(12) STANDARD PATENT (11) Application No. **AU 2018379077 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Heterocycle substituted pyridine derivative antifungal agents

(51) International Patent Classification(s)
C07D 247/02 (2006.01) ***A61K 31/506*** (2006.01)
A61K 31/42 (2006.01) ***C07D 261/02*** (2006.01)
A61K 31/505 (2006.01) ***C07D 261/06*** (2006.01)

(21) Application No: **2018379077** (22) Date of Filing: **2018.12.07**

(87) WIPO No: **WO19/113542**

(30) Priority Data

(31) Number	(32) Date	(33) Country
62/649,225	**2018.03.28**	**US**
62/595,894	**2017.12.07**	**US**

(43) Publication Date: **2019.06.13**
(44) Accepted Journal Date: **2023.04.27**

(71) Applicant(s)
Amplyx Pharmaceuticals, Inc.

(72) Inventor(s)
TRZOSS, Michael;COVEL, Jonathan;SHAW, Karen Joy;WEBB, Peter

(74) Agent / Attorney
FB Rice Pty Ltd, L 33 477 Collins Street, Melbourne, VIC, 3000, AU

(56) Related Art
EP 2628738 A1
EP 1944303 A1
WO 2011/051198 A2
EP 2345328 A1
Chemistry Letters, 2010, vol. 39, pages 1033-1035

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 June 2019 (13.06.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/113542 A1

(51) International Patent Classification:
A61K 31/42 (2006.01) *C07D 247/02* (2006.01)
A61K 31/505 (2006.01) *C07D 261/02* (2006.01)
A61K 31/506 (2006.01) *C07D 261/06* (2006.01)

(21) International Application Number:
PCT/US2018/064609

(22) International Filing Date:
07 December 2018 (07.12.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/595,894 07 December 2017 (07.12.2017) US
62/649,225 28 March 2018 (28.03.2018) US

(71) Applicant: **AMPLYX PHARMACEUTICALS, INC.** [US/US]; 12730 High Bluff Drive, Suite 160, San Diego, California 92130 (US).

(72) Inventors: **TRZOSS, Michael**; 12730 High Bluff Drive, Suite 160, San Diego, California 92037 (US). **COVEL, Jonathan**; 12730 High Bluff Drive, Suite 160, San Diego, California 92130 (US). **SHAW, Karen Joy**; 12730 High Bluff Drive, Suite 160, San Diego, California 92037 (US). **WEBB, Peter**; 12730 High Bluff Drive, Suite 160, San Diego, California 92037 (US).

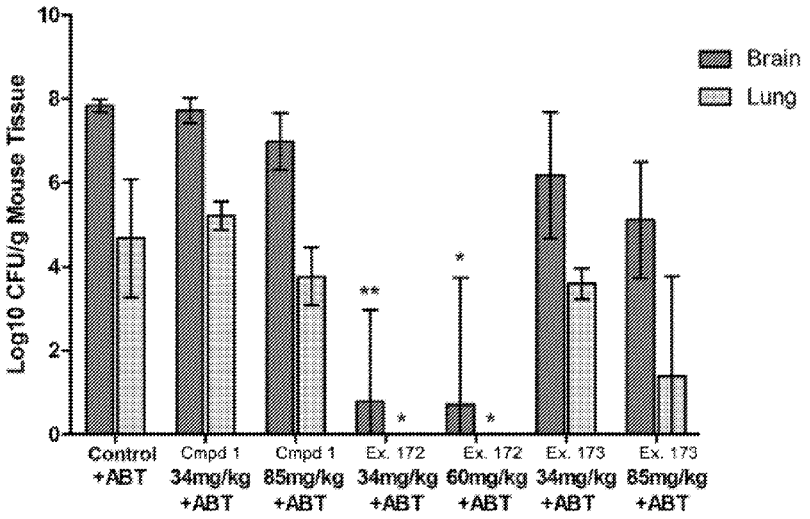
(74) Agent: **YVON, Brigitte**; Wilson Sonsini Goodrich & Rosati, 650 Page Mill Road, Palo Alto, California 94304 (US).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,

(54) Title: HETEROCYCLE SUBSTITUTED PYRIDINE DERIVATIVE ANTIFUNGAL AGENTS

FIG. 1



(57) Abstract: Described herein are heterocycle substituted pyridine derivative antifungal agents and pharmaceutical compositions comprising said compounds. The subject compounds and compositions are useful for the treatment of fungal diseases and infections.

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[Continued on next page]

EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

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

Published:

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

HETEROCYCLE SUBSTITUTED PYRIDINE DERIVATIVE ANTIFUNGAL AGENTS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/595,894, filed December 7, 2017, and U.S. Provisional Application No. 62/649,225, filed March 28, 2018; the disclosure of each of the prior applications is considered part of and is incorporated by reference in the disclosure of this application.

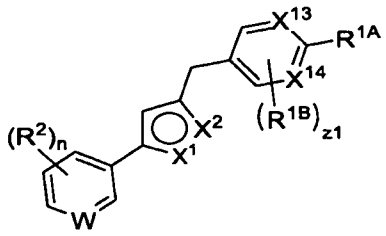
BACKGROUND

[0002] A need exists in the art for an effective treatment of fungal diseases.

BRIEF SUMMARY OF THE INVENTION

[0003] Provided herein are compounds of Formula (I), (Ia), (II), (IIa), (IIb), (IIc), (II'), (II''), (III), (IIIa), or (III-B) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, and pharmaceutical compositions comprising said compounds. The subject compounds and compositions are useful for treating fungal diseases. Furthermore, the subject compounds and compositions are useful for the treatment of cryptococcosis.

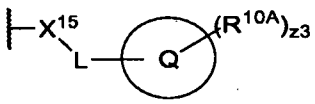
[0004] Provided herein are compounds having the structure of Formula (III), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof:



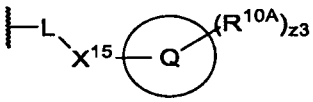
Formula (III);

wherein:

R^{1A} is –OH, substituted or unsubstituted $C_{1\text{-}6}$ alkyl, $-(CH_2)_2S(CH_2)_2OC(O)H$, $-X^{15}-L-C\equiv N$, $-L-X^{15}-(CH_2)_{z2}C\equiv N$, $-X^{15}-L-CH=CR^{29}R^{30}$,



, or



;

one of X^1 and X^2 is N while the other is O;

X^{13} and X^{14} are independently N or $C(R^{1B})$;

X^{15} is a bond, –NH–, –O–,–S–, or $–SO_2–$;

L is a bond or substituted or unsubstituted $C_{1\text{-}6}$ alkylene;

W is N or $N^+–CH_2OPO_3H^-$;

Ring Q is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^2 is independently hydrogen, $–NH_2$, or halogen;

each R^{1B} and R^{10A} is independently hydrogen, halogen, $-CF_3$, -CN, $-CH_2$-OH, $-OR^a$, $-SR^a$, $-S(=O)R^b$, $-NO_2$, $-NR^cR^d$, $-S(=O)_2R^d$, $-NR^aS(=O)_2R^d$, $-S(=O)_2NR^cR^d$, $-C(=O)R^b$, $-OC(=O)R^b$, $-CO_2R^a$, $-OCO_2R^a$, $-C(=O)NR^cR^d$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)NR^cR^d$, $-NR^aC(=O)R^b$, $-NR^aC(=O)OR^a$, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{29} and R^{30} are independently hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl;

R^a is hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^b is substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

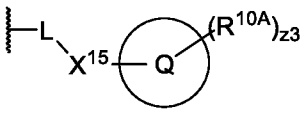
R^c and R^d is independently hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

n is 0-3;

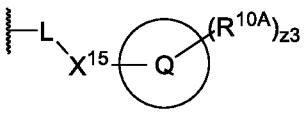
z1 is 0-2;

z2 is 0-3; and

z3 is 1-3.

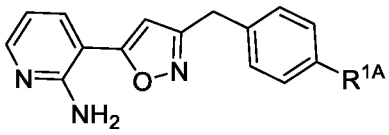


[0005] In some embodiments of a compound of Formula (III), if R^{1A} is , R^2 is $-NH_2$, Ring Q is 2-pyridinyl, L is methylene, R^{10A} is hydrogen, X^1 is O, X^2 is N, X^{13} is CH, X^{14} is CH, n is 1, and z1 is 0, then X^{15} is a bond, –NH–,–S–, or $–SO_2–$.



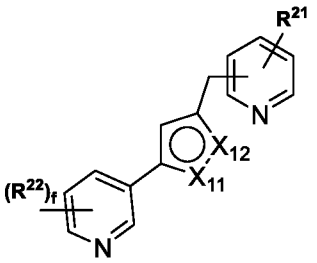
[0006] In some embodiments of a compound of Formula (III), if R^{1A} is , R^2 is 2-amino, Ring Q is 2-pyridinyl, L is methylene, R^{10A} is hydrogen, X^1 is O, X^2 is N, X^{13} is CH, X^{14} is CH, n is 1, and z1 is 0, then X^{15} is a bond, –NH–,–S–, or $–SO_2–$.

[0007] In some embodiments, the compound of Formula (III) is of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof:



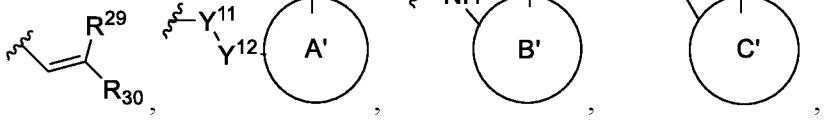
Formula (IIIa).

