of any one of the preceding embodiments, wherein at least one R^{Za} is NH_2 , $NH(C_1-C_6 \text{ alkyl})$, or $N(C_1-C_6 \text{ alkyl})_2$, wherein the $NH(C_1-C_6 \text{ alkyl})$ or $N(C_1-C_6 \text{ alkyl})_2$ is optionally substituted with one or more R^{Zb} .

[0746] Embodiment 52. The compound of any one of the preceding embodiments, wherein at least one R^{Za} is $-S(=O)_2-(C_1-C_6 \text{ alkyl})$ optionally substituted with one or more R^{Zb} .

[0747] Embodiment 53. The compound of any one of the preceding embodiments, wherein at least one R^{Za} is $-C(=O)-(C_1-C_6 \text{ alkyl})$ or $-C(=O)-(C_2-C_6 \text{ alkenyl})$, wherein the $-C(=O)-(C_1-C_6 \text{ alkyl})$ or $-C(=O)-(C_2-C_6 \text{ alkenyl})$ is optionally substituted with one or more R^{Zb} .

[0748] Embodiment 54. The compound of any one of the preceding embodiments, wherein at least

one R^{Za} is $-C(=O)-CH=CH_2$.

[0749] Embodiment 55. The compound of any one of the preceding embodiments, wherein at least one R^{Za} is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, or C_1 - C_6 alkoxy, wherein the C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, or C_1 - C_6 alkoxy is optionally substituted with one or more R^{Zb} .

[0750] Embodiment 56. The compound of any one of the preceding embodiments, wherein at least one R^{Za} is C_3 - C_8 cycloalkyl or 3- to 8-membered heterocycloalkyl, wherein the C_3 - C_8 cycloalkyl or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{Zb} .

[0751] Embodiment 57. The compound of any one of the preceding embodiments, wherein at least one R^{Zb} is oxo, halogen, cyano, or $-OH$.

[0752] Embodiment 58. The compound of any one of the preceding embodiments, wherein at least one R^{Zb} is NH_2 , $NH(C_1-C_6 \text{ alkyl})$, or $N(C_1-C_6 \text{ alkyl})_2$.

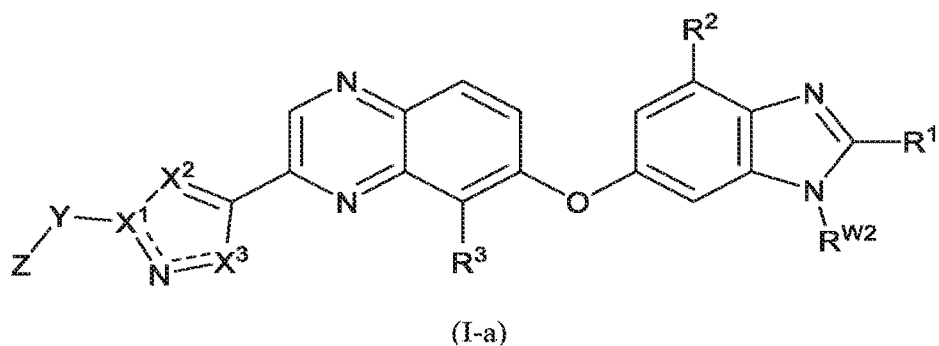
[0753] Embodiment 59. The compound of any one of the preceding embodiments, wherein at least one R^{Zb} is $-S(=O)_2-(C_1-C_6 \text{ alkyl})$.

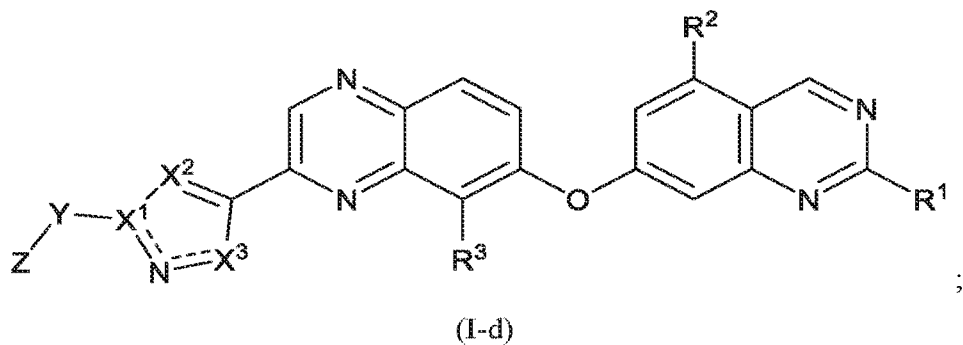
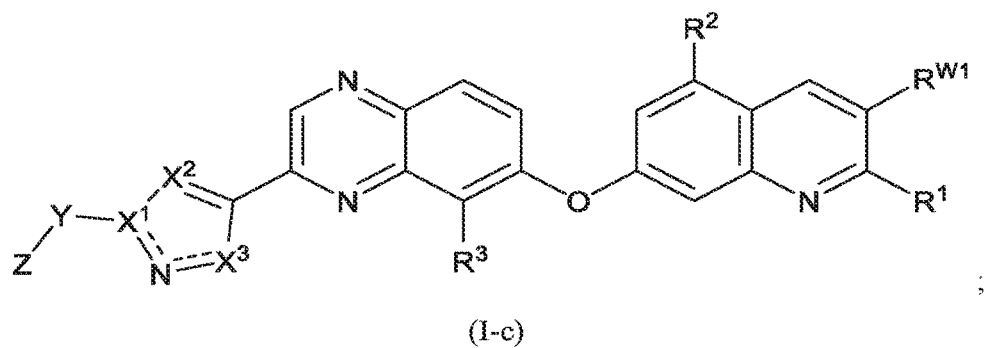
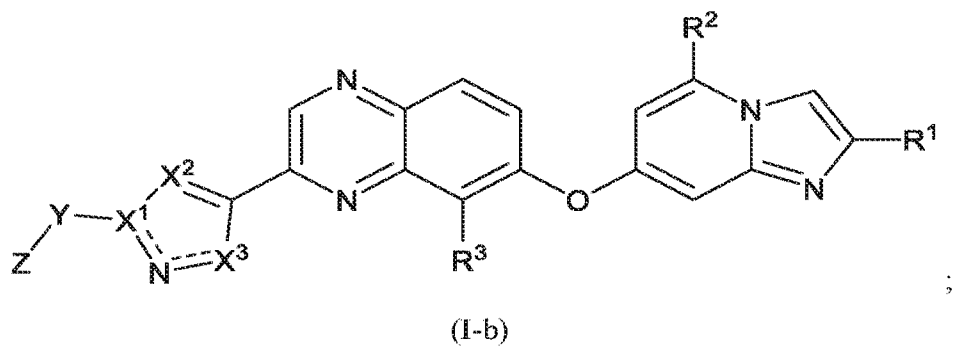
[0754] Embodiment 60. The compound of any one of the preceding embodiments, wherein at least one R^{Zb} is $-C(=O)-(C_1-C_6 \text{ alkyl})$ or $-C(=O)-(C_2-C_6 \text{ alkenyl})$.

[0755] Embodiment 61. The compound of any one of the preceding embodiments, wherein at least one R^{Zb} is $-C(=O)-CH=CH_2$.

[0756] Embodiment 62. The compound of any one of the preceding embodiments, wherein at least one R^{Zb} is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, or C_1 - C_6 alkoxy.

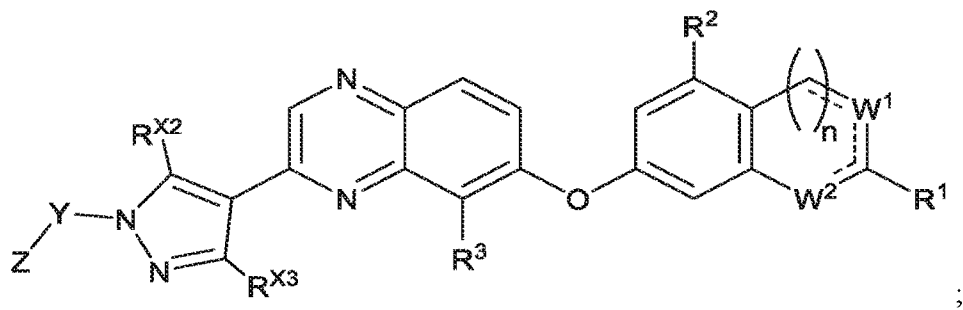
[0757] Embodiment 63. The compound of any one of the preceding embodiments, being of Formula (I-a), (I-b), (I-c), or (I-d):





or a pharmaceutically acceptable salt or stereoisomer thereof.

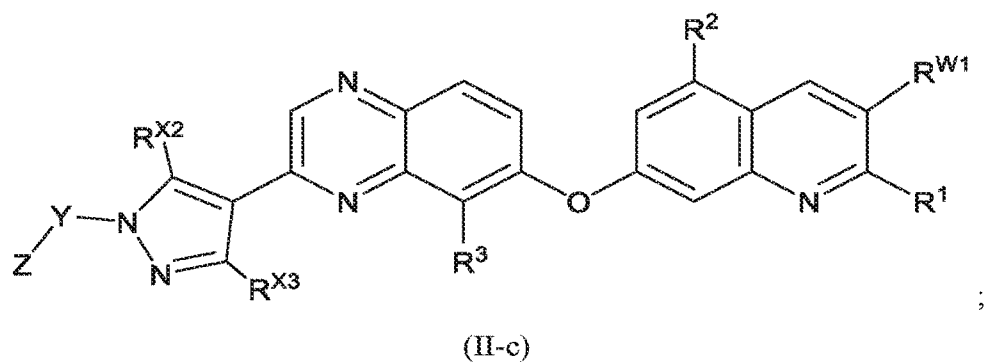
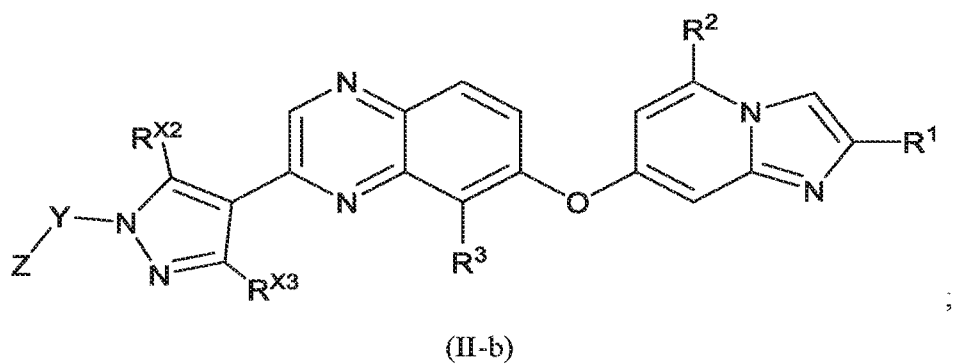
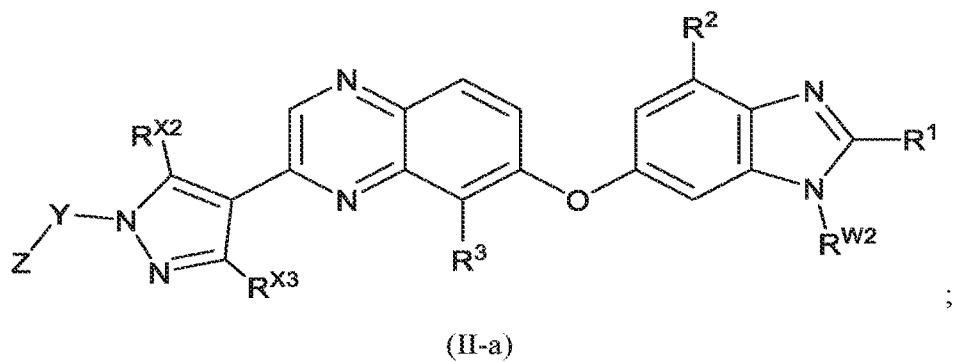
[0758] Embodiment 64. The compound of any one of the preceding embodiments, being of Formula (II):

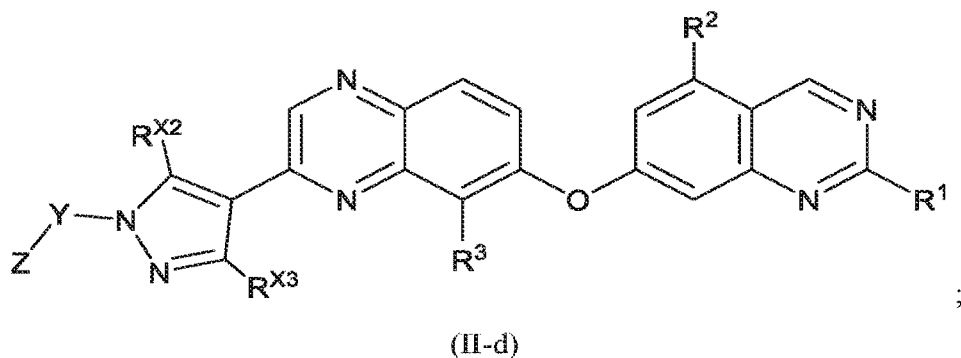


(II)

or a pharmaceutically acceptable salt or stereoisomer thereof.

[0759] Embodiment 65. The compound of any one of the preceding embodiments, being of Formula (II-a), (II-b), (II-c), or (II-d):





or a pharmaceutically acceptable salt or stereoisomer thereof.

[0760] Embodiment 66. The compound of any one of the preceding embodiments, being selected from the compounds described in Table I and Table II, or a pharmaceutically acceptable salt or stereoisomer thereof.

[0761] Embodiment 67. An isotopic derivative of the compound of any one of the preceding embodiments.

[0762] Embodiment 68. A method of preparing the compound of any one of the preceding embodiments.

[0763] Embodiment 69. A pharmaceutical composition comprising the compound of any one of the preceding embodiments and one or more pharmaceutically acceptable carriers or excipients.

[0764] Embodiment 70. A method of treating or preventing cancer in a subject, the method comprising administering to the subject a compound of any one of the preceding embodiments.

[0765] Embodiment 71. A compound of any one of the preceding embodiments for treating or preventing cancer in a subject.

[0766] Embodiment 72. Use of the compound of any one of the preceding embodiments in the manufacture of a medicament for treating or preventing cancer in a subject.

[0767] Embodiment 73. Use of the compound of any one of the preceding embodiments for treating or preventing cancer in a subject.

[0768] Embodiment 74. The method, compound, or use of any one of embodiments 70-73, wherein the subject is a human.

[0769] Embodiment 75. The method, compound, or use of any one of embodiments 70-74, wherein the subject has previously undergone at least one round of anti-cancer therapy.

[0770] Embodiment 76. The method, compound, or use of any one of embodiments 70-75, wherein the cancer is characterized by at least one oncogenic mutation in the *FGFR2* gene.

- [0771] Embodiment 77. The method, compound, or use of any one of embodiments 70-75, wherein the cancer is characterized by at least one oncogenic mutation in the *FGFR3* gene.
- [0772] Embodiment 78. The method, compound, or use of any one of embodiments 70-75, wherein the cancer is characterized by overexpression of the *FGFR2* gene.
- [0773] Embodiment 79. The method, compound, or use of any one of embodiments 70-75, wherein the cancer is characterized by overexpression of the *FGFR3* gene.
- [0774] Embodiment 80. The method, compound, or use of any one of embodiments 70-75, wherein the cancer is characterized by at least one oncogenic variant of FGFR2.
- [0775] Embodiment 81. The method, compound, or use of any one of embodiments 70-75, wherein the cancer is characterized by at least one oncogenic variant of FGFR3.
- [0776] Embodiment 82. The method, compound, or use of any one of embodiments 70-75, wherein the cancer is characterized by overexpression of FGFR2.
- [0777] Embodiment 83. The method, compound, or use of any one of embodiments 70-75, wherein the cancer is characterized by overexpression of FGFR3.
- [0778] Embodiment 84. The method, compound, or use of any one of embodiments 70-83, wherein the cancer is a carcinoma, a lymphoma, a blastoma, a sarcoma, a leukemia, a brain cancer, a breast cancer, a blood cancer, a bone cancer, a lung cancer, a skin cancer, a liver cancer, an ovarian cancer, a bladder cancer, a renal cancer, a kidney cancer, a gastric cancer, a thyroid cancer, a pancreatic cancer, an esophageal cancer, a prostate cancer, a cervical cancer, a uterine cancer, a stomach cancer, a soft tissue cancer, a laryngeal cancer, a small intestine cancer, a testicular cancer, an anal cancer, a vulvar cancer, a joint cancer, an oral cancer, a pharynx cancer or a colorectal cancer.
- [0779] Embodiment 85. The method, compound, or use of any one of embodiments 70-83, wherein the cancer is adrenocortical carcinoma, bladder urothelial carcinoma, breast invasive carcinoma, cervical squamous cell carcinoma, endocervical adenocarcinoma, cholangiocarcinoma, colon adenocarcinoma, lymphoid neoplasm diffuse large B-cell lymphoma, esophageal carcinoma, glioblastoma multiforme, head and neck squamous cell carcinoma, kidney chromophobe, kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma, acute myeloid leukemia, brain lower grade glioma, liver hepatocellular carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, mesothelioma, ovarian serous cystadenocarcinoma, pancreatic adenocarcinoma, pheochromocytoma, paraganglioma, prostate

adenocarcinoma, rectum adenocarcinoma, sarcoma, skin cutaneous melanoma, stomach adenocarcinoma, testicular germ cell tumors, thyroid carcinoma, thymoma, uterine carcinosarcoma, uveal melanoma. Other examples include breast cancer, lung cancer, lymphoma, melanoma, liver cancer, colorectal cancer, ovarian cancer, bladder cancer, renal cancer or gastric cancer. Further examples of cancer include neuroendocrine cancer, non-small cell lung cancer (NSCLC), small cell lung cancer, thyroid cancer, endometrial cancer, biliary cancer, esophageal cancer, anal cancer, salivary, cancer, vulvar cancer, cervical cancer, Acute lymphoblastic leukemia (ALL), Acute myeloid leukemia (AML), Adrenal gland tumors, Anal cancer, Bile duct cancer, Bladder cancer, Bone cancer, Bowel cancer, Brain tumors, Breast cancer, Cancer of unknown primary (CUP), Cancer spread to bone, Cancer spread to brain, Cancer spread to liver, Cancer spread to lung, Carcinoid, Cervical cancer, Children's cancers, Chronic lymphocytic leukemia (CLL), Chrome myeloid leukemia (CML), Colorectal cancer, Ear cancer, Endometrial cancer, Eye cancer, Follicular dendritic cell sarcoma, Gallbladder cancer, Gastric cancer, Gastro esophageal junction cancers, Germ cell tumors, Gestational trophoblastic disease (GIT)), Hairy cell leukemia, Head and neck cancer, Hodgkin lymphoma, Kaposi's sarcoma, Kidney cancer, Laryngeal cancer, Leukemia, Gastric linitis plastica, Liver cancer, Lung cancer, Lymphoma, Malignant schwannoma, Mediastinal germ cell tumors, Melanoma skin cancer, Men's cancer, Merkel cell skin cancer, Mesothelioma, Molar pregnancy, Mouth and oropharyngeal cancer, Myeloma, Nasal and paranasal sinus cancer, Nasopharyngeal cancer, Neuroblastoma, Neuroendocrine tumors, Non-Hodgkin lymphoma (NHL), Esophageal cancer, Ovarian cancer, Pancreatic cancer, Penile cancer, Persistent trophoblastic disease and choriocarcinoma, Pheochromocytoma, Prostate cancer, Pseudomyxoma peritonei, Rectal cancer. Retinoblastoma, Salivary gland cancer, Secondary' cancer, Signet cell cancer, Skin cancer, Small bowel cancer, Soft tissue sarcoma, Stomach cancer, T cell childhood non Hodgkin lymphoma (NHL), Testicular cancer, Thymus gland cancer, Thyroid cancer, Tongue cancer, Tonsil cancer, Tumors of the adrenal gland, Uterine cancer. Vaginal cancer, Vulval cancer, Wilms' tumor, Womb cancer and Gynaecological cancer. Examples of cancer also include, but are not limited to, Hematologic malignancies, Lymphoma, Cutaneous T-cell lymphoma, Peripheral T-cell lymphoma, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, Multiple myeloma, Chrome lymphocytic leukemia, chronic myeloid leukemia, acute myeloid leukemia, Myelodysplastic syndromes, Myelofibrosis, Biliary tract cancer, Hepatocellular cancer, Colorectal cancer, Breast cancer, Lung cancer, Non-small cell lung cancer,

Ovarian cancer, Thyroid Carcinoma, Renal Cell Carcinoma, Pancreatic cancer, Bladder cancer, skin cancer, malignant melanoma, merkel cell carcinoma, Uveal Melanoma or Glioblastoma multiforme.