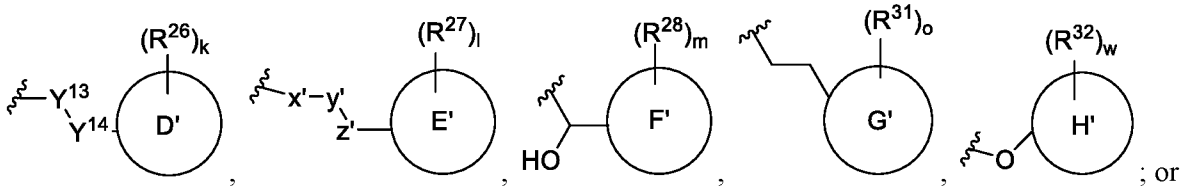
[0008] Provided herein are compounds having the structure of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



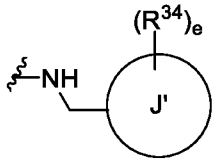
Formula (II),

wherein:

R^{21} is halogen, 



; or



one of X_{11} and X_{12} is N while the other is O;

one of Y^{11} and Y^{12} is -NH- or -O- while the other is -CH_2-;

one of Y^{13} and Y^{14} is -S- while the other is -CH_2-;

one of x' y' and z' is -O- while the others are -CH_2-;

Ring A' is heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring B' is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring C' is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring D' is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring E' is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring F' is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring G' is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring H' is bicyclic aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring J' is aryl;

R^{22} is hydrogen, $-NH_2$, or halogen;

R^{29} and R^{30} are independently hydrogen, halogen, C_1-C_6 alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl;

each R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{31}, and R^{32} is independently hydrogen, halogen, $-CF_3$, -CN, $-OR^a$, $-SR^a$, $-S(=O)R^b$, $-NO_2$, $-NR^cR^d$, $-S(=O)_2R^d$, $-NR^aS(=O)_2R^d$, $-S(=O)_2NR^cR^d$, $-C(=O)R^b$, $-OC(=O)R^b$, $-CO_2R^a$, $-OCO_2R^a$, $-C(=O)NR^cR^d$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)NR^cR^d$, $-NR^aC(=O)R^b$, $-NR^aC(=O)OR^a$, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^a is hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^b is substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^c and R^d is independently hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or R^c and R^d, together with the nitrogen atom to which they are attached, form an substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

f is 1;

h is 1-3;

i is 1-3;

j is 1-3;

k is 1-3;

l is 1-3;

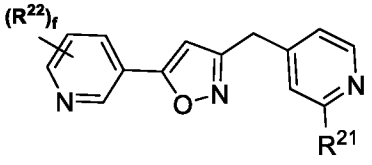
m is 1-3;

o is 1-3;

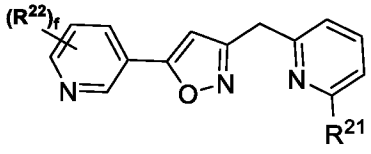
w is 1-3; and

e is 1-3.

[0009] In some embodiments provided herein are compounds compound having the structure of Formula (II') or Formula (II''), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:

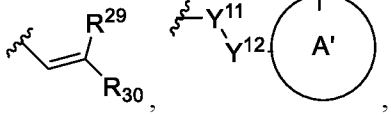
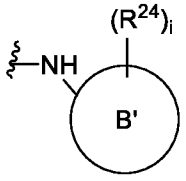
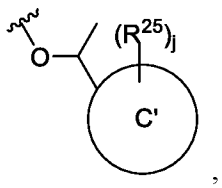
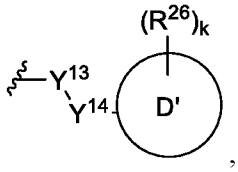
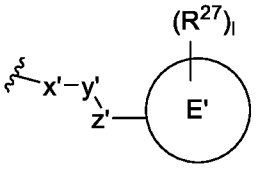
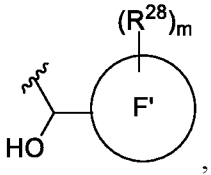
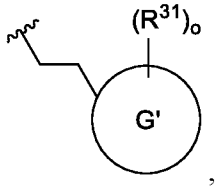
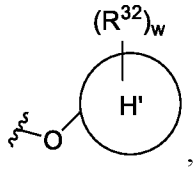
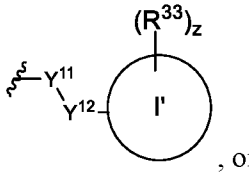
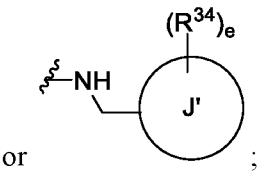


Formula (II')



Formula (II")

wherein:

R^{21} is halogen,  , ,  ,  ,  ,  ,  ,  ,  ,  ,  , , or ;

one of X_{11} and X_{12} is N while the other is O;

one of Y^{11} and Y^{12} is -NH- or -O- while the other is $-CH_2-$;

one of Y^{13} and Y^{14} is -S- while the other is $-CH_2-$;

one of x' y' and z' is -O- while the others are $-CH_2-$;

Ring A' is heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring B' is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring C' is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring D' is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring E' is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring F' is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring G' is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring H' is bicyclic aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring I' is aryl,

Ring J' is aryl,

R^{22} is hydrogen, $-NH_2$, or halogen;

each R^{29} and R^{30} is independently hydrogen, halogen, C_1-C_6 alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl;

each R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{31}, R^{32}, R^{33}, R^{34} is independently hydrogen, halogen, $-CF_3$, -CN, $-OR^a$, $-SR^a$, $-S(=O)R^b$, $-NO_2$, $-NR^cR^d$, $-S(=O)_2R^d$, $-NR^aS(=O)_2R^d$, $-S(=O)_2NR^cR^d$, $-C(=O)R^b$, $-OC(=O)R^b$, $-CO_2R^a$, $-OCO_2R^a$, $-C(=O)NR^cR^d$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)NR^cR^d$, $-NR^aC(=O)R^b$, $-NR^aC(=O)OR^a$, substituted or unsubstituted C_1-C_6 alkyl, substituted or

unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^a is hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^b is substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^c and R^d is independently hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or R^c and R^d, together with the nitrogen atom to which they are attached, form an substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

f is 1;

h is 1-3;

i is 1-3;

j is 1-3;

k is 1-3;

l is 1-3;

m is 1-3;

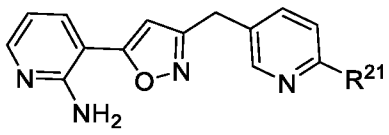
o is 1-3;

w is 1-3;

z is 1-3; and

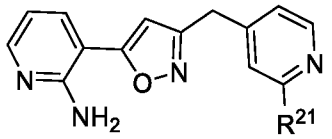
e is 1-3.

[0010] In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, the compound of Formula (II) is of Formula (IIa):



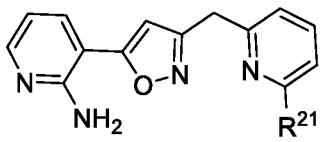
Formula (IIa).

[0011] In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, the compound of Formula (II) is of Formula (IIb):



Formula (IIb).

[0012] In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, the compound of Formula (II) is of Formula (IIc):



Formula (IIc).

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] **FIG. 1** shows the efficacy of certain compounds of the present disclosure in a murine model of cryptococcal meningitis when dosed in the presence of the pan-CYP inhibitor 1-aminobenzotriazole (ABT).

[0014] **FIG. 2** shows a dose response study with (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate (**Example 172**) and (2-amino-3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate (**Example 173**).

[0015] **FIG. 3** shows the efficacy of (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate (**Example 172**) and amphotericin B (AMB) in a delayed model of cryptococcal meningitis.

DETAILED DESCRIPTION OF THE INVENTION

[0016] The incidence of fungal infections has increased over the last few decades. Such infections have risen in the last few decades in part due to an increase in individuals that are immunocompromised. Immunocompromised individuals, include, for example, elderly individuals, individuals with HIV/AIDS, or individuals undergoing chemotherapy treatment or immunosuppressive therapy after a transplant.

[0017] Current antifungal therapies exploit differences between mammalian cells and fungal cells to kill the fungi. However, because fungi and mammals are both eukaryotes, many antifungal therapies cause side effects in the host mammal. Additionally, many fungal organisms have developed resistance to front line antifungal treatments. Thus, there exists a need for new compositions and methods for treating fungal diseases.

Definitions

[0018] As used herein and in the appended claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an agent"

includes a plurality of such agents, and reference to "the cell" includes reference to one or more cells (or to a plurality of cells) and equivalents thereof known to those skilled in the art, and so forth. When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range, in some instances, will vary between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, "consist of" or "consist essentially of" the described features.

[0019] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

[0020] "Alkyl" refers to an substituted or unsubstituted straight-chain, or substituted or unsubstituted branched-chain saturated hydrocarbon monoradical having from one to about ten carbon atoms, or from one to six carbon atoms, wherein a sp3-hybridized carbon of the alkyl residue is attached to the rest of the molecule by a single bond. Examples include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, tert-amyl and hexyl, and longer alkyl groups, such as heptyl, octyl, and the like. Whenever it appears herein, a numerical range such as "C_1-C_6 alkyl" means that the alkyl group consists of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated. In some embodiments, the alkyl is a C_1-C_{10} alkyl, a C_1-C_9 alkyl, a C_1-C_8 alkyl, a C_1-C_7 alkyl, a C_1-C_6 alkyl, a C_1-C_5 alkyl, a C_1-C_4 alkyl, a C_1-C_3 alkyl, a C_1-C_2 alkyl, or amethyl. Unless stated otherwise specifically in the specification, an alkyl group is substituted or unsubstituted as described below, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkyl is substituted or unsubstituted with oxo, halogen, -CN, -CF_3, -OH, -OMe, -NH_2, or -NO_2. In some embodiments, the alkyl is substituted or unsubstituted with oxo, halogen, -CN, -CF_3, -OH, or –OMe.

[0021] "Alkenyl" refers to a7 substituted or unsubstituted straight-chain, or substituted or unsubstituted branched-chain hydrocarbon monoradical having one or more carbon-carbon double-bonds and having from two to about ten carbon atoms, more preferably two to about six carbon atoms, wherein an sp2-hybridized carbon of the alkenyl residue is attached to the rest of the molecule by a single bond. The group may be in either the *cis* or *trans* conformation about the double bond(s), and should be understood to include both isomers. Examples include, but are not limited to ethenyl (-CH=CH_2), 1-propenyl

($-CH_2CH=CH_2$), isopropenyl [$-C(CH_3)=CH_2$], butenyl, 1,3-butadienyl and the like. Whenever it appears herein, a numerical range such as "C_2-C_6 alkenyl" means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkenyl" where no numerical range is designated. In some embodiments, the alkenyl is a C_2-C_{10} alkenyl, a C_2-C_9 alkenyl, a C_2-C_8 alkenyl, a C_2-C_7 alkenyl, a C_2-C_6 alkenyl, a C_2-C_5 alkenyl, a C_2-C_4 alkenyl, a C_2-C_3 alkenyl, or a C_2 alkenyl. Unless stated otherwise specifically in the specification, an alkenyl group is substituted or unsubstituted as described below, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, an alkenyl is substituted or unsubstituted with oxo, halogen, -CN, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, an alkenyl is substituted or unsubstituted with oxo, halogen, -CN, $-CF_3$, -OH, or –OMe.

[0022] "Alkynyl" refers to a substituted or unsubstituted straight-chain or substituted or unsubstituted branched-chain hydrocarbon monoradical having one or more carbon-carbon triple-bonds and having from two to about ten carbon atoms, more preferably from two to about six carbon atoms. Examples include, but are not limited to ethynyl, 2-propynyl, 2-butynyl, 1,3-butadiynyl and the like. Whenever it appears herein, a numerical range such as "C_2-C_6 alkynyl" means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkynyl" where no numerical range is designated. In some embodiments, the alkynyl is a C_2-C_{10} alkynyl, a C_2-C_9 alkynyl, a C_2-C_8 alkynyl, a C_2-C_7 alkynyl, a C_2-C_6 alkynyl, a C_2-C_5 alkynyl, a C_2-C_4 alkynyl, a C_2-C_3 alkynyl, or a C_2 alkynyl. Unless stated otherwise specifically in the specification, an alkynyl group is substituted or unsubstituted as described below, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, an alkynyl is substituted or unsubstituted with oxo, halogen, -CN, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, an alkynyl is substituted or unsubstituted with oxo, halogen, -CN, $-CF_3$, -OH, or –OMe.

[0023] "Alkylene" refers to a straight or branched divalent hydrocarbon chain. Unless stated otherwise specifically in the specification, an alkylene group may be substituted or unsubstituted as described below, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, an alkylene is substituted or unsubstituted with oxo, halogen, -CN, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, an alkylene is substituted or unsubstituted with oxo, halogen, -CN, $-CF_3$, -OH, or –OMe.

[0024] "Alkoxy" refers to a radical of the formula $-OR_a$ where R_a is an alkyl radical as defined. Unless stated otherwise specifically in the specification, an alkoxy group may be substituted or unsubstituted as described below, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, an alkoxy is substituted or unsubstituted with oxo, halogen, -CN, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, an alkoxy is substituted or unsubstituted with oxo, halogen, -CN, $-CF_3$, -OH, or –OMe.

[0025] "Aryl" refers to a radical derived from a hydrocarbon ring system comprising hydrogen, 6 to 30 carbon atoms and at least one aromatic ring. The aryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the aryl is bonded through an aromatic ring atom) or bridged ring systems. In some embodiments, the aryl is a 6- to 10-membered aryl. In some embodiments, the aryl is a 6-membered aryl. Aryl radicals include, but are not limited to, aryl radicals derived from the hydrocarbon ring systems of anthrylene, naphthylene, phenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, as-indacene, s-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. In some embodiments, the aryl is phenyl. Unless stated otherwise specifically in the specification, an aryl may be substituted or unsubstituted as described below, for example, with halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, an aryl is substituted or unsubstituted with halogen, methyl, ethyl, -CN, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, an aryl is substituted or unsubstituted with halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe.

[0026] "Cycloalkyl" refers to a stable, partially or fully saturated, monocyclic or polycyclic carbocyclic ring, which may include fused (when fused with an aryl or a heteroaryl ring, the cycloalkyl is bonded through a non-aromatic ring atom) or bridged ring systems. Representative cycloalkyls include, but are not limited to, cycloalkyls having from three to fifteen carbon atoms (C_3-C_{15} cycloalkyl), from three to ten carbon atoms (C_3-C_{10} cycloalkyl), from three to eight carbon atoms (C_3-C_8 cycloalkyl), from three to six carbon atoms (C_3-C_6 cycloalkyl), from three to five carbon atoms (C_3-C_5 cycloalkyl), or three to four carbon atoms (C_3-C_4 cycloalkyl). In some embodiments, the cycloalkyl is a 3- to 6-membered cycloalkyl. In some embodiments, the cycloalkyl is a 5- to 6-membered cycloalkyl. Monocyclic cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls or carbocycles include, for example, adamantyl, norbornyl, decalinyl, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, cis-decalin, trans-decalin, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, and bicyclo[3.3.2]decane, and 7,7-dimethyl-bicyclo[2.2.1]heptanyl. Partially saturated cycloalkyls include, for example cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Unless stated otherwise specifically in the specification, a cycloalkyl is substituted or unsubstituted as described below, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a cycloalkyl is substituted or unsubstituted with oxo, halogen, methyl, ethyl, -CN, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, a cycloalkyl is substituted or unsubstituted with oxo, halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe.

[0027] "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo. In some embodiments, halogen is fluoro or chloro. In some embodiments, halogen is fluoro.

[0028] "Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like.

[0029] "Heterocycloalkyl" refers to a stable 3- to 24-membered partially or fully saturated ring radical comprising 2 to 23 carbon atoms and from one to 8 heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous and sulfur. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused (when fused with an aryl or a heteroaryl ring, the heterocycloalkyl is bonded through a non-aromatic ring atom) or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocycloalkyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. In some embodiments, the heterocycloalkyl is a 3- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 5- to 6-membered heterocycloalkyl. Examples of such heterocycloalkyl radicals include, but are not limited to, aziridinyl, azetidinyl, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, 1,3-dihydroisobenzofuran-1-yl, 3-oxo-1,3-dihydroisobenzofuran-1-yl, methyl-2-oxo-1,3-dioxol-4-yl, and 2-oxo-1,3-dioxol-4-yl. The term heterocycloalkyl also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. Unless otherwise noted, heterocycloalkyls have from 2 to 10 carbons in the ring. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e. skeletal atoms of the heterocycloalkyl ring). Unless stated otherwise specifically in the specification, a heterocycloalkyl is substituted or unsubstituted as described below, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heterocycloalkyl is substituted or unsubstituted with oxo, halogen, methyl, ethyl, -CN, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, a heterocycloalkyl is substituted or unsubstituted with oxo, halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe.

[0030] "Heteroalkyl" refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, e.g., oxygen, nitrogen (e.g. –NH-, -N(alkyl)-), sulfur, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a C_1-C_6 heteroalkyl. Unless stated otherwise specifically in the specification, a Heteroalkyl is substituted or unsubstituted as described below, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heteroalkyl is substituted or unsubstituted with oxo, halogen, methyl, ethyl, -CN, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, a heteroalkyl is substituted or unsubstituted with oxo, halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe.

[0031] "Heteroaryl" refers to a 5- to 14-membered ring system radical comprising hydrogen atoms, one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous and sulfur, and at least one aromatic ring. The heteroaryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the heteroaryl is bonded through an aromatic ring atom) or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. In some embodiments, the heteroaryl is a 5- to 10-membered heteroaryl. In some embodiments, the heteroaryl is a 5- to 6-membered heteroaryl. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e., thienyl). Unless stated otherwise specifically in the specification, a heteroaryl is substituted or unsubstituted as described below, for example, with halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heteroaryl is substituted or unsubstituted with halogen, methyl, ethyl, -CN, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, a heteroaryl is substituted or unsubstituted with halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe.

[0032] All the above groups may be either substituted or unsubstituted. The term "substituted" as used herein means any of the above groups (*e.g.*, alkyl, alkylene, alkoxy, aryl, cycloalkyl, haloalkyl, heterocyclyl and/or heteroaryl) may be further functionalized wherein at least one hydrogen atom is replaced by a bond to a non-hydrogen atom substituent. Unless stated specifically in the specification, a substituted group may include one or more substituents selected from: oxo, amino, $-CO_2H$, nitrile, nitro, hydroxyl, thiooxy, alkyl, alkylene, alkoxy, aryl, cycloalkyl, heterocyclyl, heteroaryl, dialkylamines, arylamines, alkylarylamines, diarylamines, trialkylammonium ($-N^+R_3$), N-oxides, imides, and enamines; a silicon atom in groups such as trialkylsilyl groups, dialkylarylsilyl groups, alkyldiarylsilyl groups, triarylsilyl groups, perfluoroalkyl, or perfluoroalkoxy, for example, trifluoromethyl or trifluoromethoxy. "Substituted" also means any of the above groups in which one or more hydrogen atoms are replaced by a higher-order bond (*e.g.*, a double- or triple-bond) to a heteroatom such as oxygen in oxo, carbonyl, carboxyl, and ester groups; and nitrogen in groups such as imines, oximes, hydrazones, and nitriles. For example, "substituted" includes any of the above groups in which one or more hydrogen atoms are

replaced with $-NH_2$, $-NR_gC(=O)NR_gR_h$, $-NR_gC(=O)OR_h$, $-NR_gSO_2R_h$, $-OC(=O)NR_gR_h$, $-OR_g$, $-SR_g$, $-SOR_g$, $-SO_2R_g$, $-OSO_2R_g$, $-SO_2OR_g$, $=NSO_2R_g$, and $-SO_2NR_gR_h$. In the foregoing, R_g and R_h are the same or different and independently hydrogen, alkyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl. In addition, each of the foregoing substituents may also be substituted or unsubstituted with one or more of the above substituents. Furthermore, any of the above groups may be substituted to include one or more internal oxygen, sulfur, or nitrogen atoms. For example, an alkyl group may be substituted with one or more internal oxygen atoms to form an ether or polyether group. Similarly, an alkyl group may be substituted with one or more internal sulfur atoms to form a thioether, disulfide, etc.

[0033] The term "optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "substituted or unsubstituted alkyl" means either "alkyl" or "substituted alkyl" as defined above. Further, a substituted or unsubstituted group may be un-substituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), mono-substituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and mono-substituted (e.g., $-CH_2CHF_2$, $-CH_2CF_3$, $-CF_2CH_3$, $-CFHCHF_2$, etc.). It will be understood by those skilled in the art with respect to any group containing one or more substituents that such groups are not intended to introduce any substitution or substitution patterns (e.g., substituted alkyl includes substituted or unsubstituted cycloalkyl groups, which in turn are defined as including substituted or unsubstituted alkyl groups, potentially ad infinitum) that are sterically impractical and/or synthetically non-feasible. Thus, any substituents described should generally be understood as having a maximum molecular weight of about 1,000 daltons, and more typically, up to about 500 daltons.

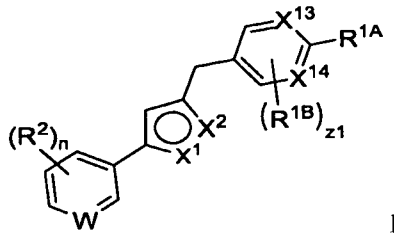
[0034] The terms "inhibit," "block," "suppress," and grammatical variants thereof are used interchangeably herein and refer to any statistically significant decrease in biological activity, including full blocking of the activity. In some embodiments, "inhibition" refers to a decrease of about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90% or about 100% in biological activity.