[0780] Embodiment 86. The method, compound, or use of any one of embodiments 70-83, wherein the cancer is gastric cancer, triple negative breast cancer, melanoma, hepatobiliary cancer, cancer of unknown primary, esophagogastric cancer, cervical cancer, head and neck cancer, CNS cancer, brain cancer, NSCLC, ovarian cancer, breast cancer, soft tissue sarcoma, pancreatic cancer, prostate cancer, renal cell carcinoma, thyroid cancer, lung cancer, bladder cancer, endometrial carcinoma, intrahepatic cholangiocarcinoma or glioblastoma.

EXAMPLES

[0781] For exemplary purpose, salts of the compounds of Formula (I') and (I) are synthesized and tested in the examples. It is understood that neutral compounds of Formula (I') and (I) may be similarly synthesized and tested using the exemplary procedures described in the examples. Further, it is understood that the salts (e.g., sodium salt) of the compounds of Formula (I') and (I) may be converted to the corresponding neutral compounds using routine techniques in the art (e.g., pH adjustment and, optionally, extraction (e.g., into an aqueous phase)).

[0782] Compounds of Formula (I') and (I) can be prepared using the methods detailed herein. Those skilled in the art may be able to envisage alternative synthetic routes, using a variety of starting materials and reagents to prepare the disclosed compounds of Formula (I') and (I) and to make further modifications. For exemplary purpose, salts of some of the compounds of Formula (I') and (I) are synthesized and tested in the examples. It is understood that neutral compounds of Formula (I') and (I) may be similarly synthesized and tested using the exemplary procedures described in the examples. Further, it is understood that the salts (e.g., hydrochloride salt) of the compounds of Formula (I') and (I) may be converted to the corresponding neutral compounds using routine techniques in the art (e.g., pH adjustment and, optionally, extraction (e.g., into an aqueous phase)).

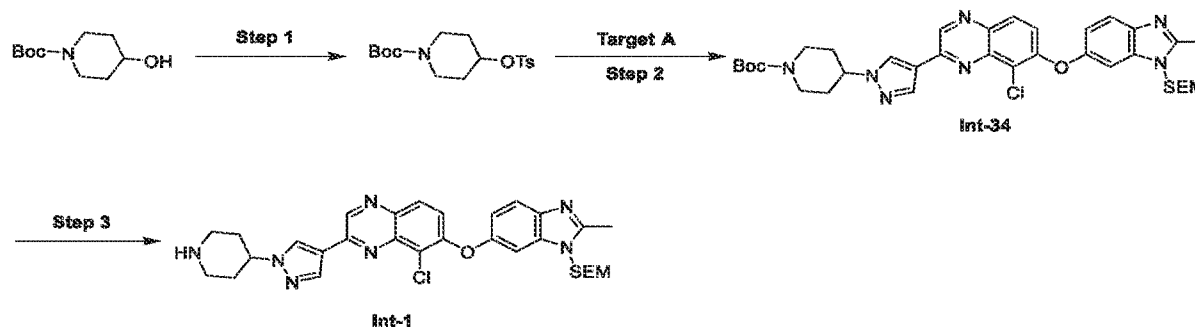
[0783] Abbreviations:

aq.	Aqueous
ACN	Acetonitrile
¹ H NMR	Proton nuclear magnetic resonance spectroscopy

CDCl ₃	Deuterated chloroform
DCM	Dichloromethane
DMF	Dimethylformamide
DMSO- <i>d</i> ₆	Hexadeuterodimethylsulfoxide
EtOAc	Ethyl acetate
eq.	Equivalents
h	Hour(s)
HPLC	high performance liquid chromatography
LC-MS	Liquid chromatography-mass spectrometry
min	Minute(s)
prep-HPLC	preparative high performance liquid chromatography
Et ₃ N	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Y	Yield

Synthesis of Intermediates

Intermediate 1 and 34: 8-chloro-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)-2-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)quinoxaline and *tert*-butyl 4-(4-(8-chloro-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxalin-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate



[0784] **Step 1.** *tert*-Butyl 4-(tosyloxy)piperidine-1-carboxylate

[0785] To a solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (500 mg, 2.48 mmol) in dichloromethane (10 mL) was added triethylamine (754 mg, 7.45 mmol) and *p*-toluenesulfonyl chloride (947 mg, 4.97 mmol). The mixture was stirred at 25 °C for 16 h. On completion, the mixture was poured into water (50 mL) and extracted with ethyl acetate (30 mL x 3). The organic layers were washed with 1 M hydrochloric acid (10 mL) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate=10/1 to 3/1) to give *tert*-butyl 4-(tosyloxy)piperidine-1-carboxylate (600 mg, 1.69 mmol, 67%) as a white solid.

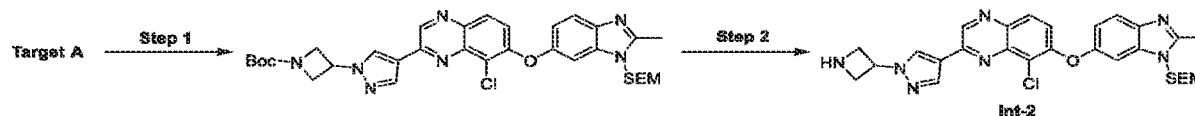
[0786] **Step 2.** *tert*-Butyl 4-[4-[8-chloro-7-[2-methyl-3-(2-trimethylsilylethoxymethyl)benzimidazol-5-yl]oxy-quinoxalin-2-yl]pyrazol-1-yl]piperidine-1-carboxylate

[0787] To a solution of 2-[[6-[5-chloro-3-(1H-pyrazol-4-yl)quinoxalin-6-yl]oxy-2-methylbenzimidazol-1-yl]methoxy]ethyl-trimethyl-silane (1 g, 1.97 mmol) in *N,N*-dimethyl formamide (10 mL) was added cesium carbonate (1.29 g, 3.94 mmol) and *tert*-butyl 4-(*p*-tolylsulfonyloxy)piperidine-1-carboxylate (841 mg, 2.37 mmol). The mixture was stirred at 80 °C for 3 h. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with saturated brine (20 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give *tert*-butyl 4-[4-[8-chloro-7-[2-methyl-3-(2-trimethylsilylethoxymethyl)benzimidazol-5-yl]oxy-quinoxalin-2-yl]pyrazol-1-yl]piperidine-1-carboxylate (2 g, crude) as a yellow oil. ¹H NMR (400 MHz, CD₃OD) δ 9.29 (d, *J* = 2.8 Hz, 1H), 8.76 (s, 1H), 8.48 (s, 1H), 7.74 (dd, *J* = 7.2, 8.8 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.48 (dd, *J* = 9.2, 11.2 Hz, 1H), 7.38 (dd, *J* = 2.0, 13.8 Hz, 1H), 7.23 - 7.16 (m, 1H), 5.79 - 5.64 (m, 2H), 4.38 (d, *J* = 13.2 Hz, 2H), 3.80 - 3.56 (m, 4H), 2.29 - 2.08 (m, 4H), 1.62 - 1.54 (m, 9H), 1.08 - 0.81 (m, 2H), 0.13 - 0.08 (m, 9H); *m/z* ES+ [M+H]⁺ 690.4.

[0788] **Step 3.** 2-[[6-[5-chloro-3-[1-(4-piperidyl)pyrazol-4-yl]quinoxalin-6-yl]oxy-2-methylbenzimidazol-1-yl]methoxy]ethyl-trimethyl-silane

[0789] To a solution of *tert*-butyl 4-[4-[8-chloro-7-[2-methyl-3-(2-trimethylsilylethoxymethyl)benzimidazol-5-yl]oxy-quinoxalin-2-yl]pyrazol-1-yl]piperidine-1-carboxylate (2 g, 2.90 mmol) in dichloromethane (20 mL) was added trifluoroacetic acid (4 mL). The mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by reversed-phase HPLC (mobile phase: [water (0.225% formic acid)-acetonitrile]; (B%: 50%-55%, 10 min) to give 2-[[6-[5-chloro-3-[1-(4-piperidyl)pyrazol-4-yl]quinoxalin-6-yl]oxy-2-methylbenzimidazol-1-yl]methoxy]ethyl-trimethyl-silane (700 mg, 1.19 mmol, 41%) as a yellow solid. ¹H NMR (400 MHz, CD₃OD): δ = 9.28 (s, 1H), 8.73 (s, 1H), 8.46 (s, 1H), 8.08 - 7.93 (m, 1H), 7.77 - 7.70 (m, 1H), 7.54 - 7.43 (m, 1H), 7.40 - 7.38 (m, 1H), 7.32 - 7.08 (m, 1H), 5.82 - 5.59 (m, 2H), 4.62 - 4.45 (m, 1H), 3.83 - 3.60 (m, 2H), 3.40 - 3.17 (m, 2H), 2.99 - 2.86 (m, 2H), 2.77 (d, *J* = 6.4 Hz, 3H), 2.37 - 2.26 (m, 2H), 1.09 - 0.83 (m, 2H), 0.08 (s, 9H); *m/z* ES+ [M+H]⁺ 590.1.

Intermediate 2: 2-(1-(Azetidin-3-yl)-1H-pyrazol-4-yl)-8-chloro-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxaline



[0790] **Step 1.** *tert*-Butyl 3-(4-(8-chloro-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxalin-2-yl)-1H-pyrazol-1-yl)azetidine-1-carboxylate

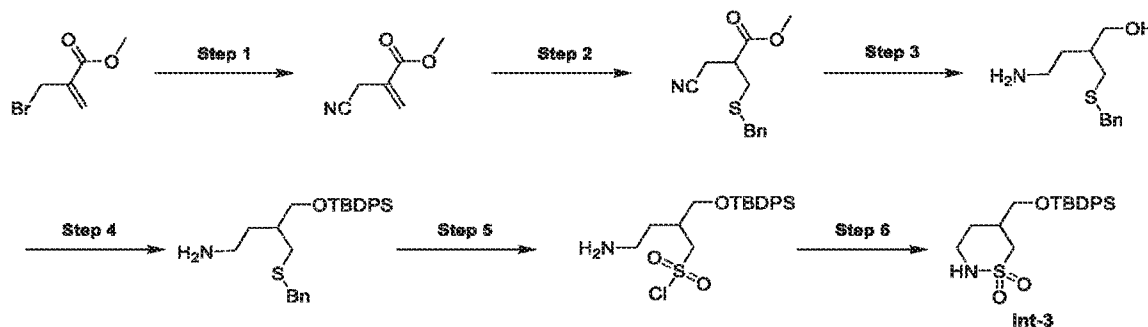
[0791] To a solution of 2-[[6-[5-chloro-3-(1H-pyrazol-4-yl)quinoxalin-6-yl]oxy-2-methylbenzimidazol-1-yl]methoxy]ethyl-trimethyl-silane (2 g, 3.94 mmol), *tert*-butyl 3-iodoazetidine-1-carboxylate (1.67 g, 5.92 mmol) in *N,N*-dimethyl formamide (20 mL) was added potassium carbonate (1.09 g, 7.89 mmol). The mixture was stirred at 60 °C for 32 h. The reaction mixture was quenched by addition water (200 mL) at 20 °C, and then diluted with ethyl acetate (200 mL) and extracted with ethyl acetate (200 mL x 3). The combined organic layers were washed with water (100 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate=10/1 to 1/1) to give *tert*-butyl 3-[4-[8-chloro-7-[2-methyl-3-(2-trimethylsilylethoxymethyl)benzimidazol-5-yl]oxy-quinoxalin-2-yl]pyrazol-1-yl]azetidine-1-carboxylate (2.70 g, 3.67 mmol, 93%) as a yellow solid. *m/z* ES+ [M+H]⁺ 662.4.

[0792] **Step 2.** 2-(1-(azetidin-3-yl)-1H-pyrazol-4-yl)-8-chloro-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxaline

[0793] A solution of *tert*-butyl 3-[4-[8-chloro-7-[2-methyl-3-(2-trimethylsilylethoxymethyl)benzimidazol-5-yl]oxy-quinoxalin-2-yl]pyrazol-1-yl]azetidine-1-carboxylate (2.5 g, 3.77 mmol) in trifluoroacetic acid (2 mL) and dichloromethane (20 mL) was stirred at 25 °C for 16 h. The reaction mixture was quenched with saturated sodium bicarbonate (50 mL) at 25 °C, and then diluted with dichloromethane (50 mL) and extracted with dichloromethane (50 mL x 3). The combined organic layers were washed with water (20 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 2-(1-(azetidin-3-yl)-1H-pyrazol-4-yl)-8-chloro-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxaline (2.0 g, 2.49 mmol, 66%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.48 - 9.37 (m, 1H), 9.27 - 9.01 (m, 1H), 8.86 (s, 1H), 8.60 (s, 1H), 8.07 (d, *J* = 9.2 Hz, 1H), 7.84 (d, *J* = 9.2 Hz, 1H), 7.56 - 7.48 (m, 2H), 7.31 (dd, *J* = 2.4, 8.8 Hz,

1H), 5.66 - 5.49 (m, 1H), 4.70 (s, 1H), 4.60 - 4.39 (m, 4H), 4.02 (q, $J = 7.2$ Hz, 2H), 1.98 (s, 2H); m/z ES+ $[M+H]^+$ 562.4.

Intermediate 3: 5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-1,2-thiazinane 1,1-dioxide



[0794] **Step 1.** Methyl 2-(cyanomethyl)acrylate

[0795] To a solution of methyl methyl 2-(bromomethyl)acrylate (23.0 g, 128 mmol), trimethylsilylformonitrile (12.7 g, 128 mmol) in acetonitrile (500 mL) was added tetrabutylammonium fluoride (1 M in THF, 128.48 mL) dropwise at 25 °C, the mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate=3/1) to give methyl 2-(cyanomethyl)acrylate (13.0 g, 103 mmol, 80%) as a colourless oil. ^1H NMR (400 MHz, CDCl_3) δ 6.40 (d, $J = 0.8$ Hz, 1H), 6.01 (s, 1H), 3.75 (d, $J = 0.8$ Hz, 3H), 3.35 (s, 2H).

[0796] **Step 2.** Methyl 3-(benzylthio)-2-(cyanomethyl)propanoate

[0797] To a solution of methyl 2-(cyanomethyl)acrylate (6.50 g, 51.9 mmol) in tetrahydrofuran (80 mL) was added triethylamine (15.7 g, 155 mmol) and phenylmethanethiol (7.74 g, 62.3 mmol), the mixture was stirred at 20 °C for 1 h. The reaction mixture was diluted with water (250 mL) and extracted with ethyl acetate (3 $\times$ 150 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether:ethyl acetate=30:1 to 15:1) to give methyl 3-(benzylthio)-2-(cyanomethyl)propanoate (22.0 g, 88.2 mmol, 85%) as a colorless oil.

[0798] **Step 3.** 4-Amino-2-((benzylthio)methyl)butan-1-ol

[0799] To a solution of methyl 3-(benzylthio)-2-(cyanomethyl)propanoate (10.0 g, 40.1 mmol) in tetrahydrofuran (200 mL) was carefully added lithium aluminum hydride (4.57 g, 120 mmol) portion-wise at 0 °C. The mixture was stirred at 25 °C for 1 h. The mixture was carefully quenched with sodium sulfate decahydride (10 g) and water (5 mL). The resulting precipitate was filtered.

The filtrate was dried over sodium sulfate, filtered and concentrated *in vacuo* to give 4-amino-2-((benzylthio)methyl)butan-1-ol (9 g, crude) as a yellow oil.

[0800] **Step 4.** 4-(Benzylthio)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)butan-1-amine

[0801] A solution of 4-amino-2-((benzylthio)methyl)butan-1-ol (7 g, 31.0 mmol), *tert*-butylchlorodimethylsilane (8.54 g, 31.0 mmol), imidazole (3.17 g, 46.5 mmol) in dichloromethane (50 mL) was stirred at 25 °C for 16 h. The mixture was poured into water (20 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layers were dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by reversed-phase HPLC (0.1% formic acid condition) to give 4-(benzylthio)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)butan-1-amine (6.60 g, 14.2 mmol, 45%) as a yellow oil. *m/z* ES+ [M+H]⁺ 464.2.