[0035] As used herein, "treatment" or "treating," or "palliating" or "ameliorating" are used interchangeably. These terms refer to an approach for obtaining beneficial or desired results including but not limited to therapeutic benefit and/or a prophylactic benefit. By "therapeutic benefit" is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient is still afflicted with the underlying disorder. For prophylactic benefit, the compositions are, in some embodiments, administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease has not been made.

Compounds

Described herein are compounds of Formula (I), (Ia), (II), (IIa), (IIb), (IIc), (II'), (II"), (III), (IIIa), and (III-B). These compounds, and compositions comprising these compounds, are useful for the treatment of fungal diseases in humans and in animals.

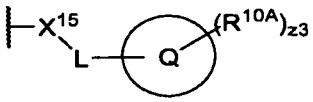
[0036] In an aspect, provided herein is a compound having the structure of Formula (III), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof:



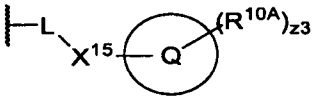
Formula (III);

wherein:

R^{1A} is –OH, substituted or unsubstituted C_{1-6} alkyl, $-(CH_2)_2S(CH_2)_2OC(O)H$, $-X^{15}-L-C\equiv N$, $-L-X^{15}-(CH_2)_{z2}C\equiv N$, $-X^{15}-L-CH=CR^{29}R^{30}$,



, or



;

one of X^1 and X^2 is N while the other is O;

X^{13} and X^{14} are independently N or $C(R^{1B})$;

X^{15} is a bond, –NH–, –O–,–S–, or $–SO_2–$;

L is a bond or substituted or unsubstituted C_{1-6} alkylene;

W is N or $N^+–CH_2OPO_3H^-$;

Ring Q is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^2 is independently hydrogen, $–NH_2$, or halogen;

each R^{1B} and R^{10A} is independently hydrogen, halogen, $-CF_3$, -CN, $-CH_2-OH$, $-OR^a$, $-SR^a$, $-S(=O)R^b$, $-NO_2$, $-NR^cR^d$, $-S(=O)_2R^d$, $-NR^aS(=O)_2R^d$, $-S(=O)_2NR^cR^d$, $-C(=O)R^b$, $-OC(=O)R^b$, $-CO_2R^a$, $-OCO_2R^a$, $-C(=O)NR^cR^d$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)NR^cR^d$, $-NR^aC(=O)R^b$, $-NR^aC(=O)OR^a$, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{29} and R^{30} are independently hydrogen, halogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl;

R^a is hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted

or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^b is substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

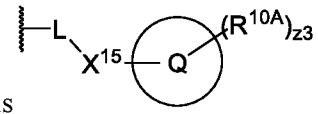
R^c and R^d is independently hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

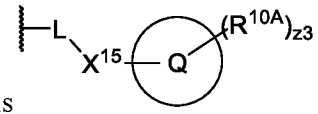
n is 0-3;

z1 is 0-2;

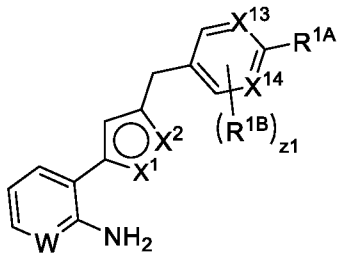
z2 is 0-3; and

z3 is 1-3.

[0037] In some embodiments of a compound of Formula (III), if R^{1A} is  , R^2 is –NH_2, Ring Q is 2-pyridinyl, L is methylene, R^{10A} is hydrogen, X^1 is O, X^2 is N, X^{13} is CH, X^{14} is CH, n is 1, and z1 is 0, and then X^{15} is a bond, –NH–,–S–, or –SO_2–.

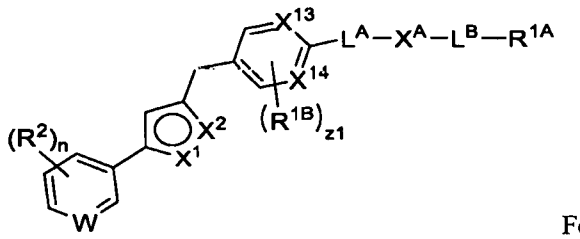
[0038] In some embodiments of a compound of Formula (III), if R^{1A} is  , R^2 is 2-amino, Ring Q is 2-pyridinyl, L is methylene, R^{10A} is hydrogen, X^1 is O, X^2 is N, X^{13} is CH, X^{14} is CH, n is 1, and z1 is 0, then X^{15} is a bond, –NH–,–S–, or –SO_2–.

[0039] In some embodiments, R^2 is 2-amino and R^2 is –NH_2 are synonymous and refer to an amino group (i.e., –NH_2 group) on the 2-position of the pyridinyl or pyridinium ring of a compound of Formula (III) as shown in Formula (IV):



Formula (IV).

[0040] In some embodiments of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, the compound of Formula (III) is of Formula (III'):



Formula (III');

wherein:

[0037] R^2, W, X^1, X^2, R^{1B}, X^{13}, X^{14}, R^{1A}, z1, z2, z3, and n are as described herein, including embodiments.

[0038] L^A and L^B are independently a bond or substituted or unsubstituted C_{1-6} alkylene; and X^A is a bond, –NH–, –O–,–S–, or $–SO_2–$.

[0039] In some embodiments, the compound is not hydrogen (2-(2-amino-3-(3-(4-((pyridin-2-yloxy)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)ethyl)phosphonate or 3-(3-(4-((pyridin-2-yloxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine.

[0044] In some embodiments of the compounds disclosed herein, W is N. In some embodiments of the compounds disclosed herein, W is $N^+–CH_2OPO_3H^-$.

[0045] In some embodiments of the compounds disclosed herein, X^1 is -O-; and X^2 is N.

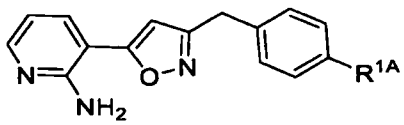
[0046] In some embodiments of the compounds disclosed herein, R^2 is $–NH_2$. In some embodiments of the compounds disclosed herein, R^{10A} is hydrogen or halogen. In some embodiments of the compounds disclosed herein, z3 is 0. In some embodiments of the compounds disclosed herein, z3 is 1. In some embodiments of the compounds disclosed herein, z3 is 2. In some embodiments of the compounds disclosed herein, z3 is 3.

[0047] In some embodiments of the compounds disclosed herein, z3 is 1-2.

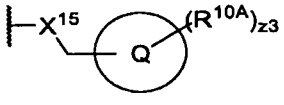
[0048] In some embodiments of the compounds disclosed herein, z2 is 0. In some embodiments of the compounds disclosed herein, z2 is 1. In some embodiments of the compounds disclosed herein, z2 is 2. In some embodiments of the compounds disclosed herein, z2 is 3.

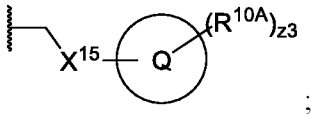
[0049] In some embodiments of the compounds disclosed herein, z1 is 0. In some embodiments of the compounds disclosed herein, z1 is 1. In some embodiments of the compounds disclosed herein, z1 is 2.

[0050] In some embodiments of the compounds disclosed herein, the compound of Formula (III) is of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof:



Formula (IIIa).

[0051] In some embodiments of the compounds disclosed herein, R^{1A} is  ; and Ring Q is bicyclic aryl, bicyclic heteroaryl, monocylic heteroaryl containing at least 2 N atoms in the ring, or oxazolyl.

[0052] In some embodiments of the compounds disclosed herein, R^{1A} is  ; and Ring Q is bicyclic aryl, bicyclic heteroaryl, monocylic 5-membered heteroaryl, or cycloalkyl.

[0053] In some embodiments of the compounds disclosed herein, X^{15} is –O–.

[0054] In some embodiments of the compounds disclosed herein, Ring Q is bicyclic aryl or bicyclic heteroaryl.

[0055] In some embodiments of the compounds disclosed herein, Ring Q is bicyclic heteroaryl selected from the group consisting of indolizinyl, indolyl, benzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, purinyl, quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, and pteridinyl.

[0056] In some embodiments of the compounds disclosed herein, Ring Q is quinolinyl or quinoxalinyl.

[0057] In some embodiments of the compounds disclosed herein, Ring Q is monocylic heteroaryl containing at least 2 N atoms in the ring.

[0058] In some embodiments of the compounds disclosed herein, Ring Q is monocylic heteroaryl containing at least 2 N atoms in the ring is selected from the group consisting of pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

[0059] In some embodiments of the compounds disclosed herein, Ring Q is pyrimidinyl.

[0060] In some embodiments of the compounds disclosed herein, Ring Q is monocylic 5-membered heteroaryl.

[0061] In some embodiments of the compounds disclosed herein, Ring Q is monocylic 5-membered heteroaryl selected from the group consisting of imidazolyl, triazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, and thiadiazolyl.

[0062] In some embodiments of the compounds disclosed herein, Ring Q is imidazolyl or oxazolyl.

[0063] In some embodiments of the compounds disclosed herein, Ring Q is cycloalkyl.

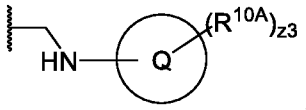
[0064] In some embodiments of the compounds disclosed herein, Ring Q is cyclohexyl.

[0065] In some embodiments of the compounds disclosed herein, X^{15} is –NH–.

[0066] In some embodiments of the compounds disclosed herein, Ring Q is heteroaryl or cycloalkyl.

[0067] In some embodiments of the compounds disclosed herein, Ring Q is heteroaryl selected from the group consisting of azaindolyl, pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl.

[0068] In some embodiments of the compounds disclosed herein, Ring Q is pyridinyl, thiadiazolyl, pyrimidinyl, azaindolyl, benzimidazolyl, or thiazolyl.

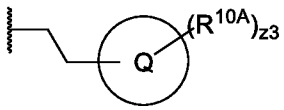
[0069] In some embodiments of the compounds disclosed herein, R^{1A} is  ; and Ring Q is heteroaryl or cycloalkyl.

[0070] In some embodiments of the compounds disclosed herein, Ring Q is heteroaryl.

[0071] In some embodiments of the compounds disclosed herein, Ring Q is heteroaryl selected from the group consisting of azaindolyl, pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl.

[0072] In some embodiments of the compounds disclosed herein, Ring Q is pyridinyl, thiadiazolyl, pyrimidinyl, azaindolyl, benzimidazolyl, or thiazolyl.

[0073] In some embodiments of the compounds disclosed herein, Ring Q is cycloalkyl.

[0074] In some embodiments of the compounds disclosed herein, R^{1A} is  ; and Ring Q is aryl, bicyclic heteroaryl, or cycloalkyl.

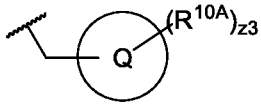
[0075] In some embodiments of the compounds disclosed herein, Ring Q is aryl selected from phenyl and naphthyl.

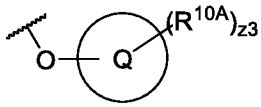
[0076] In some embodiments of the compounds disclosed herein, Ring Q is bicyclic heteroaryl selected from the group consisting of indolizinyl, indolyl, benzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, purinyl, quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, and pteridinyl.

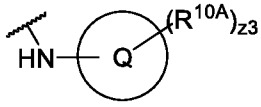
[0077] In some embodiments of the compounds disclosed herein, Ring Q is C_3-C_6 cycloalkyl.

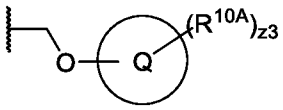
[0078] In some embodiments of the compounds disclosed herein, z3 is 1. In some embodiments of the compounds disclosed herein, z3 is 2.

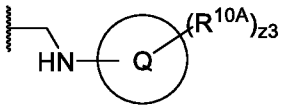
In some embodiments of the compounds disclosed herein, R^{10A} is hydrogen, $-CF_3$, halogen, or methyl.

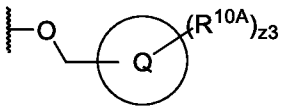
[0079] In some embodiments of the compounds disclosed herein, R^{1A} is  ; and Ring Q is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl.

[0080] In some embodiments of the compounds disclosed herein, R^{1A} is  ; and Ring Q is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl.

[0081] In some embodiments of the compounds disclosed herein, R^{1A} is  ; and Ring Q is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl.

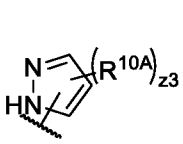
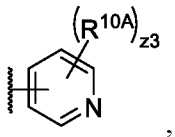
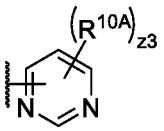
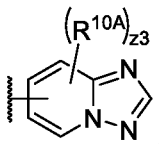
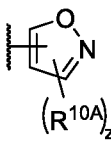
[0082] In some embodiments of the compounds disclosed herein, R^{1A} is  ; and Ring Q is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl.

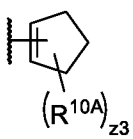
[0083] In some embodiments of the compounds disclosed herein, R^{1A} is  ; and Ring Q is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl.

[0084] In some embodiments of the compounds disclosed herein, R^{1A} is  ; and Ring Q is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl.

[0085] In some embodiments of the compounds disclosed herein, Ring Q is aryl selected from phenyl and naphthyl. In some embodiments of the compounds disclosed herein, Ring Q is substituted or unsubstituted phenyl. In some embodiments of the compounds disclosed herein, Ring Q is substituted or unsubstituted heteroaryl. In some embodiments of the compounds disclosed herein, Ring Q is substituted or unsubstituted 5- or 6-membered heteroaryl. In some embodiments of the compounds disclosed herein, Ring Q is substituted or unsubstituted pyridinyl. In some embodiments of the compounds disclosed herein, Ring Q is substituted or unsubstituted furanyl.

[0086] In some embodiments of the compounds disclosed herein, Ring Q is heteroaryl containing at least 1 N atom in the ring.

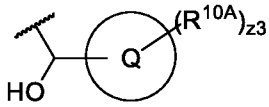
[0087] In some embodiments of the compounds disclosed herein, Ring Q is selected from  ,  ,  ,  , and  .

[0088] In some embodiments of the compounds disclosed herein, Ring Q is  .

[0089] In some embodiments of the compounds disclosed herein, R^{10A} is selected from the group consisting of hydrogen, -CN, halogen, $-CH_2$-OH, $-CF_3$, methyl, ethyl, isobutyl, and butyl.

[0090] In some embodiments of the compounds disclosed herein, R^{10A} is -F, isobutyl, or $-CH_2$-OH.

[0091] In some embodiments of the compounds disclosed herein, R^{10A} is –F.

[0092] In some embodiments of the compounds disclosed herein, R^{1A} is  ; and

Ring Q is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl.

[0093] In some embodiments of the compounds disclosed herein, R^{1A} is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or subsituted or unsubstituted cycloalkyl. In some embodiments of the compounds disclosed herein, R^{1A} is substituted or unsubstituted phenyl, substituted or unsubstituted 5-membered heteroaryl, or substituted or unsubstituted 6-membered heteroaryl. In some embodiments of the compounds disclosed herein, R^{1A} is heteroaryl selected from pyridinyl and furanyl.

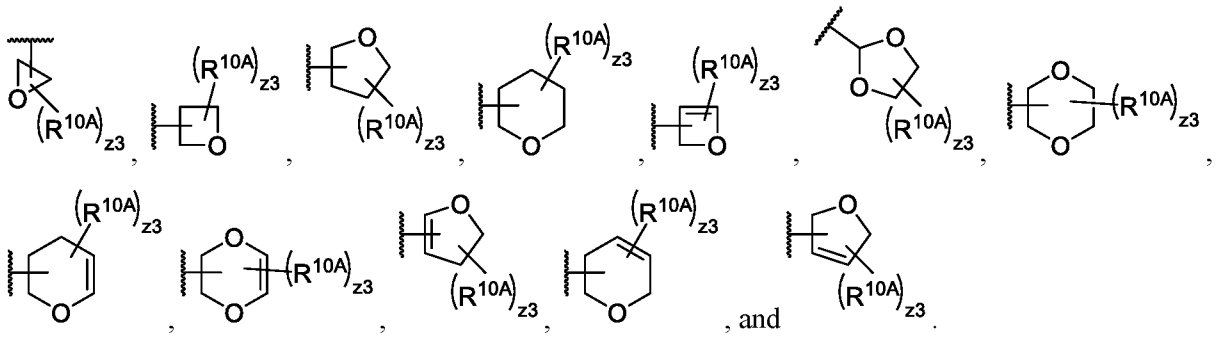
[0094] In some embodiments of the compounds disclosed herein, Ring Q is heteroaryl selected from the group consisting of azaindolyl, pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl.

[0095] In some embodiments of the compounds disclosed herein, Ring Q is heteroaryl selected from furyl and benzofuranyl.

[0096] In some embodiments of the compounds disclosed herein, Ring Q is cycloalkyl selected from C_3-C_6 cycloalkyl.

[0097] In some embodiments of the compounds disclosed herein, Ring Q is heterocycloalkyl wherein the heterocycloalkyl contains at least one O atom.

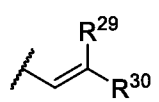
[0098] In some embodiments of the compounds disclosed herein, Ring Q is heterocycloalkyl that contains at least one O atom selected from the group consisting of



[0099] In some embodiments of the compounds disclosed herein, R^{10A} is hydrogen, methyl, -CF_3, or halogen.

[0100] In some embodiments of the compounds disclosed herein, R^{1A} is $-CClR^5R^6$; and R^5 and R^6 are is independently hydrogen, halogen, or C_1-C_6 alkyl.

[0101] In some embodiments of the compounds disclosed herein, R^5 and R^6 are hydrogen.

[0102] In some embodiments of the compounds disclosed herein, R^{1A} is  .

[0103] In some embodiments of the compounds disclosed herein, R^{29} and R^{30} are hydrogen.

[0104] In some embodiments of the compounds disclosed herein, R^{29} is hydrogen and R^{30} is cyclohexyl.

[0105] In some embodiments of the compounds disclosed herein, L is $-CH_2-$; and Ring Q is bicyclic aryl, bicyclic heteroaryl, monocylic heteroaryl containing at least 2 N atoms in the ring, or oxazolyl.

[0106] In some embodiments of the compounds disclosed herein, X^{15} is a bond; L is $-CH_2-$; and Ring Q is aryl, heteroaryl containing at least 1 N atom in the ring, or cycloalkyl.

[0107] In some embodiments of the compounds disclosed herein, X^{15} is a bond; L is $-(CH_2)_2-$; and Ring Q is aryl, bicyclic heteroaryl, or cycloalkyl.

[0108] In some embodiments of the compounds disclosed herein, X^{15} is a bond; L is –CH(OH)–; and Ring Q is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl.

[0109] In some embodiments of the compounds disclosed herein, X^{15} is a bond; L is –NH–; and Ring Q is heteroaryl or cycloalkyl.

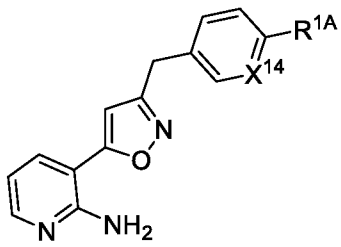
[0110] In some embodiments of the compounds disclosed herein, X^{15} is –NH–; L is $-CH_2-$; and Ring Q is heteroaryl or cycloalkyl.

[0111] In some embodiments of the compounds disclosed herein, X^{15} is –O– or –S–; L is $-CH_2-$; and Ring Q is bicyclic aryl, bicyclic heteroaryl, monocylic 5-membered heteroaryl, or cycloalkyl.

[0112] In some embodiments of the compounds disclosed herein, X^{13} is CH. In some embodiments of the compounds disclosed herein, X^{13} is N. In some embodiments of the compounds disclosed herein, X^{14} is CH. In some embodiments of the compounds disclosed herein, X^{14} is N.

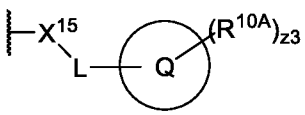
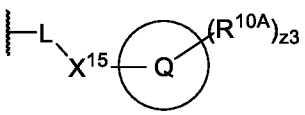
[0113] In some embodiments of the compounds disclosed herein, X^{13} and X^{14} are CH. In some embodiments of the compounds disclosed herein, X^{13} is CH; and X^{14} is N.