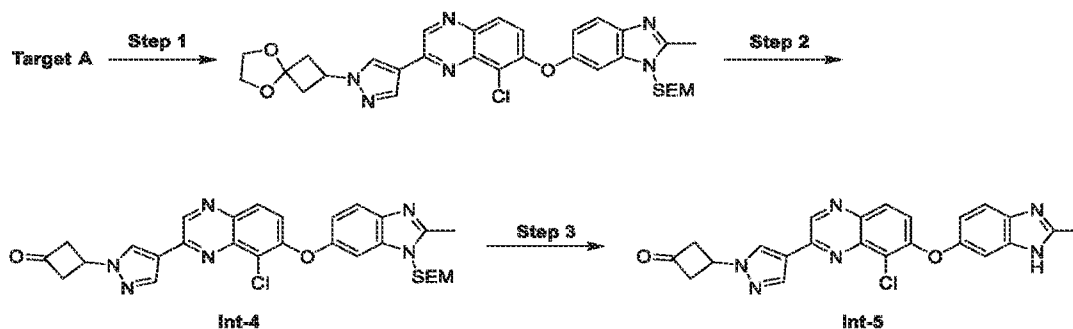
[0802] **Step 5.** 4-Amino-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)butane-1-sulfonyl chloride

[0803] To a solution of 4-(benzylthio)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)butan-1-amine (3 g, 6.47 mmol) in acetic acid (30 mL) and water (9 mL) was added *N*-chlorosuccinimide (2.59 g, 19.4 mmol). The reaction was stirred at 25 °C for 0.5 h. The mixture was concentrated under reduced pressure to give 4-amino-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)butane-1-sulfonyl chloride (2.80 g, crude) as a yellow oil.

[0804] **Step 6.** Methyl 3-(benzylthio)-2-(cyanomethyl)propanoate

[0805] A solution of 4-amino-2-[[*tert*-butyl(diphenyl)silyl]oxymethyl]butane-1-sulfonyl chloride (2.8 g, 6.36 mmol) and triethylamine (1.93 g, 19.0 mmol) in dichloromethane (30 mL) was stirred at 25 °C for 16 h. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate=1/0 to 3/1) to give 5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-1,2-thiazinane 1,1-dioxide (1 g, 2.48 mmol, 38%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, *J* = 7.2 Hz, 4H), 7.56 - 7.36 (m, 7H), 3.73 - 3.26 (m, 4H), 2.82 (t, *J* = 12.8 Hz, 1H), 2.52 (s, 1H), 1.55 - 1.38 (m, 2H), 1.13 - 1.04 (m, 9H).

Intermediate 4 and 5: 3-(4-(8-Chloro-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxalin-2-yl)-1H-pyrazol-1-yl)cyclobutan-1-one and 3-(4-(8-chloro-7-((2-methyl-1H-benzo[d]imidazol-6-yl)oxy)quinoxalin-2-yl)-1H-pyrazol-1-yl)cyclobutan-1-one



[0806] **Step 1.** 2-(1-(5,8-Dioxaspiro[3.4]octan-2-yl)-1H-pyrazol-4-yl)-8-chloro-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxaline

[0807] To a solution of 2-[[6-[5-chloro-3-(1H-pyrazol-4-yl)quinoxalin-6-yl]oxy-2-methylbenzimidazol-1-yl]methoxy]ethyl-trimethyl-silane (830 mg, 1.65 mmol) and 2-bromo-5,8-dioxaspiro[3.4]octane (350 mg, 1.80 mmol) in *N,N*-dimethyl formamide (9 mL) was added potassium carbonate (680 mg, 4.90 mmol) and potassium iodide (27.0 mg, 165 μ mol). The mixture was stirred at 100 °C for 12 h. The reaction mixture was diluted with **water** (30 mL) and extracted with ethyl acetate (100 mL $\times$ 3). The combined organic layers were washed with brine (25 mL $\times$ 2), dried over **anhydrous sodium sulfate**, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (dichloromethane:methanol= 100:1 to 10:1) to give 2-(1-(5,8-dioxaspiro[3.4]octan-2-yl)-1H-pyrazol-4-yl)-8-chloro-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxaline (680 mg, 1.05 mmol, 64%) as a yellow solid. *m/z* ES+ [M+H]⁺ 619.1.

[0808] **Step 2.** 3-[4-[8-Chloro-7-[2-methyl-3-(2-trimethylsilylethoxymethyl)benzimidazol-5-yl]oxy-quinoxalin-2-yl]pyrazol-1-yl]cyclobutanone

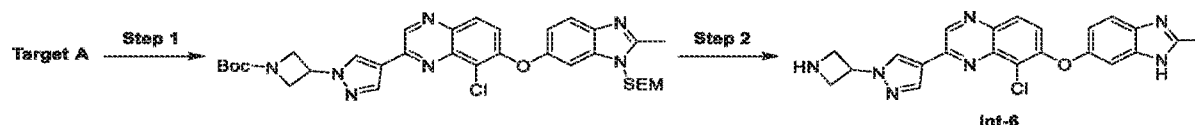
[0809] To a solution of 2-[[6-[5-chloro-3-[1-(5,8-dioxaspiro[3.4]octan-2-yl)pyrazol-4-yl]quinoxalin-6-yl]oxy-2-methyl-benzimidazol-1-yl]methoxy]ethyl-trimethyl-silane (680 mg, 1.10 mmol) in dichloromethane (6.8 mL) and water (0.5 mL) was added formic acid (8.30 g, 180 mmol). The mixture was stirred at 40 °C for 12 h. The reaction mixture was concentrated under reduced pressure and then diluted with water (20 mL). The mixture was adjusted to pH = 8~9 with saturated sodium bicarbonate (30 mL), and then extracted with ethyl acetate (100 mL $\times$ 3). The combined organic layers were washed with brine (25 mL $\times$ 2), dried over **anhydrous sodium sulfate**, filtered and concentrated under reduced pressure to give 3-[4-[8-chloro-7-[2-methyl-3-(2-trimethylsilylethoxymethyl)benzimidazol-5-yl]oxy-quinoxalin-2-yl]pyrazol-1-yl]cyclobutanone

(550 mg, crude) as a white solid. m/z ES+ $[M+H]^+$ 575.3.

[0810] **Step 3.** 3-[4-[8-Chloro-7-[(2-methyl-3H-benzimidazol-5-yl)oxy]quinoxalin-2-yl]pyrazol-1-yl]cyclobutanone

[0811] A solution of 3-[4-[8-chloro-7-[2-methyl-3-(2-trimethylsilylethoxymethyl)benzimidazol-5-yl]oxy-quinoxalin-2-yl]pyrazol-1-yl]cyclobutanone (350 mg, 0.61 mmol) in trifluoroacetic acid (3.5 mL) was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure and then diluted with water (30 mL). The mixture was adjusted to pH = 9 with sat. sodium carbonate solution and then extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give 3-[4-[8-chloro-7-[(2-methyl-3H-benzimidazol-5-yl)oxy]quinoxalin-2-yl]pyrazol-1-yl]cyclobutanone (300 mg, crude) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ = 9.33 (s, 1H), 8.95 (s, 1H), 8.45 (s, 1H), 7.96 (d, J = 9.2 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.33 (d, J = 9.2 Hz, 1H), 7.23 (d, J = 2.0 Hz, 1H), 6.96 (dd, J = 2.4, 8.8 Hz, 1H), 5.41 - 5.31 (m, 1H), 3.70 - 3.64 (m, 4H), 2.50 (s, 3H); m/z ES+ $[M+H]^+$ 445.0.

Intermediate 6: 2-(1-(Azetidin-3-yl)-1H-pyrazol-4-yl)-8-chloro-7-((2-methyl-1H-benzo[d]imidazol-6-yl)oxy)quinoxaline



[0812] **Step 1.** *tert*-Butyl 3-[4-[8-chloro-7-[2-methyl-3-(2-trimethylsilylethoxymethyl)benzimidazol-5-yl]oxy-quinoxalin-2-yl]pyrazol-1-yl]azetidine-1-carboxylate

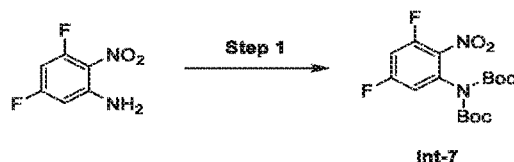
[0813] To a solution of 2-[[6-[5-chloro-3-(1H-pyrazol-4-yl)quinoxalin-6-yl]oxy-2-methylbenzimidazol-1-yl]methoxy]ethyl-trimethyl-silane (1 g, 1.97 mmol) in *N,N*-dimethylformamide (15 mL) was added cesium carbonate (1.29 g, 3.94 mmol) and *tert*-butyl 3-iodoazetidine-1-carboxylate (614 mg, 2.17 mmol). The mixture was stirred at 50 °C for 12 h. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (40 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 150*40 mm*15um; mobile phase: [water (0.1% TFA)-acetonitrile]; (B%: 35%-65%, 11 min) to give *tert*-butyl 3-[4-[8-chloro-7-[2-methyl-3-(2-trimethylsilylethoxymethyl)benzimidazol-5-yl]oxy-quinoxalin-2-

yl]pyrazol-1-yl]azetidine-1-carboxylate (800 mg, 1.21 mmol, 61%) as a white solid. m/z ES+ $[M+1]^+$ 662.4.

[0814] **Step 2.** 2-[1-(Azetidin-3-yl)pyrazol-4-yl]-8-chloro-7-[(2-methyl-3H-benzimidazol-5-yl)oxy]quinoxaline

[0815] A mixture of *tert*-butyl 3-[4-[8-chloro-7-[2-methyl-3-(2-trimethylsilylethoxymethyl)benzimidazol-5-yl]oxy-quinoxalin-2-yl]pyrazol-1-yl]azetidine-1-carboxylate (790 mg, 1.19 mmol) in trifluoroacetic acid (3 mL) was stirred at 25 °C for 6 h. The reaction mixture was concentrated under reduced pressure to give 2-[1-(azetidin-3-yl)pyrazol-4-yl]-8-chloro-7-[(2-methyl-3H-benzimidazol-5-yl)oxy]quinoxaline (500 mg, crude, TFA salt) as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ = 9.37 (s, 1H), 9.26 (d, J = 6.4 Hz, 1H), 8.86 (s, 1H), 8.59 (s, 1H), 8.02 (d, J = 9.2 Hz, 1H), 7.72 - 7.63 (m, 1H), 7.42 (d, J = 9.2 Hz, 1H), 7.37 (d, J = 2.4 Hz, 1H), 7.15 - 7.09 (m, 1H), 5.64 - 5.54 (m, 1H), 4.54 - 4.39 (m, 4H), 2.64 (s, 3H); m/z ES+ $[M+1]^+$ 432.2.

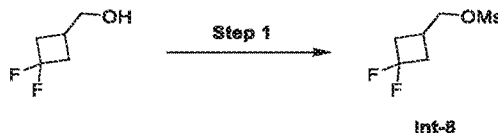
Intermediate 7: *tert*-Butyl *N*-*tert*-butoxycarbonyl-*N*-(3,5-difluoro-2-nitro-phenyl)carbamate



[0816] **Step 1.** *tert*-Butyl *N*-*tert*-butoxycarbonyl-*N*-(3, 5-difluoro-2-nitro-phenyl) carbamate

[0817] To a solution of 3, 5-difluoro-2-nitro-aniline (500 mg, 2.87 mmol) in dichloromethane (8 mL) was added 4-dimethylaminopyridine (35.1 mg, 287 μ mol), di-*tert*-butyl dicarbonate (1.25 g, 5.74 mmol) and triethylamine (872 mg, 8.62 mmol), the mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate=10/1 to 4/1) to give *tert*-butyl *N*-*tert*-butoxycarbonyl-*N*-(3,5-difluoro-2-nitro-phenyl)carbamate (800 mg, 1.34 mmol, 74%) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 7.35 - 6.98 (m, 1H), 6.94 - 6.82 (m, 1H), 1.44 (s, 18H).

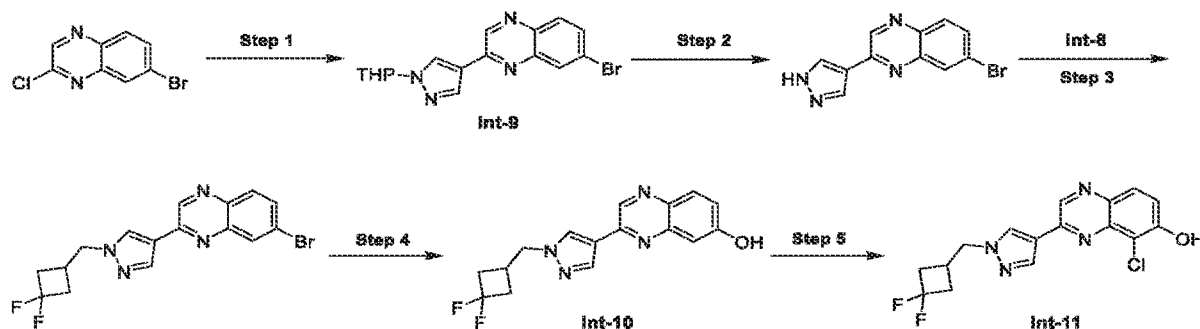
Intermediate 8: (3,3-Difluorocyclobutyl) methyl methanesulfonate



[0818] **Step 1.** (3,3-Difluorocyclobutyl)methylmethanesulfonate

[0819] To a solution of (3,3-difluorocyclobutyl)methanol (5 g, 41.0 mmol) and triethylamine (10.4 g, 102 mmol) in dichloromethane (60 mL) was added methanesulfonyl chloride (7.04 g, 61.4 mmol, 4.75 mL) at 0 °C, the mixture was stirred at 20 °C for 1 h. The reaction mixture was quenched with water (15 mL), and then extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give (3,3-difluorocyclobutyl)methylmethanesulfonate (9 g, crude) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 4.25 (d, *J* = 6.4 Hz, 2H), 3.03 (d, *J* = 1.2 Hz, 3H), 2.79 - 2.65 (m, 2H), 2.63 - 2.50 (m, 1H), 2.49 - 2.32 (m, 2H).

Intermediate 9, 10 and 11: 7-bromo-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)quinoxaline and 3-(1-((3,3-difluorocyclobutyl)methyl)-1H-pyrazol-4-yl)quinoxalin-6-ol and 5-chloro-3-(1-((3,3-difluorocyclobutyl)methyl)-1H-pyrazol-4-yl)quinoxalin-6-ol



[0820] **Step 1.** 7-Bromo-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)quinoxaline

[0821] To a mixture of 7-bromo-2-chloro-quinoxaline (3 g, 12.3 μmol) and 1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (3.61 g, 13.0 μmol) in dioxane (30 mL) and water (6 mL) was added potassium acetate (3.63 g, 37.0 μmol) and cyclopenta-2,4-dien-1-yl(diphenyl)phosphane;dichloropalladium;iron(II) (902 mg, 1.23 μmol). The mixture was stirred at 60 °C for 12 hours under nitrogen. On completion, the mixture was quenched with water (100 mL) and extracted with ethyl acetate (125 mL × 3). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated and the residue was purified by column chromatography (petroleum ether:ethyl acetate = 30:1 to 0:1) to give 7-bromo-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)quinoxaline (2.80 g, crude) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 9.06 (s, 1H), 8.41 (s, 1H), 8.29 - 8.20 (m, 2H), 7.92 (d, *J* = 8.8 Hz, 1H), 7.76 (dd, *J* = 2.0, 8.8 Hz, 1H), 5.54 - 5.45 (m, 1H), 4.21 - 4.08 (m, 1H), 3.83 - 3.72 (m, 1H), 2.23 - 2.15 (m, 2H), 2.12 - 2.06 (m, 1H), 1.76 - 1.66 (m, 3H).

[0822] **Step 2.** 7-Bromo-2-(1*H*-pyrazol-4-yl)quinoxaline

[0823] To a solution of 7-bromo-2-(1-tetrahydropyran-2-ylpyrazol-4-yl)quinoxaline (5.20 g, 14.5 mmol) in dichloromethane (60 mL) was added trifluoroacetic acid (20 mL), the mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with saturated sodium bicarbonate solution (100 mL) and extracted with ethyl acetate (3 × 60 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to give 7-bromo-2-(1*H*-pyrazol-4-yl)quinoxaline (5 g, crude) as a black solid. *m/z* ES+ [M+H]⁺ 274.7.

[0824] **Step 3.** 7-Bromo-2-(1-((3,3-difluorocyclobutyl)methyl)-1*H*-pyrazol-4-yl)quinoxaline

[0825] To a solution of 7-bromo-2-(1*H*-pyrazol-4-yl)quinoxaline (2.30 g, 8.36 mmol) in *N,N*-dimethylformamide (40 mL) was added potassium carbonate (2.31 g, 16.7 mmol) and (3,3-difluorocyclobutyl)methyl methanesulfonate (1.67 g, 8.36 mmol), the mixture was stirred at 80 °C for 12 h. The reaction mixture was diluted with water (200 mL) and extracted with ethyl acetate (3 × 200 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate=5/1 to 1/1) to give a residue. The residue was triturated with petroleum ether/ethyl acetate (20:1, 40 mL) at 20 °C for 30 min to give 7-bromo-2-(1-((3,3-difluorocyclobutyl)methyl)-1*H*-pyrazol-4-yl)quinoxaline (800 mg, 2.11 mmol, 12%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.43 - 9.31 (m, 1H), 8.73 (s, 1H), 8.34 (s, 1H), 8.20 (d, *J* = 2.0 Hz, 1H), 7.99 (d, *J* = 8.8 Hz, 1H), 7.88 (dd, *J* = 2.0, 8.8 Hz, 1H), 4.37 (d, *J* = 6.0 Hz, 2H), 3.30 (s, 1H), 2.77 - 2.57 (m, 4H); *m/z* ES+ [M+H]⁺ 378.8.

[0826] **Step 4.** 3-(1-((3,3-Difluorocyclobutyl) methyl)-1*H*-pyrazol-4-yl) quinoxalin-6-ol

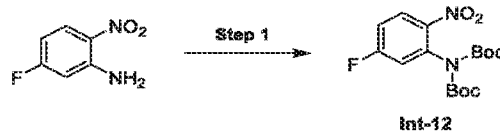
[0827] A mixture of 7-bromo-2-[1-[(3,3-difluorocyclobutyl)methyl]pyrazol-4-yl]quinoxaline (600 mg, 1.58 mmol), tris(dibenzylideneacetone)dipalladium (145mg, 158 μmol), di*tert*-butyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane (67.2 mg, 158 μmol) and potassium hydroxide (888 mg, 15.8 mmol) in dioxane (10 mL) and water (2 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 100 °C for 1 h under nitrogen atmosphere. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate=5/1 to 1/1) to give 3-(1-((3,3-difluorocyclobutyl)methyl)-1*H*-pyrazol-4-yl)quinoxalin-6-ol (400 mg, 1.26 mmol, 68%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.69 - 10.25 (m, 1H), 9.05 (s, 1H), 8.66 (s, 1H), 8.28 (s, 1H), 7.86 (d, *J* = 9.2 Hz,

1H), 7.28 (dd, $J = 2.4, 9.2$ Hz, 1H), 7.18 (d, $J = 2.4$ Hz, 1H), 4.34 (d, $J = 5.6$ Hz, 2H), 2.75 - 2.56 (m, 4H), 2.47 (s, 1H); m/z ES+ $[M+H]^+$ 317.1.