[0114] In an aspect provided herein, is a compound of Formula (III-B), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof:



Formula (III-B);

wherein:

R^{1A} is  or  .

[0115] In some embodiments of the compounds of Formula (III-B), X^{14} is N or CH;

X^{15} is a bond, –NH– or –O–;

L is a bond or unsubstituted C_{1-2} alkylene;

Ring Q is cycloalkyl, aryl, or heteroaryl;

R^{10A} is hydrogen or halogen; and

z3 is 1-2.

[0116] In some embodiments of the compounds of Formula (III-B), X^{14} is N.

[0117] In some embodiments of the compounds of Formula (III-B), X^{14} is CH. In some embodiments of the compounds disclosed herein, X^{15} is a bond; and L is $–CH_2–$. In some embodiments of the compounds disclosed herein, X^{15} is a bond; and L is $–(CH_2)_2–$.

[0118] In some embodiments of the compounds of Formula (III-B), X^{15} is –O– or –NH–; and L is a bond.

[0119] In some embodiments of the compounds disclosed herein, $–X^{15}–L–$ is – #– X^{15}–L–* or #– X^{15}–L–*, wherein # is the attachment point to Ring Q and * is the attachment point to the rest of the molecule.

[0120] In some embodiments of the compounds disclosed herein, X^{15}–L is $–CH_2–O–$ or $–CH_2–NH–$. In some embodiments of the compounds disclosed herein, X^{15}–L is $#–CH_2–O–*$ or $#–CH_2–NH–*$, wherein # is the attachment point to Ring Q and * is the attachment point to the rest of the molecule. In other embodiments of the compounds disclosed herein, X^{15}–L is $*–CH_2–O–#$ or $*–CH_2–NH–#$, wherein # is the attachment point to Ring Q and * is the attachment point to the rest of the molecule.

[0121] In some embodiments of the compounds disclosed herein, X^{15}–L is $–(CH_2)_2–O–$ or $–(CH_2)_2–NH–$.

[0122] In an aspect provided herein, is a compound selected from the compounds in **Table 1**.

[0123] In an aspect provided herein, is a compound selected from the compounds in **Table 2**.

[0124] In an aspect provided herein, is a compound selected from:

3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-(4-((6-chloropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-(4-((3-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-(4-((3,5-difluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-((6-(3-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-(4-((5-fluorofuran-2-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-((6-phenoxypyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-((6-((3-fluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine;

5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(2-fluorophenyl)pyridin-2-amine;

5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(2,6-difluorophenyl)pyridin-2-amine;

3-(3-(4-benzylbenzyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-(4-((6-fluoropyridin-2-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-((6-(2-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-((6-(3,5-difluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-((6-(cyclopropylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine;

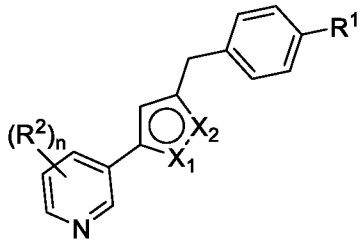
3-(3-(4-(3,5-difluorobenzyl)benzyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-((2-((3-fluorobenzyl)oxy)pyridin-4-yl)methyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-(4-(3-fluorobenzyl)benzyl)isoxazol-5-yl)pyridin-2-amine; and

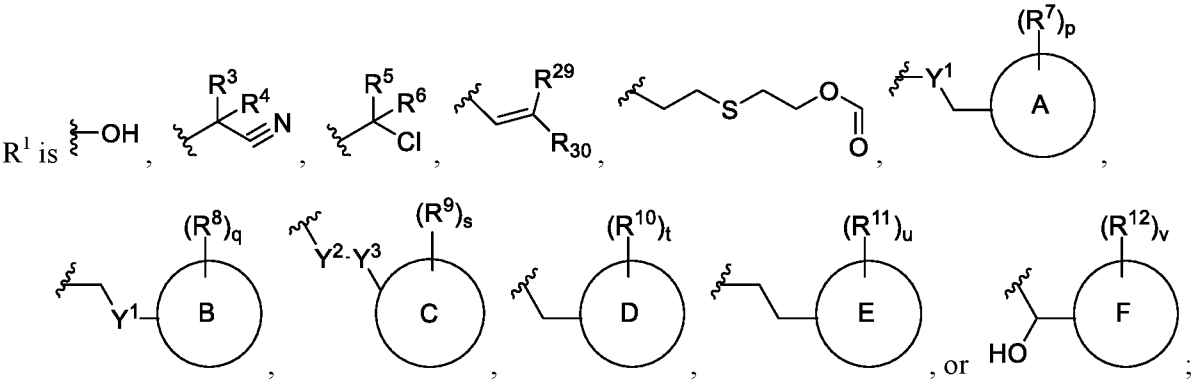
3-(3-(4-(((3-fluorophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof.

[0125] In some embodiments provided herein is a compound having the structure of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (I);

wherein:

R^1 is  ;

one of X_1 and X_2 is N while the other is O;

Y^1 is -O- or -S-;

one of Y^2 and Y^3 is -NH- while the other is -CH_2-;

Ring A is bicyclic aryl, bicyclic heteroaryl, monocylic heteroaryl containing at least 2 N atoms in the ring, or oxazolyl;

Ring B is bicyclic aryl, bicyclic heteroaryl, monocylic 5-membered heteroaryl, or cycloalkyl;

Ring C is heteroaryl or cycloalkyl;

Ring D is aryl, heteroaryl containing at least 1 N atom in the ring, or cycloalkyl;

Ring E is aryl, bicyclic heteroaryl, or cycloalkyl;

Ring F is aryl, heteroaryl, cycloalkyl, heterocycloalkyl;

each R^2 is independently hydrogen, -NH_2, or halogen;

each R^3, R^4, R^5, and R^6 are independently hydrogen, halogen, or C_1-C_6 alkyl;

each R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} is independently hydrogen, halogen, -CF_3, -CN, -CH_2-OH, -OR^a, -SR^a, -S(=O)R^b, -NO_2, -NR^cR^d, -S(=O)$_2R^d$, -$NR^aS(=O)_2R^d$, -S(=O)$_2NR^cR^d$, -C(=O)R^b, -OC(=O)R^b, -CO_2R^a, -OCO_2R^a, -C(=O)NR^cR^d, -OC(=O)NR^cR^d, -$NR^aC(=O)NR^cR^d$, -$NR^aC(=O)R^b$, -$NR^aC(=O)OR^a$, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R^{29} and R^{30} is independently hydrogen, halogen, C_1-C_6 alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl;

R^a is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

R^b is optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R^c and R^d is independently hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

or R^c and R^d, together with the nitrogen atom to which they are attached, form an optionally substituted heterocycloalkyl or optionally substituted heteroaryl;

n is 1-3;

p is 1-3;

q is 1-3;

s is 1-3;

t is 1-3;

u is 1-3; and

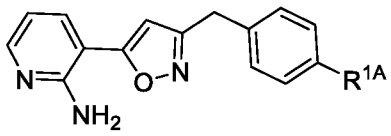
v is 1-3.

[0126] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, X^1 is O and X^2 is N. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, X^1 is N and X^2 is O. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, R^2 is $-NH_2$. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, R^2 is hydrogen. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, R^2 is a halogen. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, R^2 is -F, -Cl, or -Br.

[0127] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, n is 1. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, n is 2. In some

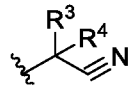
embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, n is 3.

[0128] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, the compound of Formula (I) is of Formula (Ia):



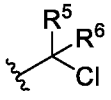
Formula (Ia).

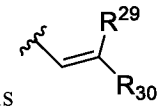
[0129] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^1 is 

. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^1 is 

. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^3 is hydrogen and R^4 is hydrogen. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^3 is hydrogen and R^4 is halogen. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^3 is halogen and R^4 is hydrogen. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^3 is C_1-C_6 alkyl and R^4 is hydrogen. In some embodiments of a compound of Formula (I) or (Ia), R^3 is methyl. In some embodiments of a compound of Formula (I) or (Ia), R^3 is ethyl. In some embodiments of a compound of Formula (I) or (Ia), R^3 is propyl. In some embodiments of a compound of Formula (I) or (Ia), R^3 is butyl. In some embodiments of a compound of Formula (I) or (Ia), R^3 is pentyl. In some embodiments of a compound of Formula (I) or (Ia), R^3 is hexyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^3 is hydrogen and R^4 is C_1-C_6 alkyl. In some embodiments of a compound of Formula (I) or (Ia), R^4 is methyl. In some embodiments of a compound of Formula (I) or (Ia), R^4 is ethyl. In some embodiments of a compound of Formula (I) or (Ia), R^4 is propyl. In some embodiments of a compound of Formula (I) or (Ia), R^4 is butyl. In some embodiments of a compound of Formula (I) or (Ia), R^4 is pentyl. In some embodiments of a compound of Formula (I) or (Ia), R^4 is hexyl.

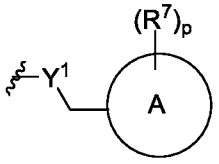
[0130] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^1

is  . In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^5 is hydrogen and R^6 is hydrogen. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^5 is hydrogen and R^6 is hydrogen. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^5 is C_1-C_6 alkyl and R^6 is hydrogen. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^5 is C_1-C_6 alkyl and R^6 is C_1-C_6 alkyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^5 is hydrogen and R^6 is C_1-C_6 alkyl. In some embodiments of a compound of Formula (I) or (Ia), R^5 is methyl. In some embodiments of a compound of Formula (I) or (Ia), R^5 is ethyl. In some embodiments of a compound of Formula (I) or (Ia), R^5 is propyl. In some embodiments of a compound of Formula (I) or (Ia), R^5 is butyl. In some embodiments of a compound of Formula (I) or (Ia), R^5 is pentyl. In some embodiments of a compound of Formula (I) or (Ia), R^5 is hexyl. In some embodiments of a compound of Formula (I) or (Ia), R^6 is methyl. In some embodiments of a compound of Formula (I) or (Ia), R^6 is ethyl. In some embodiments of a compound of Formula (I) or (Ia), R^6 is propyl. In some embodiments of a compound of Formula (I) or (Ia), R^6 is butyl. In some embodiments of a compound of Formula (I) or (Ia), R^6 is pentyl. In some embodiments of a compound of Formula (I) or (Ia), R^6 is hexyl.