[0828] **Step 5.** 5-Chloro-3-(1-((3,3-difluorocyclobutyl)methyl)-1H-pyrazol-4-yl)quinoxalin-6-ol

[0829] To a solution of 3-[1-((3,3-difluorocyclobutyl)methyl)] pyrazol-4-yl]quinoxalin-6-ol (400 mg, 1.26 mmol) in chloroform (5 mL) was added *N*-chlorosuccinimide (338 mg, 2.53 mmol), nickel chloride (164 mg, 1.26 mmol) and triethylamine (128 mg, 1.26 mmol). The mixture was stirred at 60 °C for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate=5/1 to 1/1) to give 5-chloro-3-(1-((3,3-difluorocyclobutyl)methyl)-1H-pyrazol-4-yl)quinoxalin-6-ol (500 mg, 1.43 mmol, 95%) as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ = 9.14 (s, 1H), 8.69 (s, 1H), 8.32 (s, 1H), 7.86 (d, $J = 9.2$ Hz, 1H), 7.48 (d, $J = 9.2$ Hz, 1H), 4.37 (d, $J = 6.0$ Hz, 2H), 3.16 (s, 1H), 2.77 - 2.59 (m, 4H); m/z ES+ $[M+H]^+$ 351.0.

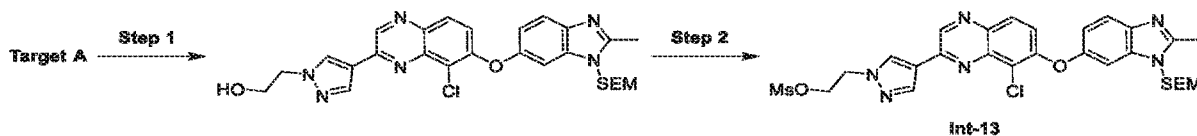
Intermediate 12: *tert*-Butyl *N*-*tert*-butoxycarbonyl-*N*-(5-fluoro-2-nitro-phenyl)carbamate



[0830] **Step 1.** *tert*-Butyl *N*-*tert*-butoxycarbonyl-*N*-(5-fluoro-2-nitro-phenyl)carbamate

[0831] To a solution of 5-fluoro-2-nitro-aniline (10 g, 64.1 μmol) in dichloromethane (100 mL) was added di-*tert*-butyl dicarbonate (28.0 g, 128 μmol), triethylamine (19.5 g, 192 μmol) and *N,N*-dimethylpyridin-4-amine (783 mg, 6.41 μmol). The mixture was stirred at 20 °C for 1 h. On completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 10/1 to 8/1) to give *tert*-butyl *N*-*tert*-butoxycarbonyl-*N*-(5-fluoro-2-nitro-phenyl)carbamate (20 g, 56.1 μmol , 88%) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ = 8.14 (dd, $J = 5.6, 9.2$ Hz, 1H), 7.23 - 7.14 (m, 1H), 7.05 (dd, $J = 2.8, 8.4$ Hz, 1H), 1.40 (s, 18H).

Intermediate 13: 2-(4-(8-chloro-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxalin-2-yl)-1H-pyrazol-1-yl)ethyl methanesulfonate



[0832] **Step 1.** 2-[4-[8-Chloro-7-[2-methyl-3-(2-trimethylsilylethoxymethyl)benzimidazol-5-

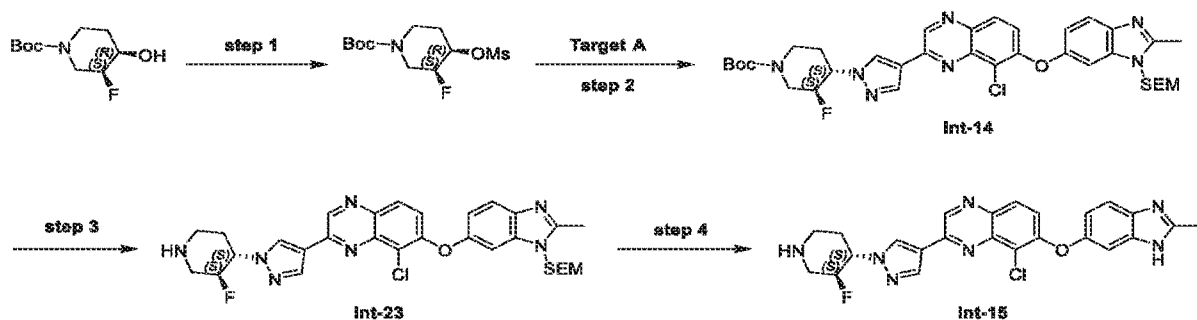
yl]oxy-quinoxalin-2-yl]pyrazol-1-yl]ethanol

[0833] To a mixture of 2-[[6-[5-chloro-3-(1H-pyrazol-4-yl)quinoxalin-6-yl]oxy-2-methylbenzimidazol-1-yl]methoxy]ethyl-trimethyl-silane (2 g, 3.94 mmol) and 2-bromoethanol (1.48 g, 11.83 mmol, 840 μ L) in *N,N*-dimethylformamide (15 mL) was added potassium carbonate (1.64 g, 11.83 mmol). The mixture was then heated to 80 °C and stirred for 16 h. On completion, the reaction mixture was quenched with water (150 mL) at 20 °C, and then extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with water (50 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (dichloromethane:methanol = 100:1 to 20:1) to give 2-[4-[8-chloro-7-[2-methyl-3-(2-trimethylsilylethoxymethyl) benzimidazol-5-yl]oxy-quinoxalin-2-yl]pyrazol-1-yl]ethanol (2.5 g, 3.86 mmol, 98%) as a yellow oil. *m/z* ES+ [M+H]⁺ 551.4.

[0834] **Step 2.** 2-[4-[8-Chloro-7-[2-methyl-3-(2-trimethylsilylethoxymethyl)benzimidazol-5-yl]oxy-quinoxalin-2-yl]pyrazol-1-yl]ethyl methanesulfonate

[0835] To a mixture of 2-[4-[8-chloro-7-[2-methyl-3-(2-trimethylsilylethoxymethyl)benzimidazol-5-yl]oxy-quinoxalin-2-yl]pyrazol-1-yl]ethanol (2.5 g, 4.54 mmol) in dichloromethane (30 mL) was added triethylamine (1.38 g, 13.61 mmol) and methanesulfonyl chloride (1.04 g, 9.07 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h. On completion, the reaction mixture was quenched with water (30 mL) at 0 °C, and then extracted with dichloromethane (30 mL x 3). The combined organic layers were washed with brine (30 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 2-[4-[8-chloro-7-[2-methyl-3-(2-trimethylsilylethoxymethyl)benzimidazol-5-yl]oxy-quinoxalin-2-yl]pyrazol-1-yl]ethyl methanesulfonate (2.6 g, 3.64 mmol, 80%) as a yellow oil. *m/z* ES+ [M+H]⁺ 629.4.

Intermediate 14, 23 and 15: *tert*-Butyl (3*S*,4*S*)-4-(4-(8-chloro-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[d]imidazol-6-yl)oxy)quinoxalin-2-yl)-1*H*-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate, 8-chloro-2-(1-((3*S*,4*S*)-3-fluoropiperidin-4-yl)-1*H*-pyrazol-4-yl)-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[d]imidazol-6-yl)oxy)quinoxaline and 8-chloro-2-(1-((3*S*,4*S*)-3-fluoropiperidin-4-yl)-1*H*-pyrazol-4-yl)-7-((2-methyl-1*H*-benzo[d]imidazol-6-yl)oxy)quinoxaline



[0836] **Step 1.** (3S,4R)-tert-Butyl 3-fluoro-4-((methylsulfonyl)oxy)piperidine-1-carboxylate

[0837] To a solution of (3S,4R)-tert-butyl 3-fluoro-4-hydroxypiperidine-1-carboxylate (500 mg, 2.28 mmol) in dichloromethane (5 mL) was added methanesulfonyl chloride (392 mg, 3.42 mmol) and triethylamine (692 mg, 6.84 mmol), the mixture was stirred at 0 °C for 0.5 h. The reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine (3 × 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give (3S,4R)-tert-butyl 3-fluoro-4-((methylsulfonyl)oxy)piperidine-1-carboxylate (720 mg, crude) as an orange solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 4.99 - 4.92 (m, 1H), 4.91 - 4.83 (m, 1H), 4.13 - 4.02 (m, 1H), 3.88 (s, 1H), 3.26 (s, 3H), 3.24 - 3.07 (m, 1H), 3.06 - 2.86 (m, 1H), 1.91 - 1.77 (m, 2H), 1.39 (s, 9H).

[0838] **Step 2.** (3S,4S)-tert-Butyl 4-(4-(8-chloro-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxalin-2-yl)-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate

[0839] To a solution of 8-Chloro-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)-2-(1H-pyrazol-4-yl)quinoxaline (600 mg, 1.18 mmol) in *N,N*-dimethylformamide (4 mL) was added potassium carbonate (491 mg, 3.55 mmol) and (3S,4R)-tert-butyl 3-fluoro-4-((methylsulfonyl)oxy)piperidine-1-carboxylate (704 mg, 2.37 mmol), the mixture was stirred at 100 °C for 12 h. The reaction mixture was quenched with water (0.5 mL) and concentrated under reduced pressure and the residue was purified by reversed-phase HPLC (0.1% formic acid condition, 85-90% acetonitrile, 5 min) to give (3S,4S)-tert-butyl 4-(4-(8-chloro-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxalin-2-yl)-1H-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate (600 mg, 849 μmol, 72%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.33 (d, *J* = 3.6 Hz, 1H), 8.87 (s, 1H), 8.44 (s, 1H), 8 - 7.95 (m, 1H), 7.70 - 7.57 (m, 1H), 7.47 - 7.29 (m, 2H), 7.10 - 6.99 (m, 1H), 5.65 - 5.52 (m, 2H),

5.01 - 4.80 (m, 1H), 4.78 - 4.70 (m, 1H), 4.41 - 4.27 (m, 1H), 4.10 - 3.96 (m, 1H), 3.57 - 3.46 (m, 2H), 3.10 - 2.93 (m, 2H), 2.57 (d, $J = 6.8$ Hz, 3H), 2.17 - 2 (m, 2H), 1.45 (s, 9H), 0.87 - 0.77 (m, 2H), -0.06 - -0.15 (m, 9H); m/z ES+ $[M+H]^+$ 708.3.

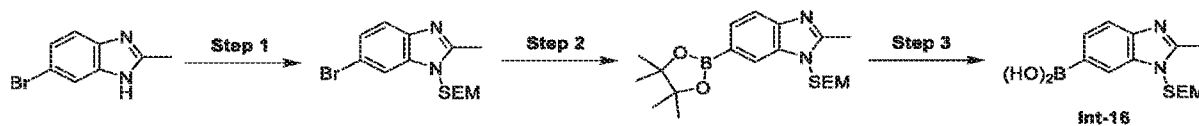
[0840] **Step 3.** 8-Chloro-2-(1-((3*S*,4*S*)-3-fluoropiperidin-4-yl)-1*H*-pyrazol-4-yl)-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-6-yl)oxy)quinoxaline

[0841] A solution of (3*S*,4*S*)-*tert*-butyl 4-(4-(8-chloro-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-6-yl)oxy)quinoxalin-2-yl)-1*H*-pyrazol-1-yl)-3-fluoropiperidine-1-carboxylate (300 mg, 424 μ mol) in dichloromethane (1 mL) and trifluoroacetic acid (0.1 mL) was stirred at 25 °C for 1.5 h. The reaction mixture was concentrated under reduced pressure to give 8-chloro-2-(1-((3*S*,4*S*)-3-fluoropiperidin-4-yl)-1*H*-pyrazol-4-yl)-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-6-yl)oxy)quinoxaline (250 mg, crude) as a yellow oil. ^1H NMR (400 MHz, DMSO-*d*₆) δ = 9.52 - 9.45 (m, 1H), 8.89 (s, 1H), 8.53 (s, 1H), 8.43 (s, 2H), 8.10 (d, $J = 9.2$ Hz, 1H), 7.83 - 7.72 (m, 1H), 7.60 - 7.42 (m, 2H), 7.25 - 7.12 (m, 1H), 5.81 - 5.61 (m, 2H), 4.77 - 4.66 (m, 1H), 4.17 (q, $J = 7.2$ Hz, 1H), 3.63 (d, $J = 7.6$ Hz, 3H), 3.52 - 3.43 (m, 3H), 3.17 - 3.05 (m, 2H), 2.71 (d, $J = 6.4$ Hz, 3H), 2.37 - 2.25 (m, 3H), 1.02 - 0.90 (m, 2H), 0.09 - 0.01 (m, 9H); m/z ES+ $[M+H]^+$ 608.3.

[0842] **Step 4.** 8-Chloro-2-(1-((3*S*,4*S*)-3-fluoropiperidin-4-yl)-1*H*-pyrazol-4-yl)-7-((2-methyl-1*H*-benzo[*d*]imidazol-6-yl)oxy)quinoxaline

[0843] To a solution of 8-chloro-2-(1-((3*S*,4*S*)-3-fluoropiperidin-4-yl)-1*H*-pyrazol-4-yl)-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-6-yl)oxy)quinoxaline (250 mg, 411 μ mol) in tetrahydrofuran (2 mL) was added pyridine hydrofluoride (407 mg, 4.11 mmol), the mixture was stirred at 80 °C for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by reversed-phase HPLC (0.1% formic acid condition, 30%-40% acetonitrile, 5 min) to give 8-chloro-2-(1-((3*S*,4*S*)-3-fluoropiperidin-4-yl)-1*H*-pyrazol-4-yl)-7-((2-methyl-1*H*-benzo[*d*]imidazol-6-yl)oxy)quinoxaline (120 mg, 251 μ mol, 55%) as an off-white solid. m/z ES+ $[M+H]^+$ 478.2.

Intermediate 16: (2-Methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-6-yl)boronic acid



[0844] **Step 1.** 6-Bromo-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazole

[0845] To a solution of 5-bromo-2-methyl-1H-benzimidazole (20 g, 94.8 mmol) in THF (400 mL) was added NaH (7.58 g, 189 mmol, 60% in mineral oil) portion-wise at 0 °C. The reaction was stirred at 0 °C for 0.5 h. Then (2-(chloromethoxy)ethyl)trimethylsilane (23.7 g, 142 mmol, 25 mL) was added dropwise at 0 °C. The mixture was stirred at 25 °C for 1.5 h. On completion, The reaction mixture was slowly poured into ice water (700 mL), and then extracted with ethyl acetate (300 mL x 4). The combined organic layers were washed with brine (100 mL x 2), dried over sodium sulfate, filtered and concentrated under reduced pressure to give 6-bromo-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazole (39 g, crude, mixture of regio-isomers) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.87 (s, 0.5H), 7.73 (s, 0.5H), 7.58 (d, *J* = 8.4 Hz, 0.5H), 7.48 (d, *J* = 8.4 Hz, 0.5H), 7.36 (dd, *J* = 8.4, 1.2 Hz, 0.5H), 7.34 (dd, *J* = 8.4, 1.2 Hz, 0.5H), 5.58 (s, 2H), 3.60 – 3.50 (m, 4H), 2.65 – 2.47 (m, 6H), 0.90 – 0.70 (m, 4H), 0.10 – -0.80 (m, 18H); *m/z* ES+ [M+H]⁺ 341.1.

[0846] **Step 2.** 2-Methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazole

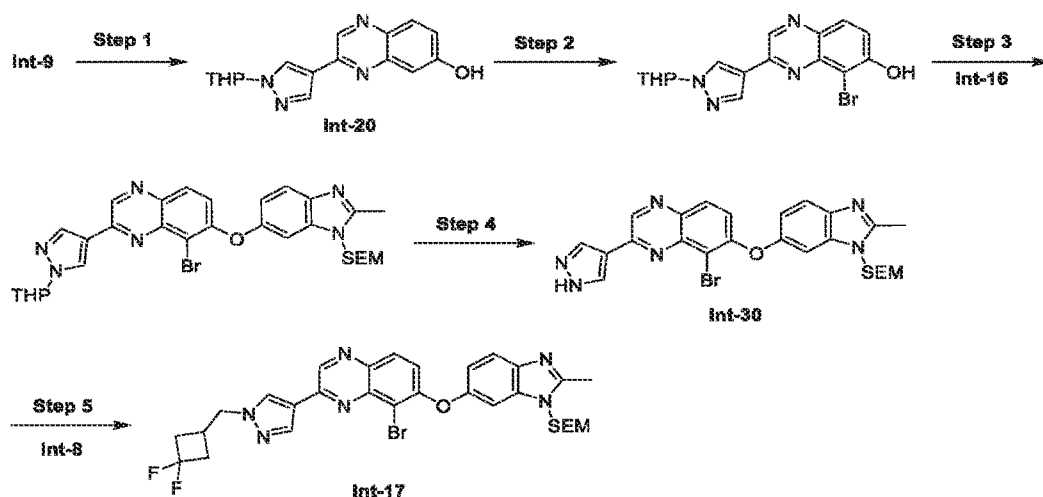
[0847] To a solution of 2-[(5-bromo-2-methyl-benzimidazol-1-yl)methoxy]ethyl-trimethyl-silane (39.29 g, 115 mmol, mixture of regio-isomers) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (87.69 g, 345 mmol) in dioxane (600 mL) was added potassium acetate (33.89 g, 345 mmol) and cyclopenta-2,4-dien-1-yl(diphenyl)phosphane;dichloropalladium;iron(II) (8.42 g, 11.51 mmol). The mixture was stirred at 60 °C for 12 h under nitrogen. On completion, the reaction mixture was concentrated under vacuum and the residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate=10/1 to 0/1) to give 2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazole (44.2 g, 114 mmol, 99%, mixture of regio-isomers) as a yellow solid. *m/z* ES+ [M+H]⁺ 389.3.

[0848] **Step 3.** (2-Methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)boronic acid

[0849] To a solution of trimethyl-[2-[[2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzimidazol-1-yl]methoxy]ethyl]silane (25 g, 64.37 mmol) in tetrahydrofuran (250 mL) and water (250 mL) was added sodium periodate (41.30 g, 193 mmol) and ammonium acetate (14.89 g, 193 mmol). The mixture was stirred at 30 °C for 12 h. On completion, the reaction mixture was

filtered and the filtrate was extracted with ethyl acetate (300 mL x 4). The combined organic layers were washed with sat. sodium sulfite (250 mL x 2), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by reversed-phase HPLC (column: I.D.100 mm*H400 mm, mobile phase: [water (10 mM ammonium bicarbonate)-acetonitrile]; (B%: 20-75%, 40min; 75%, 35 min) to give (2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)boronic acid (8.2 g, 26.78 mmol, 42%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.01 (d, *J* = 7.2 Hz, 1H), 7.94 (s, 1H), 7.92 (s, 1H), 7.67 – 7.60 (m, 1H), 7.52 (d, *J* = 8.4 Hz, 0.5H), 7.48 (d, *J* = 8.4 Hz, 0.5H), 5.56 (d, *J* = 4.0 Hz, 2H), 3.52 (q, *J* = 7.6 Hz, 2H), 2.56 (d, *J* = 4.4 Hz, 3H), 0.84 (dd, *J* = 14.0, 8.0 Hz, 2H), -0.09 (d, *J* = 2.0 Hz, 9H); *m/z* ES+ [M+H]⁺ 307.2.

Intermediate 17, 20 and 30: 8-Bromo-2-(1-((3,3-difluorocyclobutyl)methyl)-1H-pyrazol-4-yl)-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxaline, 3-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)quinoxalin-6-ol and 8-bromo-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)-2-(1H-pyrazol-4-yl)quinoxaline



[0850] **Step 1.** 3-(1-(Tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)quinoxalin-6-ol

[0851] To a solution of 7-bromo-2-(1-tetrahydropyran-2-ylpyrazol-4-yl)quinoxaline (4.90 g, 13.6 mmol) in dioxane (50 mL) and water (25 mL) was added tris(dibenzylideneacetone)dipalladium (1.25 g, 1.36 mmol), di-*tert*-butyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane (579 mg, 1.36 mmol) and potassium hydroxide (7.65 g, 136 mmol). The mixture was degassed and purged with nitrogen for 3 times, and then stirred at 100 °C for 3 h under nitrogen. The reaction mixture was

concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 10/1 to 1/1) to give 3-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)quinoxalin-6-ol (1.70 g, 5.39 mmol, 39%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.44 (s, 1H), 9.10 (s, 1H), 8.78 (s, 1H), 8.28 (s, 1H), 7.87 (d, *J* = 8.8 Hz, 1H), 7.29 (dd, *J* = 2.4, 9.2 Hz, 1H), 7.20 (d, *J* = 2.4 Hz, 1H), 5.50 (dd, *J* = 2.0, 9.6 Hz, 1H), 3.97 (d, *J* = 11.6 Hz, 1H), 3.72 - 3.62 (m, 1H), 2.22 - 2.10 (m, 1H), 2.03 - 1.92 (m, 2H), 1.77 - 1.64 (m, 1H), 1.58 (d, *J* = 3.6 Hz, 2H); *m/z* ES+ [M+H]⁺ 297.1.

[0852] **Step 2.** 5-Bromo-3-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)quinoxalin-6-ol

[0853] To a solution of 3-(1-(tetrahydropyran-2-yl)pyrazol-4-yl)quinoxalin-6-ol (1.70 g, 5.74 mmol) in chloroform (34 mL) was added *N*-bromosuccinimide (1.53 g, 8.61 mmol), dichloronickel (744 mg, 5.74 mmol) and triethylamine (581 mg, 5.74 mmol). The mixture was stirred at 60 °C for 2 h. The reaction mixture was cooled to 25 °C and filtered. The filtrate was washed with saturated sodium bicarbonate solution (2 × 50 mL), dried over sodium sulfate, filtered and concentrated to give 5-bromo-3-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)quinoxalin-6-ol (2.80 g, crude) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.13 (s, 1H), 8.79 (s, 1H), 8.31 (s, 1H), 7.87 (d, *J* = 9.2 Hz, 1H), 7.46 (d, *J* = 9.2 Hz, 1H), 5.54 (dd, *J* = 2.0, 9.6 Hz, 1H), 4.02 - 3.96 (m, 1H), 3.74 - 3.61 (m, 1H), 2.19 - 2.09 (m, 1H), 2.04 - 1.93 (m, 2H), 1.77 - 1.66 (m, 1H), 1.61 - 1.54 (m, 2H).

[0854] **Step 3.** 8-Bromo-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[d]imidazol-6-yl)oxy)-2-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)quinoxaline

[0855] To a solution of 5-bromo-3-(1-(tetrahydropyran-2-yl)pyrazol-4-yl)quinoxalin-6-ol (1.40 g, 3.73 mmol) and [2-methyl-1-(2-(trimethylsilyl)ethoxymethyl)benzimidazol-5-yl]boronic acid (1.22 g, 3.99 mmol) in 1,2-dimethoxyethane (30 mL) was added cesium carbonate (2.67 g, 8.21 mmol), 4Å MS (1.50 g) and copper(II) acetate (813 mg, 4.48 mmol). The mixture was stirred at 60 °C for 6 h under oxygen atmosphere. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 1/1 to 1/5) to give 8-bromo-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[d]imidazol-6-yl)oxy)-2-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)quinoxaline (670 mg, 980 μmol, 26%) as a yellow solid. *m/z* ES+ [M+H]⁺ 637.2.

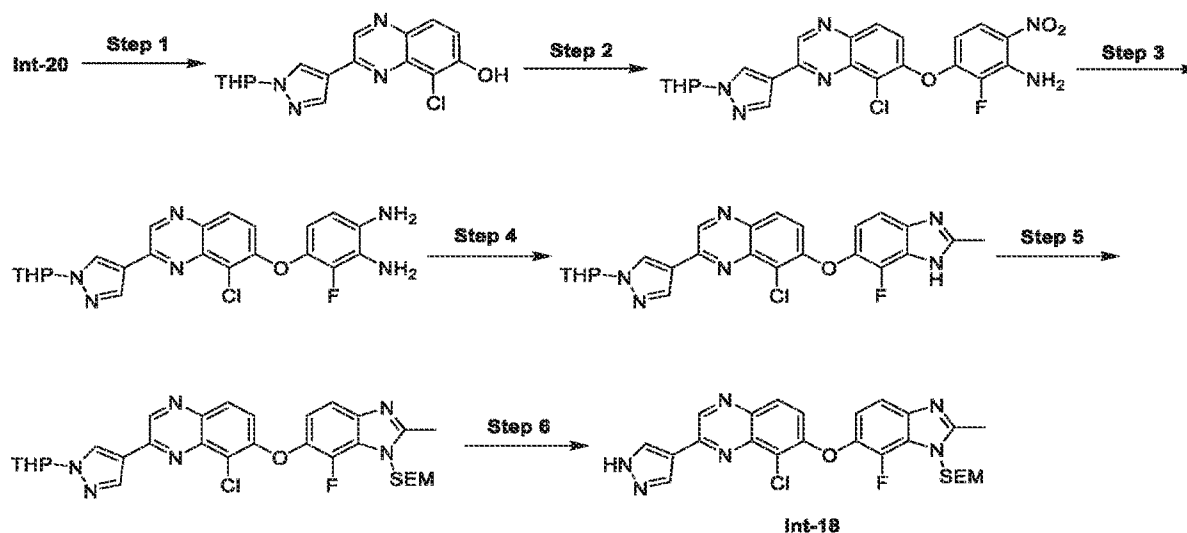
[0856] **Step 4.** 8-Bromo-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[d]imidazol-6-yl)oxy)-2-(1*H*-pyrazol-4-yl)quinoxaline

[0857] To a solution of 2-[[6-[5-bromo-3-(1-tetrahydropyran-2-yl)pyrazol-4-yl]quinoxalin-6-yl]oxy-2-methyl-benzimidazol-1-yl]methoxy]ethyl-trimethyl-silane (670 mg, 1.05 mmol) in methanol (7 mL) was added hydrochloric acid (1 M, 7 mL), the mixture was stirred at 25 °C for 12 h. The reaction mixture was diluted with saturated sodium bicarbonate solution (20 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 1/3 to 0/1) to give 8-bromo-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)-2-(1H-pyrazol-4-yl)quinoxaline (360 mg, 587 μ mol, 55%) as a yellow oil. m/z ES+ [M+H]⁺ 553.1.

[0858] **Step 5.** 8-Bromo-2-(1-((3,3-difluorocyclobutyl)methyl)-1H-pyrazol-4-yl)-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxaline

[0859] To a solution of 2-[[6-[5-bromo-3-(1H-pyrazol-4-yl)quinoxalin-6-yl]oxy-2-methyl-benzimidazol-1-yl]methoxy]ethyl-trimethyl-silane (290 mg, 526 μ mol) and (3,3-difluorocyclobutyl)methyl methanesulfonate (158 mg, 789 μ mol) in *N,N*-dimethylformamide (6 mL) was added potassium carbonate (218 mg, 1.58 mmol). The mixture was stirred at 80 °C for 3 h. The reaction mixture was poured into water (20 mL) and extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with brine (20 mL × 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 8-bromo-2-(1-((3,3-difluorocyclobutyl)methyl)-1H-pyrazol-4-yl)-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxaline (430 mg, crude) as a yellow solid. m/z ES+ [M+H]⁺ 657.2.

Intermediate 18: 8-Chloro-7-((7-fluoro-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)-2-(1H-pyrazol-4-yl)quinoxaline



[0860] **Step 1.** 5-Chloro-3-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)quinoxalin-6-ol

[0861] To a solution of 3-(1-tetrahydropyran-2-ylpyrazol-4-yl)quinoxalin-6-ol (4.50 g, 15.2 mmol) in chloroform (90 mL) was added 1-chloropyrrolidine-2,5-dione (4.06 g, 30.4 mmol), dichloronickel (1.97 g, 15.2 mmol) and diisopropylethylamine (2.94 g, 22.8 mmol). The mixture was stirred at 60 °C for 2 h. On completion, the reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 1/1 to 0/1) to give 2-chloro-3-(2-fluoro-5-methoxyphenoxy)-6-nitroaniline (7 g, 21.2 mmol, 70% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 11.05 (s, 1H), 9.19 (s, 1H), 8.80 (s, 1H), 8.32 (s, 1H), 7.87 (d, *J* = 9.2 Hz, 1H), 7.50 (d, *J* = 9.2 Hz, 1H), 5.53 (dd, *J* = 2.0, 9.6 Hz, 1H), 3.98 (d, *J* = 12.8 Hz, 1H), 3.72 - 3.64 (m, 1H), 2.21 - 2.09 (m, 1H), 2.04 - 1.98 (m, 2H), 1.77 - 1.66 (m, 1H), 1.61 - 1.54 (m, 2H); *m/z* ES+ [M+H]⁺ 331.0.

[0862] **Step 2.** 3-((5-Chloro-3-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)quinoxalin-6-yl)oxy)-2-fluoro-6-nitroaniline

[0863] To a solution of 5-chloro-3-(1-tetrahydropyran-2-ylpyrazol-4-yl)quinoxalin-6-ol (5.90 g, 17.8 mmol) and 2,3-difluoro-6-nitro-aniline (3.11 g, 17.8 mmol) in *N,N*-dimethylformamide (160 mL) was added potassium carbonate (4.93 g, 35.7 mmol). The mixture was stirred at 130 °C for 4 h. On completion, the reaction mixture was poured into water (400 mL) and extracted with ethyl acetate (200 mL × 3). The combined organic layers were washed with brine (200 mL × 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 10/1 to 0/1). The resulting

solid was triturated with petroleum ether/ethyl acetate (1/2, 30 mL) to give 3-chloro-4-(2-fluoro-5-methoxyphenoxy)benzene-1,2-diamine (6.59 g, 12.2 mmol, 69%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.44 (s, 1H), 8.90 (s, 1H), 8.38 (s, 1H), 8.09 (d, *J* = 9.2 Hz, 1H), 7.86 (dd, *J* = 1.6, 9.6 Hz, 1H), 7.69 (d, *J* = 9.2 Hz, 1H), 7.48 (s, 2H), 6.27 (dd, *J* = 7.6, 9.6 Hz, 1H), 5.56 (dd, *J* = 2.0, 9.6 Hz, 1H), 3.99 (d, *J* = 11.6 Hz, 1H), 3.74 - 3.66 (m, 1H), 2.21 - 2.10 (m, 1H), 2.04 - 1.93 (m, 2H), 1.78 - 1.67 (m, 1H), 1.62 - 1.55 (m, 2H); *m/z* ES+ [M+H]⁺ 485.1.

[0864] **Step 3.** 4-((5-Chloro-3-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)quinoxalin-6-yl)oxy)-3-fluorobenzene-1,2-diamine

[0865] To a solution of 3-[5-chloro-3-(1-tetrahydropyran-2-ylpyrazol-4-yl)quinoxalin-6-yl]oxy-2-fluoro-6-nitro-aniline (6.59 g, 13.6 mmol) in ethanol (80 mL) and water (40 mL) was added ammonium chloride (7.27 g, 136 mmol) and iron powder (3.80 g, 68.0 mmol). The mixture was stirred at 60 °C for 12 h. On completion, the reaction mixture was filtered and concentrated under reduced pressure. The residue was diluted in water (100 mL) and extracted with dichloromethane (150 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 3/1 to 1/2) to give 4-((5-chloro-3-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)quinoxalin-6-yl)oxy)-3-fluorobenzene-1,2-diamine (4.40 g, 9.38 mmol, 69%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.32 (s, 1H), 8.86 (s, 1H), 8.37 (s, 1H), 7.94 (d, *J* = 9.2 Hz, 1H), 7.23 (d, *J* = 9.2 Hz, 1H), 6.42 - 6.31 (m, 2H), 5.55 (dd, *J* = 2.4, 9.6 Hz, 1H), 4.84 (s, 2H), 4.72 (s, 2H), 4.02 - 3.95 (m, 1H), 3.74 - 3.66 (m, 1H), 2.21 - 2.11 (m, 1H), 2.06 - 1.97 (m, 2H), 1.78 - 1.67 (m, 1H), 1.62 - 1.55 (m, 2H); *m/z* ES+ [M+H]⁺ 455.1.

[0866] **Step 4.** 8-Chloro-7-((7-fluoro-2-methyl-1H-benzo[d]imidazol-6-yl)oxy)-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)quinoxaline

[0867] To a solution of 4-[5-chloro-3-(1-tetrahydropyran-2-ylpyrazol-4-yl)quinoxalin-6-yl]oxy-3-fluoro-benzene-1,2-diamine (4.40 g, 9.67 mmol) and 1,1,1-trimethoxyethane (5.81 g, 48.4 mmol) in methanol (100 mL) was added sulfamic acid (1.88 g, 19.4 mmol). The mixture was stirred at 25 °C for 1 h. On completion, the reaction mixture was quenched with saturated aqueous sodium bicarbonate (20 mL), then diluted with water (200 mL) and extracted with ethyl acetate (200 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 8-chloro-7-((7-fluoro-2-methyl-1H-benzo[d]imidazol-6-yl)oxy)-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)quinoxaline (4.80

g, crude) as a yellow solid. m/z ES⁺ [M+H]⁺ 479.0.

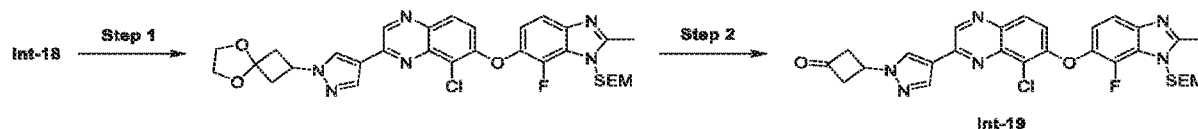
[0868] **Step 5.** 8-Chloro-7-((7-fluoro-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)quinoxaline

[0869] To a solution of 8-chloro-7-[(4-fluoro-2-methyl-3H-benzimidazol-5-yl)oxy]-2-(1-tetrahydropyran-2-yl)pyrazol-4-yl)quinoxaline (2.60 g, 5.43 mmol) in tetrahydrofuran (60 mL) was added sodium hydride (543 mg, 13.6 mmol, 60% in mineral oil) portion-wise at 0 °C. The mixture was then stirred at 0 °C for 0.5 h. Then a solution of (2-(chloromethoxy)ethyl)trimethylsilane (1.36 g, 8.14 mmol) in anhydrous tetrahydrofuran (5 mL) was added dropwise at 0 °C. The mixture was stirred at 25 °C for 1 h. On completion, the reaction mixture was poured into 50 mL of water and extracted with ethyl acetate (30 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 1/1 to 0/1) to give 8-chloro-7-((7-fluoro-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)quinoxaline (2.90 g, 4.76 mmol, 88%) as a yellow solid. m/z ES⁺ [M+H]⁺ 609.2.

[0870] **Step 6.** 8-Chloro-7-((7-fluoro-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)-2-(1H-pyrazol-4-yl)quinoxaline

[0871] To a solution of 2-[[[6-[5-chloro-3-(1-tetrahydropyran-2-yl)pyrazol-4-yl]quinoxalin-6-yl]oxy-7-fluoro-2-methyl-benzimidazol-1-yl]methoxy]ethyl-trimethyl-silane (2.90 g, 4.76 mmol) in methanol (29 mL) was added aqueous hydrochloric acid (1 N, 29 mL). The mixture was stirred at 25 °C for 12 h. The reaction mixture was basified with saturated aqueous sodium bicarbonate until pH = 8 and extracted with ethyl acetate (50 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 8-chloro-7-((7-fluoro-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)-2-(1H-pyrazol-4-yl)quinoxaline (2.60 g, crude) as a white solid. m/z ES⁺ [M+H]⁺ 525.2.