[0131] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^1 is  . In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{29} is hydrogen and R^{30} is hydrogen. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{29} is hydrogen and R^{30} is hydrogen. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{29} is C_1-C_6 alkyl and R^{30} is hydrogen. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{29} is C_1-C_6 alkyl and R^{30} is C_1-C_6 alkyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{29} is hydrogen and R^{30} is C_1-C_6 alkyl. In some embodiments of a

compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{29} is hydrogen and R^{30} is cycloalkyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{29} is hydrogen and R^{30} is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{30} is hydrogen and R^{29} is cycloalkyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{30} is hydrogen and R^{29} is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

[0132] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^1 is $-(CH_2)_2S(CH_2)_2OC(O)H$.

[0133] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^1 is 

. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Y^1 is -O-. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Y^1 is -S-.

[0134] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A is bicyclic aryl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A is naphthyl.

[0135] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A is bicyclic heteroaryl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A is bicyclic heteroaryl selected from indolizinyl, indolyl, benzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, purinyl, quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, and pteridinyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A is quinolinyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate,

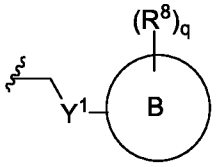
hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A is quinoxalinyl.

[0136] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A is monocylic heteroaryl containing at least 2 N atoms in the ring. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A is pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A is pyrimidinyl.

[0137] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A is oxazolyl.

[0138] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof p is 1. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof p is 2. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof p is 3. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^7 is hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^7 is hydrogen, $-CF_3$, or methyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^7 is hydrogen. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^7 is $-CF_3$. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^7 is methyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^7 is a halogen. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^7 is -F. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate,

hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^7 is -Cl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^7 is -Br.

[0139] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^1 is 

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[0140] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Y^1 is -O-. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Y^1 is -S-.

[0141] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B is bicyclic aryl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B is naphthyl.

[0142] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B is bicyclic heteroaryl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B is bicyclic heteroaryl selected from indolizinyl, indolyl, benzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, purinyl, quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, and pteridinyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B is bicyclic heteroaryl selected from indolyl, indazolyl, benzimidazolyl, quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, and pteridinyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B is quinolinyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B is quinoxalinyl.

[0143] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B is monocylic heteroaryl containing at least 2 N atoms in the ring. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a

stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B is monocylic heteroaryl containing at least 2 N atoms in the ring selected from pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B is pyrimidinyl.

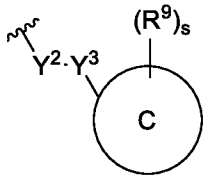
[0144] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B is oxazolyl.

[0145] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B is cycloalkyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B is cyclopropyl, cyclobutyl, cycolopentyl, or cyclohexyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B is cyclohexyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B is cyclopropyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B is cyclobutyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B is cyclopentyl.

[0146] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof q is 1. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof q is 2. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof q is 3.

[0147] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^8 is hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^8 is hydrogen, methyl, -CF_3, or halogen. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^8 is hydrogen. In some

embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^8 is methyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^8 is -CF_3. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^8 is halogen. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^8 is -Cl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^8 is -F.

[0148] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^1 is 

. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Y^2 is -CH_2- and Y^3 is -NH-. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Y^2 is -NH- and Y^3 is -CH_2-.

[0149] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C is heteroaryl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C is heteroaryl selected from azaindolyl, pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C is pyridinyl, thiadiazolyl, pyrimidinyl, azaindolyl, or thiazolyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C is pyridinyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C is thiadiazolyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically

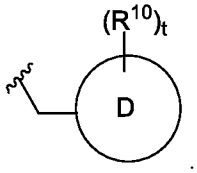
acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C is pyrimidinyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C is azaindolyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C is thiazolyl.

[0150] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C is cycloalkyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C is cyclopropyl, cyclobutyl, cycolopentyl, or cyclohexyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C is cyclohexyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C is cyclopropyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C is cyclobutyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C is cyclopentyl.

[0151] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof s is 1. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof s is 2. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof s is 3.

[0152] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^9 is hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^9 is hydrogen, methyl, -CF_3, or halogen. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^9 is hydrogen. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^9 is methyl.

In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^9 is -CF_3. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^9 is halogen. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^9 is -Cl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^9 is -F.

[0153] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^1 is 

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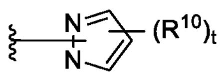
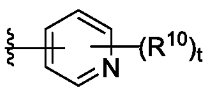
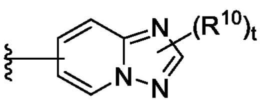
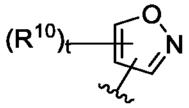
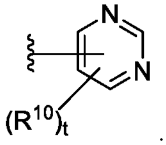
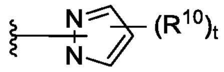
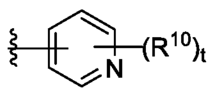
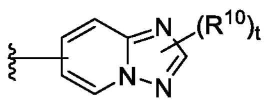
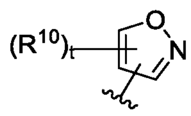
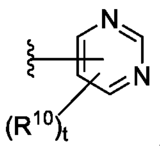
[0154] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D is aryl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C is phenyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C is naphthyl.

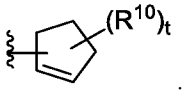
[0155] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D is heteroaryl containing at least 1 N atom in the ring. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D is heteroaryl containing at least 1 N atom in the ring including but not limited to azaindolyl, pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D is

selected from,  ,  ,  ,  , and  .

[0156] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D is  . In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D is  . In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D is  . In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D is  . In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D is

 .

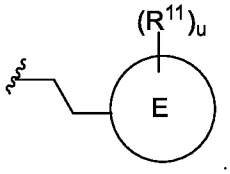
[0157] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D is cycloalkyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D is cyclopropyl, cyclobutyl, cycolopentyl, or cyclohexyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D is cyclohexyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D is cyclopropyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D is cyclobutyl. In some embodiments of a compound of Formula (I) or (Ia), or a

pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D is cyclopentyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D is partially saturated. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D is  .

[0158] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof t is 1. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof t is 2. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof t is 3.

[0159] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{10} is hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{10} is hydrogen, -CN, halogen, $-CF_3$, methyl, ethyl, and butyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{10} is hydrogen. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{10} is -CN. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{10} is -F. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{10} is $-CF_3$. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{10} is methyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{10} is ethyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{10} is propyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{10} is butyl. In some embodiments of a compound of Formula (I) or (Ia), or a

pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{10} is pentyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{10} is hexyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{10} is heptyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{10} is octyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{10} is nonyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{10} is decyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{10} is isobutyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{10} is isopentyl.

[0160] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^1 is 

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[0161] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E is aryl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E is phenyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E is naphthyl.

[0162] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E is bicyclic heteroaryl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E is bicyclic heteroaryl selected from indolizinyl, indolyl, benzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, purinyl, quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, and pteridinyl.

[0163] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof

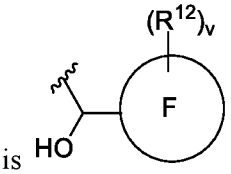
Ring E is indolyl, indazolyl, benzimidazolyl, quinazolinyl, or quinolinyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E is indolyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E is indazolyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E is benzimidazolyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E is quinazolinyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E is quinolinyl.

[0164] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E is cycloalkyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E is cyclopropyl, cyclobutyl, cycolopentyl, or cyclohexyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E is cyclohexyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E is cyclopropyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E is cyclobutyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E is cyclopentyl.

[0165] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof u is 1. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof u is 2. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof u is 3.

[0166] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{11} is hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments of a compound of Formula (I) or (Ia), or

a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{11} is hydrogen or $-CF_3$. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{11} is hydrogen. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{11} is $-CF_3$. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{11} is halogen. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{11} is -F. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{11} is -Cl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{11} is -Br.

[0167] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^1 is 

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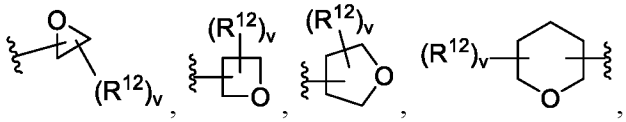
[0168] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is aryl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is phenyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is naphthyl.

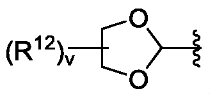
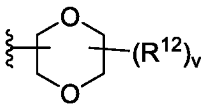
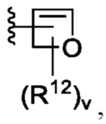
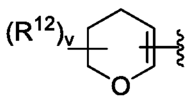
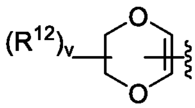
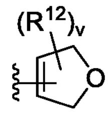
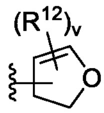
[0169] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is heteroaryl.

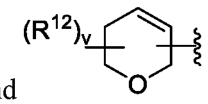
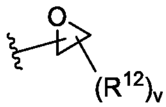
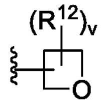
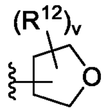
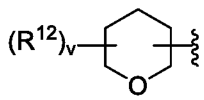
[0170] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is heteroaryl selected from azaindolyl, pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl.

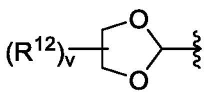
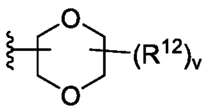
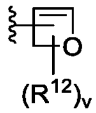
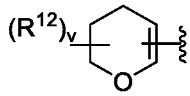
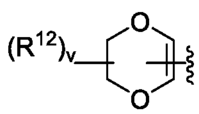
[0171] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is imidazolyl, triazolyl, pyrazinyl furyl, quinolinyl, benzofuranyl, quinazolinyl, or pyridazinyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is furyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is benzofuranyl.

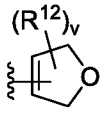
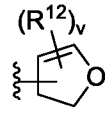
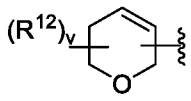
[0172] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is cycloalkyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is cyclohexyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is cyclopropyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is cyclobutyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is cyclopentyl.

[0173] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is heterocycloalkyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is a 5-membered heterocycloalkyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is a 6-membered heterocycloalkyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is heterocycloalkyl that contains at least one O atom. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is heterocycloalkyl that contains at least one O atom selected from  , , , ,

 ,  ,  ,  ,  ,  ,  ,

and  . In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is  . In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is  . In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is  . In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is  . In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is

 . In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is  . In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is  . In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is  . In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is  . In some

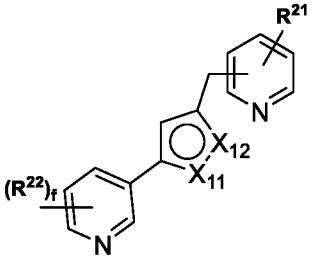
embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is  . In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is  . In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F is  .