Intermediate 19: 3-(4-(8-Chloro-7-((7-fluoro-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxalin-2-yl)-1H-pyrazol-1-yl)cyclobutan-1-one



[0872] **Step 1.** 2-(1-(5,8-Dioxaspiro[3.4]octan-2-yl)-1H-pyrazol-4-yl)-8-chloro-7-((7-fluoro-2-

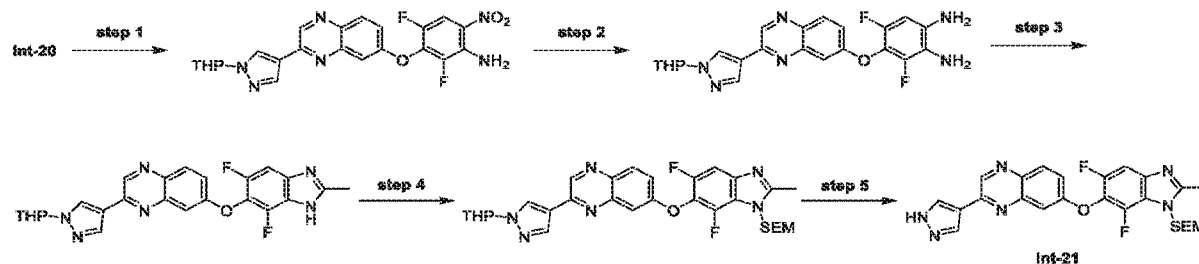
methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxaline

[0873] To a solution of 2-[[6-[5-chloro-3-(1H-pyrazol-4-yl)quinoxalin-6-yl]oxy-7-fluoro-2-methyl-benzimidazol-1-yl]methoxy]ethyl-trimethyl-silane (500 mg, 952 μ mol) and 2-bromo-5,8-dioxaspiro[3.4]octane (276 mg, 1.43 mmol) in *N,N*-dimethylformamide (8 mL) was added potassium carbonate (395 mg, 2.86 mmol) and potassium iodide (15.8 mg, 95.2 μ mol). The mixture was stirred at 100 °C for 24 h. On completion, the reaction mixture was poured into water (30 mL) and extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether / ethyl acetate = 5/1 to 1/3) to give 2-(1-(5,8-dioxaspiro[3.4]octan-2-yl)-1H-pyrazol-4-yl)-8-chloro-7-((7-fluoro-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxaline (460 mg, 686 μ mol, 72%) as a yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ 9.32 (d, *J* = 2.8 Hz, 1H), 8.82 (s, 1H), 8.42 (s, 1H), 7.95 (dd, *J* = 2.4, 9.2 Hz, 1H), 7.56 - 7.44 (m, 1H), 7.28 - 7.12 (m, 2H), 5.63 (d, *J* = 10.4 Hz, 2H), 4.89 (t, *J* = 8.0 Hz, 1H), 3.96 - 3.84 (m, 4H), 3.59 - 3.54 (m, 2H), 2.95 - 2.79 (m, 4H), 2.61 (d, *J* = 7.2 Hz, 3H), 0.87 - 0.80 (m, 2H), 0.07 (s, 4H), 0.13 (s, 5H); *m/z* ES+ [M+H]⁺ 637.2.

[0874] **Step 2.** 3-(4-(8-Chloro-7-((7-fluoro-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxalin-2-yl)-1H-pyrazol-1-yl)cyclobutanone

[0875] To a solution of 2-[[6-[5-chloro-3-[1-(5,8-dioxaspiro[3.4]octan-2-yl)pyrazol-4-yl]quinoxalin-6-yl]oxy-7-fluoro-2-methyl-benzimidazol-1-yl]methoxy]ethyl-trimethyl-silane (360 mg, 565 μ mol) in dichloromethane (1.8 mL) and water (0.5 mL) was added formic acid (4.39 g, 95.4 mmol, 3.6 mL). The mixture was stirred at 40 °C for 12 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with water (10 mL) and then adjusted to pH 8~9 with saturated aqueous sodium bicarbonate. Then the mixture was extracted with ethyl acetate (20 mL $\times$ 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether / ethyl acetate = 3/1 to 1/3) to give 3-(4-(8-chloro-7-((7-fluoro-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxalin-2-yl)-1H-pyrazol-1-yl)cyclobutanone (280 mg, 467 μ mol, 83%) as a yellow oil. *m/z* ES+ [M+H]⁺ 593.2.

Intermediate 21: 7-((5,7-Difluoro-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)-2-(1H-pyrazol-4-yl)quinoxaline



[0876] **Step 1.** 2,4-Difluoro-6-nitro-3-((3-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)quinoxalin-6-yl)oxy)aniline

[0877] To a solution of 3-(1-(tetrahydropyran-2-yl)pyrazol-4-yl)quinoxalin-6-ol (3 g, 10.1 mmol) in 1-methylpiperidin-2-one (30 mL) was added cesium carbonate (6.60 g, 20.3 mmol) and 2,3,4-trifluoro-6-nitro-aniline (1.94 g, 10.1 mmol). The mixture was stirred at 110 °C for 2 h. On completion, the reaction mixture was diluted with water (100 mL). The resulting precipitate was collected by filtration to give 2,4-difluoro-6-nitro-3-((3-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)quinoxalin-6-yl)oxy)aniline (3.9 g, crude) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.30 (s, 1H), 8.83 (s, 1H), 8.28 (s, 1H), 8.14 - 7.95 (m, 2H), 7.69 (dd, *J* = 2.8, 9.2 Hz, 1H), 7.49 (s, 2H), 7.39 (d, *J* = 2.8 Hz, 1H), 5.49 (dd, *J* = 2.4, 10.0 Hz, 1H), 3.95 (d, *J* = 11.6 Hz, 1H), 3.75 - 3.63 (m, 1H), 2.14 - 2.08 (m, 1H), 2.02 - 1.95 (m, 2H), 1.78 - 1.64 (m, 1H), 1.61 - 1.51 (m, 2H); *m/z* ES+ [M+H]⁺ 469.2.

[0878] **Step 2.** 3,5-Difluoro-4-((3-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)quinoxalin-6-yl)oxy)benzene-1,2-diamine

[0879] To a solution of 2,4-difluoro-6-nitro-3-((3-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)quinoxalin-6-yl)oxy)aniline (3.9 g, 8.33 mmol) in ethanol (60 mL) and water (6 mL) was added iron powder (2.32 g, 41.6 mmol) and ammonium chloride (4.45 g, 83.3 mmol). The mixture was stirred at 60 °C for 2 h. On completion, the reaction mixture was filtered. The filtrate was concentrated under reduced pressure to give 3,5-difluoro-4-((3-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)quinoxalin-6-yl)oxy)benzene-1,2-diamine (5 g, crude) as a yellow solid. *m/z* ES+ [M+H]⁺ 439.0.

[0880] **Step 3.** 7-((5,7-Difluoro-2-methyl-1H-benzo[d]imidazol-6-yl)oxy)-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)quinoxaline

[0881] To a solution of 3,5-difluoro-4-((3-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-

yl)quinoxalin-6-yl)oxy)benzene-1,2-diamine (5 g, 11.4 mmol) in methanol (80 mL) was added 1,1,1-trimethoxyethane (6.85 g, 57.0 mmol) and sulfamic acid (2.21 g, 22.8 mmol). The mixture was stirred at 20 °C for 2 h. On completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate/methanol = 1/0 to 10/1) to give 7-((5,7-difluoro-2-methyl-1H-benzo[d]imidazol-6-yl)oxy)-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)quinoxaline (3.9 g, 6.75 mmol, 59%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.96 (s, 1H), 8.43 - 7.93 (m, 3H), 7.71 - 7.40 (m, 2H), 7.11 (s, 1H), 5.43 (s, 1H), 4.06 (d, *J* = 10.4 Hz, 1H), 3.86 (s, 3H), 3.81 - 3.64 (m, 1H), 2.17 - 1.97 (m, 3H), 1.77 - 1.56 (m, 3H); *m/z* ES+ [M+H]⁺ 463.3.

[0882] **Step 4.** 7-((5,7-Difluoro-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)quinoxaline

[0883] To a solution of 7-((5,7-difluoro-2-methyl-1H-benzo[d]imidazol-6-yl)oxy)-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)quinoxaline (2.0 g, 4.32 mmol) in anhydrous tetrahydrofuran (60 mL) was added sodium hydride (1.04 g, 26.0 mmol, 60% in mineral oil) at 0 °C. The mixture was stirred at 0 °C for 2 h. Then (2-(chloromethoxy)ethyl)trimethylsilane (865 mg, 5.19 mmol) was added. The mixture was stirred at 20 °C for 14 h. On completion, the reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether / ethyl acetate = 1/1 to 0/1) to give 7-((5,7-difluoro-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)quinoxaline (600 mg, 810 μmol, 19%) as a yellow solid. *m/z* ES+ [M+18]⁺ 593.4.

[0884] **Step 5.** 7-((5,7-Difluoro-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)-2-(1H-pyrazol-4-yl)quinoxaline

[0885] To a solution of 7-((5,7-difluoro-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)quinoxaline (450 mg, 759 μmol) in methanol (5 mL) was added hydrochloric acid (1 M, 4.5 mL). The mixture was stirred at 20 °C for 2 h. On completion, the reaction mixture was concentrated under reduced pressure to give 7-((5,7-difluoro-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)-2-(1H-pyrazol-4-yl)quinoxaline (600 mg, crude) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 9.45 - 8.96 (m, 1H), 8.61 - 8.51 (m, 1H), 8.30 (s, 1H), 8.18 - 7.99 (m,

1H), 7.75 - 7.54 (m, 1H), 7.27 (s, 1H), 7.26 - 7.13 (m, 1H), 5.90 - 5.37 (m, 2H), 3.76 - 3.49 (m, 2H), 3.10 - 2.70 (m, 3H), 1.06 - 0.78 (m, 2H), 0.06 - -0.08 (m, 9H); m/z ES+ $[M+H]^+$ 509.3.

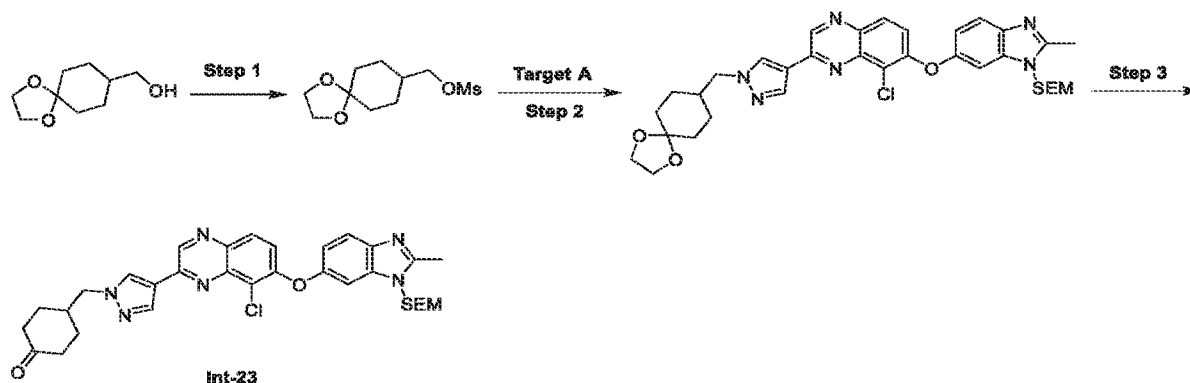
Intermediate 22: 4,4-Difluorocyclohexyl methanesulfonate



[0886] Step 1. 4,4-Difluorocyclohexyl methanesulfonate

[0887] To a solution of 4,4-difluorocyclohexanol (500 mg, 3.67 mmol) and triethylamine (743 mg, 7.35 mmol) in dichloromethane (1 mL) was added methanesulfonyl chloride (631 mg, 5.51 mmol). The mixture was stirred at 0 °C for 1 h. The mixture was poured into water (50 mL) and extracted with ethyl acetate (30 mL x 3). The organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate=1/0 to 3:1) to give 4,4-difluorocyclohexyl methanesulfonate (750 mg, 3.50 mmol, 95%) as a colourless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.95 - 4.92 (m, 1H), 3.07 (s, 3H), 2.13 - 1.87 (m, 8H).

Intermediate 23: 4-((4-(8-Chloro-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxalin-2-yl)-1H-pyrazol-1-yl)methyl)cyclohexan-1-one



[0888] Step 1. 1,4-Dioxaspiro[4.5]decan-8-ylmethyl methanesulfonate

[0889] To a solution of 1,4-dioxaspiro[4.5]decan-8-ylmethanol (500 mg, 2.90 mmol) and triethylamine (582 mg, 5.75 mmol) in dichloromethane (5 mL) was added methanesulfonyl chloride (444 mg, 3.88 mmol). The mixture was stirred at 0 °C for 1 h. The mixture was quenched with water (10 mL) and extracted with ethyl acetate (12 mL x 3). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated to give 1,4-dioxaspiro[4.5]decan-8-ylmethyl methanesulfonate (850 mg, crude) as a yellow oil. ^1H NMR (400

MHz, CDCl₃) δ 4.05 - 3.95 (m, 2H), 3.94 - 3.88 (s, 4H), 2.99 (s, 3H), 1.85 - 1.72 (m, 5H), 1.54 - 1.51 (m, 1H), 1.36 - 1.31 (m, 1H).

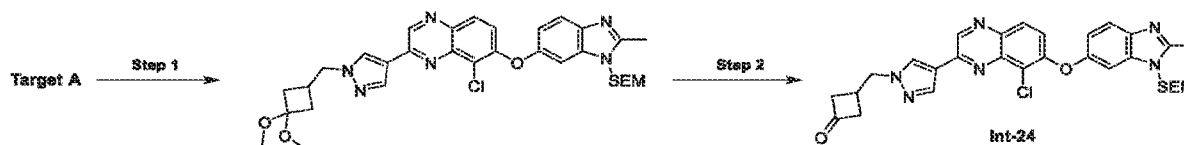
[0890] **Step 2.** 2-[[6-[5-Chloro-3-[1-(1,4-dioxaspiro[4.5]decan-8-ylmethyl)pyrazol-4-yl]quinoxalin-6-yl]oxy-2-methyl-benzimidazol-1-yl]methoxy]ethyl-trimethyl-silane

[0891] To a solution of 1,4-dioxaspiro[4.5]decan-8-ylmethyl methanesulfonate (370 mg, 1.48 mmol) and 2-[[6-[5-chloro-3-(1H-pyrazol-4-yl)quinoxalin-6-yl]oxy-2-methyl-benzimidazol-1-yl]methoxy]ethyl-trimethyl-silane (500 mg, 986 μ mol) in *N,N*-dimethylformamide (8 mL) was added potassium carbonate (300 mg, 2.17 mmol). The mixture was stirred at 80 °C for 12 h. The mixture was quenched with water (5 mL) and extracted with ethyl acetate (8 mL $\times$ 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give 2-[[6-[5-chloro-3-[1-(1,4-dioxaspiro[4.5]decan-8-ylmethyl)pyrazol-4-yl]quinoxalin-6-yl]oxy-2-methyl-benzimidazol-1-yl]methoxy]ethyl-trimethyl-silane (900 mg, crude) as a yellow oil. *m/z* ES+ [M+H]⁺ 661.3.

[0892] **Step 3.** 4-[[4-[8-Chloro-7-[2-methyl-3-(2-trimethylsilylethoxymethyl)benzimidazol-5-yl]oxy-quinoxalin-2-yl]pyrazol-1-yl]methyl]cyclohexanone

[0893] To a solution of 2-[[6-[5-chloro-3-[1-(1,4-dioxaspiro[4.5]decan-8-ylmethyl)pyrazol-4-yl]quinoxalin-6-yl]oxy-2-methyl-benzimidazol-1-yl]methoxy]ethyl-trimethyl-silane (900 mg, 1.36 mmol) in dichloromethane (4 mL) was added formic acid (4 mL). The mixture was stirred at 25 °C for 8 h. The mixture was concentrated under reduced pressure. The residue was dissolved in water (2 mL) and adjusted to pH = 7 with sat. sodium bicarbonate solution. Then the mixture was extracted with ethyl acetate (10 mL $\times$ 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give 4-[[4-[8-chloro-7-[2-methyl-3-(2-trimethylsilylethoxymethyl)benzimidazol-5-yl]oxy-quinoxalin-2-yl]pyrazol-1-yl]methyl]cyclohexanone (780 mg, crude) as a yellow oil. *m/z* ES+ [M+H]⁺ 617.3.

Intermediate 24: 3-((4-(8-Chloro-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxalin-2-yl)-1H-pyrazol-1-yl)methyl)cyclobutan-1-one



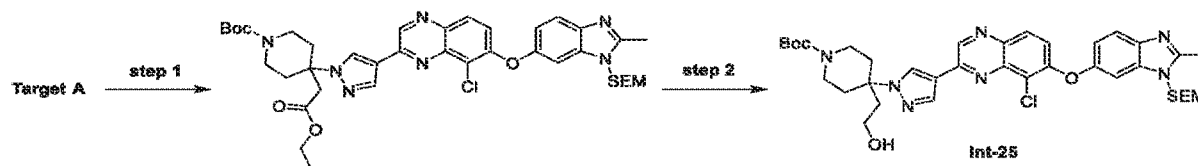
[0894] **Step 1.** 2-[[6-[5-Chloro-3-[1-[(3,3-dimethoxycyclobutyl)methyl]pyrazol-4-yl]quinoxalin-6-yl]oxy-2-methyl-benzimidazol-1-yl]methoxy]ethyl-trimethyl-silane

[0895] To a solution of 2-[[6-[5-chloro-3-(1*H*-pyrazol-4-yl)quinoxalin-6-yl]oxy-2-methyl-benzimidazol-1-yl]methoxy]ethyl-trimethyl-silane (150 mg, 296 μ mol) and (3,3-dimethoxycyclobutyl)methyl methanesulfonate (79.6 mg, 355 μ mol) in *N,N*-dimethylformamide (1.5 mL) was added potassium carbonate (123 mg, 887 μ mol) and potassium iodide (49.1 mg, 296 μ mol), the mixture was stirred at 80 °C for 16 h. The reaction mixture was diluted with water (3 mL) and extracted with ethyl acetate (3 $\times$ 3 mL). The combined organic layers were washed with brine (3 $\times$ 3 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to give 2-[[6-[5-chloro-3-[1-[(3,3-dimethoxycyclobutyl)methyl]pyrazol-4-yl]quinoxalin-6-yl]oxy-2-methyl-benzimidazol-1-yl]methoxy]ethyl-trimethyl-silane (180 mg, crude) as a yellow oil. *m/z* ES+ [M+H]⁺ 635.3.

[0896] **Step 2.** 3-[[4-[8-Chloro-7-[2-methyl-3-(2-trimethylsilylethoxymethyl)benzimidazol-5-yl]oxy-quinoxalin-2-yl]pyrazol-1-yl]methyl]cyclobutanone

[0897] To a solution of 2-[[6-[5-chloro-3-[1-[(3,3-dimethoxycyclobutyl)methyl]pyrazol-4-yl]quinoxalin-6-yl]oxy-2-methyl-benzimidazol-1-yl]methoxy]ethyl-trimethyl-silane (180 mg, 283 μ mol) in dichloromethane (1 mL) was added formic acid (13.6 mg, 283 μ mol), the mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated *in vacuo*. The residue was washed with saturated sodium bicarbonate solution (3 mL) and then extracted with ethyl acetate (3 $\times$ 5 mL). The combined organic layers were washed with brine (3 $\times$ 5 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to give 3-[[4-[8-chloro-7-[2-methyl-3-(2-trimethylsilylethoxymethyl)benzimidazol-5-yl]oxy-quinoxalin-2-yl]pyrazol-1-yl]methyl]cyclobutanone (110 mg, crude) as a yellow gum. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.31 (d, *J* = 4.4 Hz, 1H), 8.77 (s, 1H), 8.38 (s, 1H), 7.98 - 7.93 (m, 2H), 7.70 - 7.56 (m, 1H), 7.48 - 7.26 (m, 2H), 7.11 - 6.96 (m, 1H), 5.75 - 5.30 (m, 2H), 4.49 (br d, *J* = 6.4 Hz, 2H), 3.58 - 3.45 (m, 2H), 3.14 (dt, *J* = 6.4, 11.8 Hz, 2H), 3.01 (br t, *J* = 4.8 Hz, 2H), 2.57 (br d, *J* = 6.4 Hz, 3H), 0.93 - 0.71 (m, 2H), -0.05 - -0.17 (m, 9H); *m/z* ES+ [M+H]⁺ 589.3.

Intermediate 25: *tert*-Butyl 4-(4-(8-chloro-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[d]imidazol-6-yl)oxy)quinoxalin-2-yl)-1*H*-pyrazol-1-yl)-4-(2-hydroxyethyl)piperidine-1-carboxylate



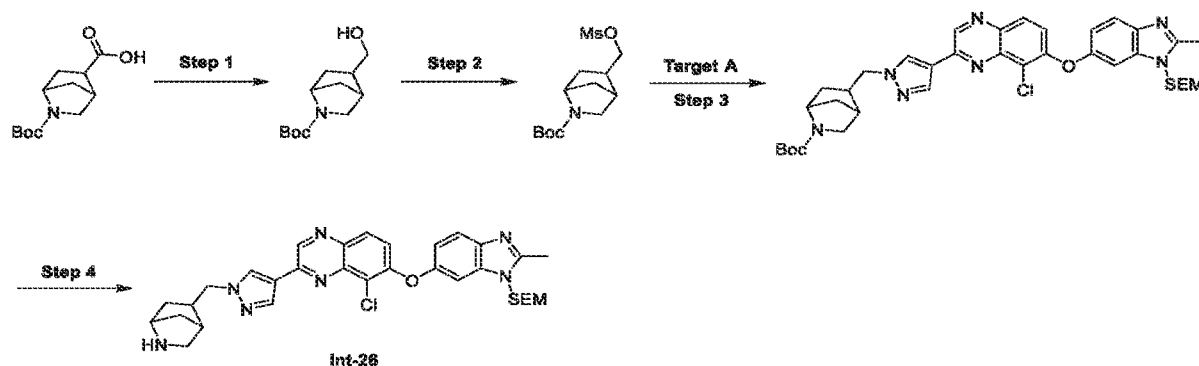
[0898] **Step 1.** *tert*-Butyl 4-(4-(8-chloro-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxalin-2-yl)-1H-pyrazol-1-yl)-4-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate

[0899] To a solution of 2-[[6-[5-chloro-3-(1H-pyrazol-4-yl)quinoxalin-6-yl]oxy-2-methylbenzimidazol-1-yl]methoxy]ethyl-trimethyl-silane (1 g, 1.97 mmol) in acetonitrile (10 mL) was added *tert*-butyl 4-(2-ethoxy-2-oxo-ethylidene)piperidine-1-carboxylate (595 mg, 2.21 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (330 mg, 2.17 mmol). The mixture was stirred at 60 °C for 24 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, dichloromethane/methanol = 1/0 to 80/1) to give *tert*-butyl 4-(4-(8-chloro-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxalin-2-yl)-1H-pyrazol-1-yl)-4-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (900 mg, 1.04 mmol, 53%) as a yellow solid. *m/z* ES+ [M+H]⁺ 776.5.

[0900] **Step 2.** *tert*-Butyl 4-(4-(8-chloro-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxalin-2-yl)-1H-pyrazol-1-yl)-4-(2-hydroxyethyl)piperidine-1-carboxylate

[0901] To a solution of *tert*-butyl 4-[4-[8-chloro-7-[2-methyl-3-(2-trimethylsilylethoxymethyl)benzimidazol-5-yl]oxy-quinoxalin-2-yl]pyrazol-1-yl]-4-(2-ethoxy-2-oxo-ethyl)piperidine-1-carboxylate (700 mg, 902 μmol) in tetrahydrofuran (14 mL) was added diisobutyl aluminium hydride (1 M in toluene, 2.7 mL) at 0 °C. The mixture was stirred at 0 °C for 1.5 h. The reaction mixture was carefully quenched with water (30 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, dichloromethane/methanol = 1/0 to 80/1) to give *tert*-butyl 4-(4-(8-chloro-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxalin-2-yl)-1H-pyrazol-1-yl)-4-(2-hydroxyethyl)piperidine-1-carboxylate (350 mg, 451 μmol, 50%) as a yellow solid. *m/z* ES+ [M+H]⁺ 734.1.

Intermediate 26: 2-(1-((2-Azabicyclo[2.2.1]heptan-5-yl)methyl)-1H-pyrazol-4-yl)-8-chloro-7-((2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-6-yl)oxy)quinoxaline



[0902] **Step 1.** *tert*-Butyl 5-(hydroxymethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate

[0903] To a solution of 2-(*tert*-butoxycarbonyl)-2-azabicyclo[2.2.1]heptane-5-carboxylic acid (500 mg, 2.07 mmol) in tetrahydrofuran (6 mL) was added borane-tetrahydrofuran complex (1 M, 12.4 mL) dropwise at 0 °C. The mixture was stirred at 25 °C for 12 h. On completion, the reaction mixture was carefully quenched with methanol (60 mL) at 25 °C, and then stirred at 60 °C for 30 min. The reaction was concentrated under reduced pressure. The residue was purified by prep-TLC (silica gel, petroleum ether/ethyl acetate = 1/1) to give *tert*-butyl 5-(hydroxymethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate (460 mg, 2.03 mmol, 78%) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 4.55 (t, *J* = 4.8 Hz, 1H), 3.95 (d, *J* = 8.8 Hz, 1H), 3.50 - 3.37 (m, 1H), 3.28 - 3.18 (m, 2H), 3.05 - 2.94 (m, 1H), 2.48 (s, 1H), 2.11 (dt, *J* = 5.6, 9.6 Hz, 1H), 1.76 - 1.59 (m, 2H), 1.52 - 1.42 (m, 1H), 1.39 (s, 9H), 1.01 - 0.89 (m, 1H).

[0904] **Step 2.** *tert*-Butyl 5-(((methylsulfonyl)oxy)methyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate

[0905] To a solution of *tert*-butyl 5-(hydroxymethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate (460 mg, 2.02 mmol) in dichloromethane (6 mL) was added triethylamine (614 mg, 6.07 mmol, 0.845 mL) and methanesulfonyl chloride (348 mg, 3.04 mmol, 0.235 mL). The mixture was stirred at 0 °C for 1 h. On completion, the reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (20 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give *tert*-butyl 5-(((methylsulfonyl)oxy)methyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 3
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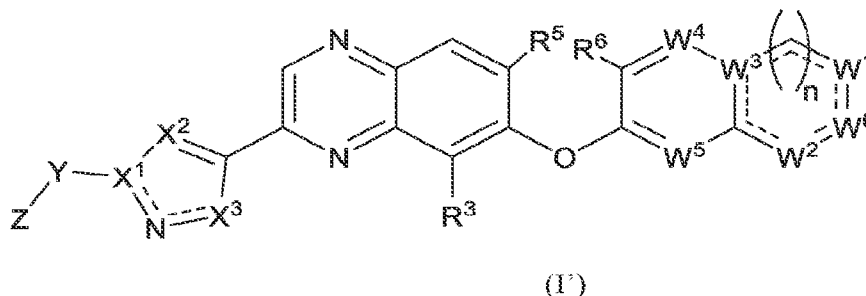
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NOTE POUR LE TOME / VOLUME NOTE:

Claims

1. A compound of Formula (I'):



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

each $\equiv$ independently represents a single bond or a double bond;

n is 0 or 1;

W^1 is $C(R^{W1})$ when connected to one double bond and one single bond, $N(R^{W1})$ when connected to two single bonds, or N when connected to one double bond and one single bond;

R^{W1} is H, C_1 - C_6 alkyl, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^2 is $C(R^{W2})$ when connected to one double bond and one single bond, $N(R^{W2})$ or O when connected to two single bonds, or N when connected to one double bond and one single bond;

R^{W2} is H, C_1 - C_6 alkyl, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^3 is C or N;

W^4 is $C(R^{W4})$ or N;

R^{W4} is H, halogen, cyano, C_1 - C_6 alkyl, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^5 is $C(R^{W5})$ or N;

R^{W5} is H, halogen, cyano, C_1 - C_6 alkyl, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^6 is $C(R^{W6})$ when connected to one double bond and one single bond, $N(R^{W6})$ when connected to two single bonds, or N when connected to one double bond and one single bond;

R^{W6} is H, halogen, cyano, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

X^1 is C or N;

X^2 is N, O, or $C(R^{X2})$;

R^{X2} is H or C_1 - C_6 alkyl;

X^3 is N, O, or $C(R^{X3})$;

R^{X3} is H or C₁-C₆ alkyl;

R^3 is H, halogen, cyano, NH₂, -NH(C₁-C₆ alkyl), -NHC(=O)(C₁-C₆ haloalkyl), -NHC(=O)O(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)H, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the -NH(C₁-C₆ alkyl), -NHC(=O)(C₁-C₆ haloalkyl), -NHC(=O)O(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)H, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, is optionally substituted with one or more R^{3a} ;

each R^{3a} independently is halogen, cyano, oxo, -OH, NH₂, -NH(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the NHC(=O)O(C₁-C₆ alkyl) is optionally substituted with one or more halogen;

R^5 is H, halogen, cyano, or C₁-C₆ alkyl;

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

Y is absent, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₁-C₆ alkoxy, wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₁-C₆ alkoxy is optionally substituted with one or more halogen, oxo, cyano, -OH, NH₂, -NH(C₁-C₆ alkyl)-OH, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy optionally substituted with -(C₁-C₆ alkyl)(C₆-C₁₀ aryl), or C₃-C₁₂ cycloalkyl;

Z is absent, H, C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl or 5- to 10-membered heteroaryl, is optionally substituted with one or more R^Z ;

each R^Z independently is oxo, halogen, cyano, -OH, =NR^{Za}, NH₂, NHR^{Za}, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(C₁-C₆ alkyl), -S(=O)(=NR^{Za})-(C₁-C₆ alkyl), -S(=O)₂-(C₁-C₆ alkyl), -S(=O)₂-(C₂-C₆ alkenyl), -C(=O)(3- to 12-membered heterocycloalkyl), -C(=O)NH(C₁-C₆ alkyl), -C(=O)NR^{Za}, -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), -C(=O)-(C₁-C₆ alkoxy), C₁-C₆ alkyl,

C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxyl, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, or 5- to 10-membered heteroaryl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxyl, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{Za};

each R^{Za} independently is H, oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxyl, C₃-C₁₂ cycloalkyl, or 3- to 12-membered heterocycloalkyl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxyl, C₃-C₁₂ cycloalkyl, or 3- to 12-membered heterocycloalkyl is optionally substituted with one or more R^{Zb}; and

each R^{Zb} independently is oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, or C₁-C₆ alkoxyl.

2. The compound of claim 1, wherein:

each ===== independently represents a single bond or a double bond;

n is 0;

W¹ is C(R^{W1}) when connected to one double bond and one single bond, N(R^{W1}) when connected to two single bonds, or N when connected to one double bond and one single bond;

R^{W1} is H;

W² is C(R^{W2}) when connected to one double bond and one single bond, N(R^{W2}) or O when connected to two single bonds, or N when connected to one double bond and one single bond;

R^{W2} is H;

W³ is N;

W⁴ is C(R^{W4});

R^{W4} is H or halogen;

W⁵ is C(R^{W5});

R^{W5} is H or halogen;

W^6 is $C(R^{W6})$ when connected to one double bond and one single bond, $N(R^{W6})$ when connected to two single bonds, or N when connected to one double bond and one single bond;

R^{W6} is H or C₁-C₆ alkyl;

X^1 is N;

X^2 is $C(R^{X2})$;

R^{X2} is H or C₁-C₆ alkyl;

X^3 is $C(R^{X3})$;

R^{X3} is H or C₁-C₆ alkyl;

R^3 is H, halogen, cyano, NH_2 , $NHC(=O)O(C_1-C_6 \text{ alkyl})$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)(C_1-C_6 \text{ alkyl})$, $-C(=O)O(C_1-C_6 \text{ alkyl})$, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, or 5- to 10-membered heteroaryl, wherein the $NHC(=O)O(C_1-C_6 \text{ alkyl})$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)(C_1-C_6 \text{ alkyl})$, $-C(=O)O(C_1-C_6 \text{ alkyl})$, C₁-C₆ alkyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, or 5- to 10-membered heteroaryl, is optionally substituted with one or more R^{3a} ;

each R^{3a} independently is halogen, oxo, $NHC(=O)O(C_1-C_6 \text{ alkyl})$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)(C_1-C_6 \text{ alkyl})$, $-C(=O)O(C_1-C_6 \text{ alkyl})$, C₁-C₆ alkyl, or C₂-C₆ alkenyl, wherein the $NHC(=O)O(C_1-C_6 \text{ alkyl})$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)(C_1-C_6 \text{ alkyl})$, $-C(=O)O(C_1-C_6 \text{ alkyl})$, C₁-C₆ alkyl, or C₂-C₆ alkenyl is optionally substituted with one or more halogen;

R^5 is H or C₁-C₆ alkyl;

R^6 is H or halogen;

Y is absent, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₁-C₆ alkoxy, wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₁-C₆ alkoxy is optionally substituted with one or more halogen, oxo, cyano, -OH, NH_2 , C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy optionally substituted with $-(C_1-C_6 \text{ alkyl})(C_6-C_{10} \text{ aryl})$, or C₃-C₁₂ cycloalkyl;

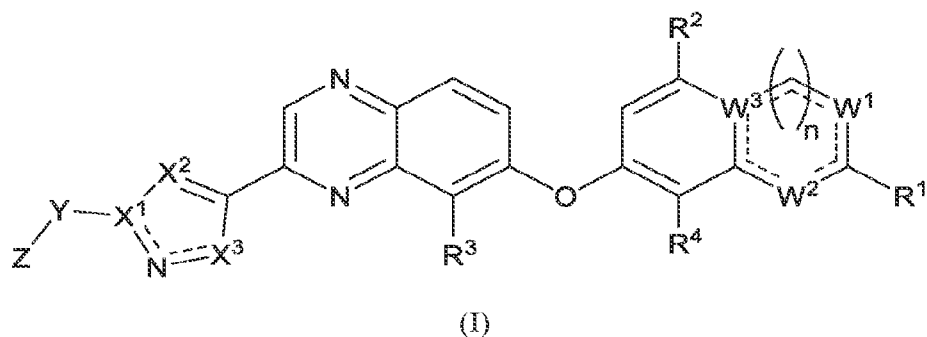
Z is absent, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl or 5- to 10-membered heteroaryl is optionally substituted with one or more R^Z ;

each R^Z independently is oxo, halogen, -OH, $=NR^{Za}$, NH_2 , NHR^{Za} , $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(C_1-C_6 \text{ alkyl})$, $-S(=O)(=NR^{Za})-(C_1-C_6 \text{ alkyl})$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-S(=O)_2-(C_2-C_6$

alkenyl), -C(=O)NH(C₁-C₆ alkyl), -C(=O)NR^{Za}, -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), -C(=O)-(C₁-C₆ alkoxy), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, or 5- to 10-membered heteroaryl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -S(=O)(=NR^{Za})-(C₁-C₆ alkyl), -S(=O)₂-(C₁-C₆ alkyl), -S(=O)₂-(C₂-C₆ alkenyl), -C(=O)NH(C₁-C₆ alkyl), -C(=O)NR^{Za}, -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), -C(=O)-(C₁-C₆ alkoxy), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{Za};

each R^{Za} independently is H, oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, or 3- to 12-membered heterocycloalkyl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₁₂ cycloalkyl, or 3- to 12-membered heterocycloalkyl is optionally substituted with one or more R^{Zb}, and
each R^{Zb} independently is oxo, halogen, -OH.

3. A compound of Formula (I):



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

each ----- independently represents a single bond or a double bond;

n is 0 or 1;

W¹ is C(R^{W1}) or N(R^{W1}) when connected to two single bonds, or C or N when connected to one double bond and one single bond;

R^{W1} is H, C₁-C₆ alkyl, or -S(=O)₂-(C₁-C₆ alkyl);

W^2 is $C(R^{W2})$ or $N(R^{W2})$ when connected to two single bonds, or C or N when connected to one double bond and one single bond;

R^{W2} is H, C₁-C₆ alkyl, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^3 is C or N;

X^1 is C or N;

X^2 is N, O, or $C(R^{X2})$;

R^{X2} is H or C₁-C₆ alkyl;

X^3 is N, O, or $C(R^{X3})$;

R^{X3} is H or C₁-C₆ alkyl;

R^1 is H, halogen, cyano, or C₁-C₆ alkyl;

R^2 is H, halogen, cyano, or C₁-C₆ alkyl;

R^3 is H, halogen, cyano, or C₁-C₆ alkyl;

R^4 is H, halogen, cyano, or C₁-C₆ alkyl;

Y is absent or C₁-C₆ alkyl optionally substituted with one or more oxo or -OH;

Z is H, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl, wherein the C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^Z ;

each R^Z independently is oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxyl, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxyl, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{Za} ,

each R^{Za} independently is oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxyl, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxyl, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{Zb} ;

and

each R^{Zb} independently is oxo, halogen, cyano, -OH, NH_2 , $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, or $C_1-C_6 \text{ alkoxy}$.

4. The compound of claim 3, wherein:

each $\equiv$ independently represents a single bond or a double bond;

n is 0 or 1;

W^1 is $C(R^{W1})$ or $N(R^{W1})$ when connected to two single bonds, or C or N when connected to one double bond and one single bond;

R^{W1} is H, $C_1-C_6 \text{ alkyl}$, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^2 is $C(R^{W2})$ or $N(R^{W2})$ when connected to two single bonds, or C or N when connected to one double bond and one single bond;

R^{W2} is H, $C_1-C_6 \text{ alkyl}$, or $-S(=O)_2-(C_1-C_6 \text{ alkyl})$;

W^3 is C or N;

X^1 is C or N;

X^2 is N, O, or $C(R^{X2})$;

R^{X2} is H or $C_1-C_6 \text{ alkyl}$;

X^3 is N, O, or $C(R^{X3})$;

R^{X3} is H or $C_1-C_6 \text{ alkyl}$;

R^1 is H, halogen, cyano, or $C_1-C_6 \text{ alkyl}$;

R^2 is H, halogen, cyano, or $C_1-C_6 \text{ alkyl}$;

R^3 is H, halogen, cyano, or $C_1-C_6 \text{ alkyl}$;

R^4 is H, halogen, cyano, or $C_1-C_6 \text{ alkyl}$;

Y is absent or $C_1-C_6 \text{ alkyl}$ optionally substituted with one or more oxo or -OH;

Z is $C_3-C_8 \text{ cycloalkyl}$ or 3- to 8-membered heterocycloalkyl, wherein the $C_3-C_8 \text{ cycloalkyl}$ or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^Z ;

each R^Z independently is oxo, halogen, cyano, -OH, NH_2 , $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_2-C_6 \text{ alkenyl})$, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, $C_1-C_6 \text{ alkoxy}$, $C_3-C_8 \text{ cycloalkyl}$, or 3- to 8-membered heterocycloalkyl, wherein the $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, $-S(=O)_2-(C_1-C_6 \text{ alkyl})$, $-C(=O)-(C_1-C_6 \text{ alkyl})$, -

C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{Za},

each R^{Za} independently is oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{Zb}, and

each R^{Zb} independently is oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, or C₁-C₆ alkoxy.

5. The compound of claim 3, wherein:

each $\equiv$ independently represents a single bond or a double bond;

n is 0 or 1;

W¹ is C(R^{W1}) or N(R^{W1}) when connected to two single bonds, or C or N when connected to one double bond and one single bond;

R^{W1} is H, C₁-C₆ alkyl, or -S(=O)₂-(C₁-C₆ alkyl);

W² is C(R^{W2}) or N(R^{W2}) when connected to two single bonds, or C or N when connected to one double bond and one single bond;

R^{W2} is H, C₁-C₆ alkyl, or -S(=O)₂-(C₁-C₆ alkyl);

W³ is C or N;

X¹ is C or N;

X² is N, O, or C(R^{X2});

R^{X2} is H or C₁-C₆ alkyl;

X³ is N, O, or C(R^{X3});

R^{X3} is H or C₁-C₆ alkyl;

R¹ is H, halogen, cyano, or C₁-C₆ alkyl;

R² is H, halogen, cyano, or C₁-C₆ alkyl;

R³ is H, halogen, cyano, or C₁-C₆ alkyl;

R^4 is H, halogen, cyano, or C₁-C₆ alkyl;

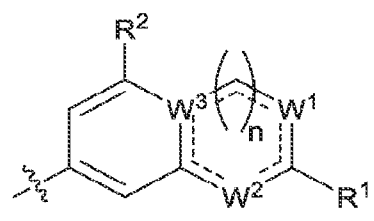
Y is C₁-C₆ alkyl optionally substituted with one or more oxo or -OH;

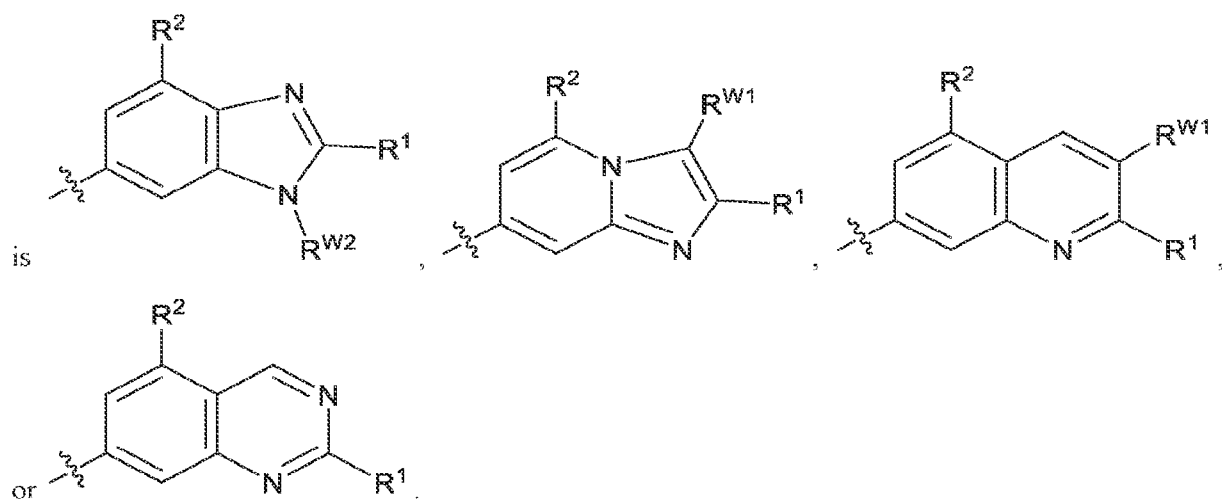
Z is C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl, wherein the C₃-C₈ cycloalkyl or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^Z ;

each R^Z independently is oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{Za} ;

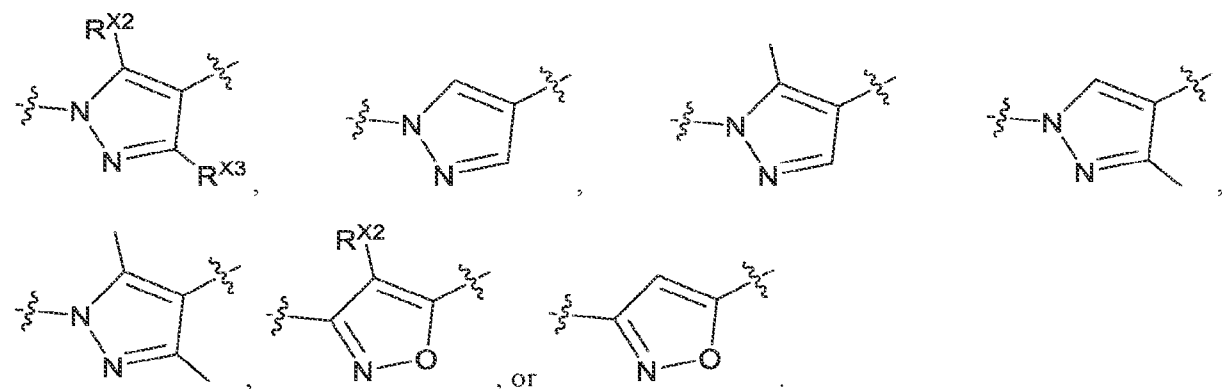
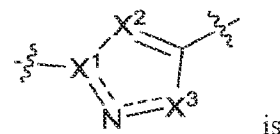
each R^{Za} independently is oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl, wherein the NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl is optionally substituted with one or more R^{Zb} ; and

each R^{Zb} independently is oxo, halogen, cyano, -OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, -S(=O)₂-(C₁-C₆ alkyl), -C(=O)-(C₁-C₆ alkyl), -C(=O)-(C₂-C₆ alkenyl), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, or C₁-C₆ alkoxy.

6. The compound of any one of the preceding claims, wherein
- 



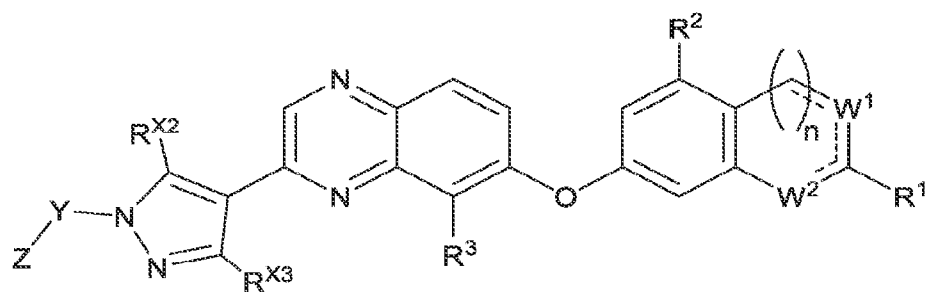
7. The compound of any one of the preceding claims, wherein



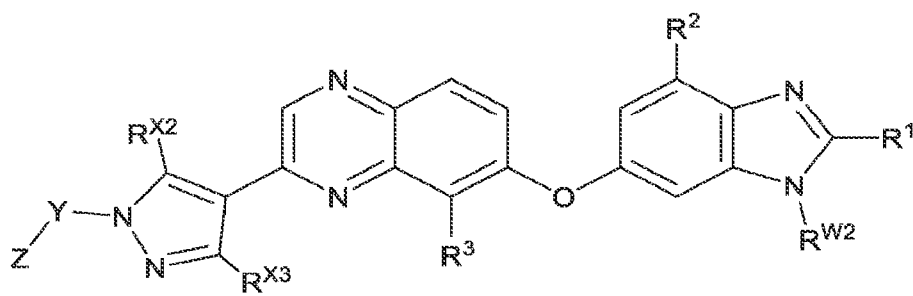
8. The compound of any one of the preceding claims, wherein R^1 is H.

9. The compound of any one of the preceding claims, wherein R^1 is halogen, cyano, or C₁-C₆ alkyl.
10. The compound of any one of the preceding claims, wherein R^2 is H.
11. The compound of any one of the preceding claims, wherein R^2 is halogen, cyano, or C₁-C₆ alkyl.
12. The compound of any one of the preceding claims, wherein R^3 is H.
13. The compound of any one of the preceding claims, wherein R^3 is halogen, cyano, or C₁-C₆ alkyl.
14. The compound of any one of the preceding claims, wherein R^4 is H.
15. The compound of any one of the preceding claims, wherein R^4 is halogen, cyano, or C₁-C₆ alkyl.
16. The compound of any one of the preceding claims, wherein Y is absent.
17. The compound of any one of the preceding claims, wherein Y is C₁-C₆ alkyl optionally substituted with one or more oxo or -OH.
18. The compound of any one of the preceding claims, wherein Z is absent.
19. The compound of any one of the preceding claims, wherein Z is C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the C₃-C₁₂ cycloalkyl, C₃-C₁₂ cycloalkenyl, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, C₆-C₁₀ aryl or 5- to 10-membered heteroaryl, is optionally substituted with one or more R^Z .

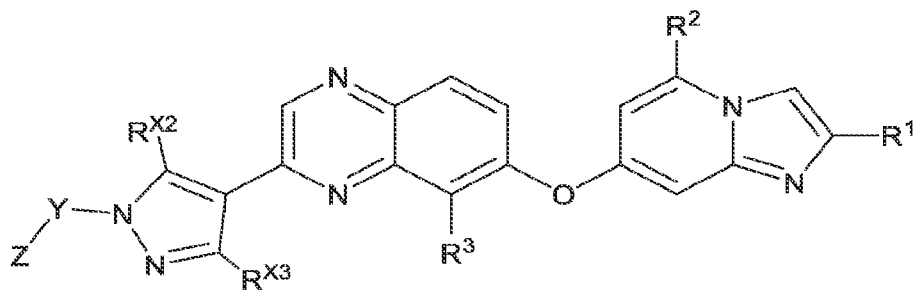
(I-d)



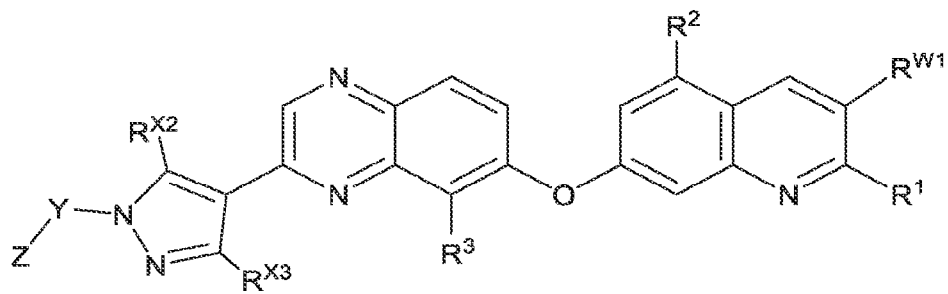
(II)



(II-a)

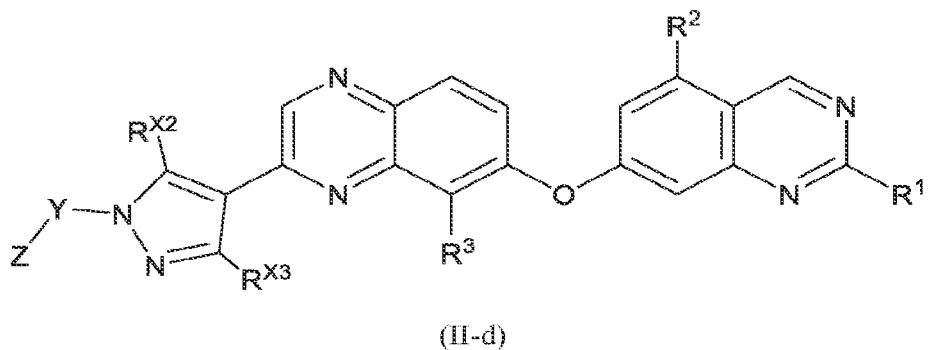


(II-b)



(II-c)

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or a pharmaceutically acceptable salt or stereoisomer thereof.

21. The compound of any one of the preceding claims, being selected from the compounds described in Table I and Table II, or a pharmaceutically acceptable salt or stereoisomer thereof.

22. A pharmaceutical composition comprising the compound of any one of the preceding claims and one or more pharmaceutically acceptable carriers or excipients.

23. A method of treating or preventing cancer in a subject, the method comprising administering to the subject a compound of any one of the preceding claims.

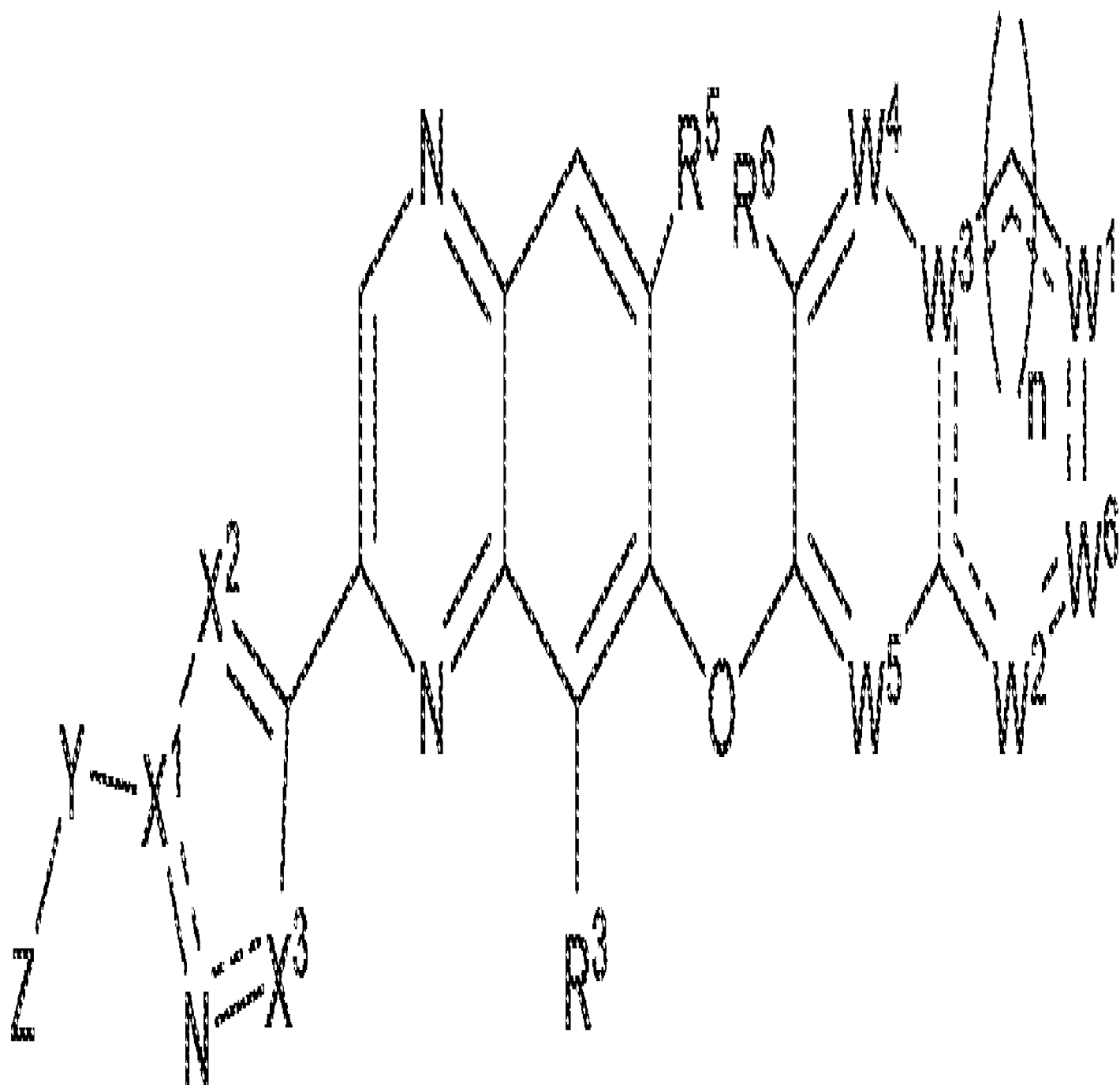
24. A compound of any one of the preceding claims for treating or preventing cancer in a subject.

25. Use of the compound of any one of the preceding claims in the manufacture of a medicament for treating or preventing cancer in a subject.

26. Use of the compound of any one of the preceding claims for treating or preventing cancer in a subject.

27. The method, compound, or use of any one of claims 23-26, wherein the subject has previously undergone at least one round of anti-cancer therapy.

28. The method, compound, or use of any one of claims 23-27, wherein the cancer is characterized by at least one oncogenic mutation in the *FGFR2* gene or the *FGFR3* gene.
29. The method, compound, or use of any one of claims 23-27, wherein the cancer is characterized by overexpression of the *FGFR2* gene or the *FGFR3* gene.
30. The method, compound, or use of any one of claims 23-27, wherein the cancer is characterized by at least one oncogenic variant of FGFR2 or FGFR3.
31. The method, compound, or use of any one of claims 23-30, wherein the cancer is a carcinoma, a lymphoma, a blastoma, a sarcoma, a leukemia, a brain cancer, a breast cancer, a blood cancer, a bone cancer, a lung cancer, a skin cancer, a liver cancer, an ovarian cancer, a bladder cancer, a renal cancer, a kidney cancer, a gastric cancer, a thyroid cancer, a pancreatic cancer, an esophageal cancer, a prostate cancer, a cervical cancer, a uterine cancer, a stomach cancer, a soft tissue cancer, a laryngeal cancer, a small intestine cancer, a testicular cancer, an anal cancer, a vulvar cancer, a joint cancer, an oral cancer, a pharynx cancer or a colorectal cancer.



(I)