[0174] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof v is 1. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof v is 2. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof v is 3.

[0175] In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{12} is hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{12} is hydrogen, $-CF_3$, methyl, or halogen. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{12} is hydrogen or $-CF_3$. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{12} is hydrogen. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{12} is $-CF_3$. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{12} is methyl. In some embodiments of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{12} is halogen. In some embodiments of a compound of Formula (I) or (Ia), or a

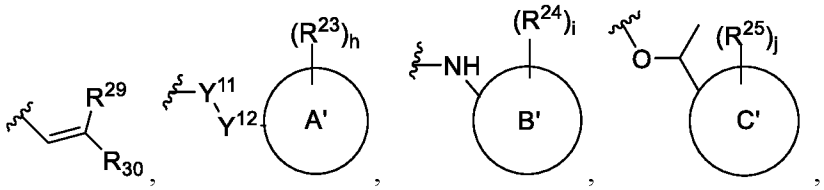
pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{12} is -F.

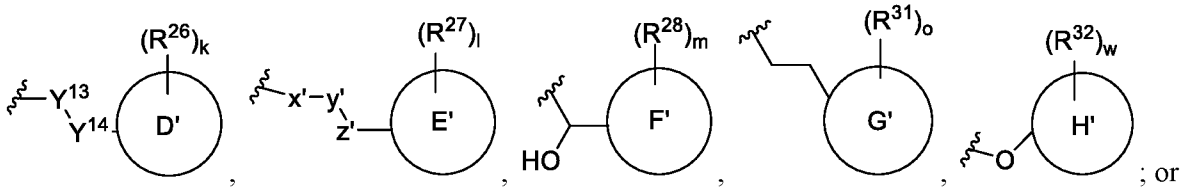
[0176] In some embodiments provided herein is a compound having the structure of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



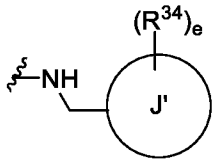
Formula (II)

wherein

R^{21} is halogen, 



; or



one of X_{11} and X_{12} is N while the other is O;

one of Y^{11} and Y^{12} is -NH- or -O- while the other is $-CH_2-$;

one of Y^{13} and Y^{14} is -S- while the other is $-CH_2-$;

one of x' y' and z' is -O- while the others are $-CH_2-$;

Ring A' is heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring B' is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring C' is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring D' is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring E' is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring F' is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring G' is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring H' is bicyclic aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring J' is aryl;

R^{22} is hydrogen, $-NH_2$, or halogen;

each R^{29} and R^{30} is independently hydrogen, halogen, C_1-C_6 alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl;

each R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{31}, R^{32} is independently hydrogen, halogen, $-CF_3$, -CN, $-OR^a$, $-SR^a$, $-S(=O)R^b$, $-NO_2$, $-NR^cR^d$, $-S(=O)_2R^d$, $-NR^aS(=O)_2R^d$, $-S(=O)_2NR^cR^d$, $-C(=O)R^b$, $-OC(=O)R^b$, $-CO_2R^a$, $-OCO_2R^a$, $-C(=O)NR^cR^d$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)NR^cR^d$, $-NR^aC(=O)R^b$, $-NR^aC(=O)OR^a$, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^a is hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^b is substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^c and R^d is independently hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or R^c and R^d, together with the nitrogen atom to which they are attached, form an substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

f is 1;

h is 1-3;

i is 1-3;

j is 1-3;

k is 1-3;

l is 1-3;

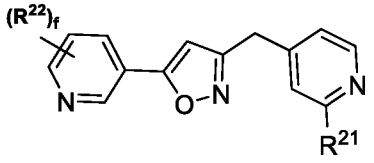
m is 1-3;

o is 1-3;

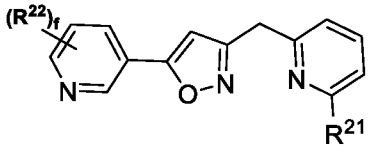
w is 1-3; and

e is 1-3.

[0177] In some embodiments provided herein is a compound having the structure of Formula (II') or Formula (II''), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:

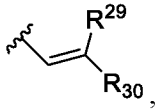
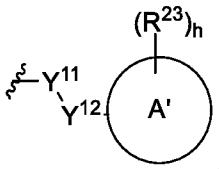
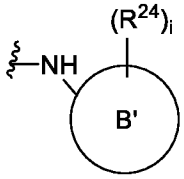
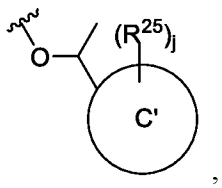
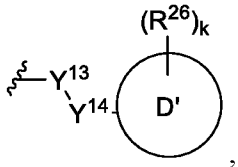
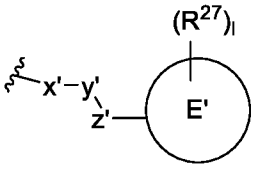
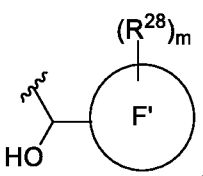
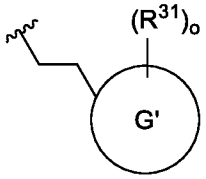
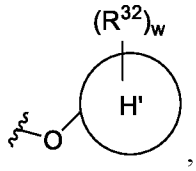
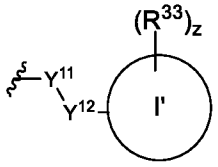
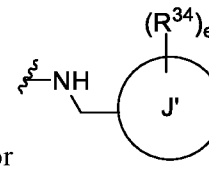


Formula (II')



Formula (II")

wherein

R^{21} is halogen,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , or ;

one of X_{11} and X_{12} is N while the other is O;

one of Y^{11} and Y^{12} is -NH- or -O- while the other is $-CH_2-$;

one of Y^{13} and Y^{14} is -S- while the other is $-CH_2-$;

one of x' y' and z' is -O- while the others are $-CH_2-$;

Ring A' is heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring B' is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring C' is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring D' is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring E' is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring F' is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring G' is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring H' is bicyclic aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Ring I' is aryl,

Ring J' is aryl,

R^{22} is hydrogen, $-NH_2$, or halogen;

R^{29} and R^{30} are independently hydrogen, halogen, C_1-C_6 alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl;

each R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{31}, R^{32}, R^{33}, R^{34} is independently hydrogen, halogen, $-CF_3$, -CN, $-OR^a$, $-SR^a$, $-S(=O)R^b$, $-NO_2$, $-NR^cR^d$, $-S(=O)_2R^d$, $-NR^aS(=O)_2R^d$, $-S(=O)_2NR^cR^d$, $-C(=O)R^b$, $-OC(=O)R^b$, $-CO_2R^a$, $-OCO_2R^a$, $-C(=O)NR^cR^d$, $-OC(=O)NR^cR^d$, $-NR^aC(=O)NR^cR^d$, $-NR^aC(=O)R^b$, $-NR^aC(=O)OR^a$, substituted or unsubstituted C_1-C_6 alkyl, substituted or

unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^a is hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^b is substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^c and R^d is independently hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

or R^c and R^d, together with the nitrogen atom to which they are attached, form an substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

f is 1;

h is 1-3;

i is 1-3;

j is 1-3;

k is 1-3;

l is 1-3;

m is 1-3;

o is 1-3;

w is 1-3;

z is 1-3; and

e is 1-3.

[0178] In some embodiments of a compound of Formula (II), (II'), or (II''), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, X_{11} is O and X_{12} is N.

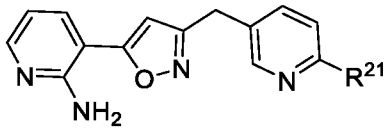
[0179] In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, X_{11} is N and X_{12} is O.

[0180] In some embodiments of a compound of Formula (II), (II'), or (II''), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic

variant thereof, R^{22} is $-NH_2$. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, R^{22} is hydrogen. In some embodiments of a compound of Formula (II), (II'), or (II''), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, R^{22} is a halogen. In some embodiments of a compound of Formula (II), (II'), or (II''), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, R^{22} is -F, -Cl, or -Br.

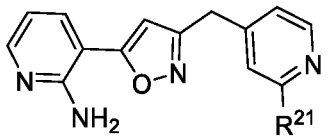
[0181] In some embodiments of a compound of Formula (II), (II'), or (II''), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, f is 1.

[0182] In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, the compound of Formula (II) is of Formula (IIa):



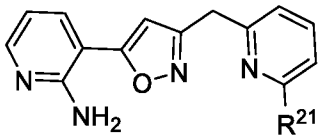
Formula (IIa).

[0183] In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, the compound of Formula (II) is of Formula (IIb):



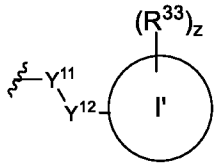
Formula (IIb).

[0184] In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, the compound of Formula (II) is of Formula (IIc):



Formula (IIc).

[0185] In some embodiments a compound of Formula (II') or (II''), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{21} is



. In some embodiments of a compound of Formula (II') or (II''), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Y^{11} is -O- and Y^{12} is $-CH_2-$. In some embodiments of a compound of Formula (II') or (II''), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of

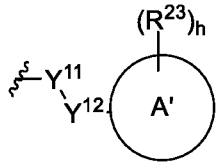
stereoisomers, or an isotopic variant thereof Y^{11} is -NH- and Y^{12} is -CH_2-. In some embodiments of a compound of Formula (II') or (II''), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Y^{12} is -O- and Y^{11} is -CH_2-. In some embodiments of a compound of Formula (II') or (II''), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Y^{12} is -NH- and Y^{11} is -CH_2-.

[0186] In some embodiments of a compound of Formula (II') or (II''), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring I' is aryl. In some embodiments of a compound of Formula (II') or (II''), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring I' is phenyl. In some embodiments of a compound of Formula (II') or (II''), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring I' is naphthyl.

[0187] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof z is 1. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof z is 2. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof z is 3. In some embodiments of a compound of Formula (II') or (II''), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{33} is hydrogen, methyl, or –F. In some embodiments of a compound of Formula (II') or (II''), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{33} is hydrogen. In some embodiments of a compound of Formula (II') or (II''), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{33} is methyl. In some embodiments of a compound of Formula (II') or (II''), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{33} is a halogen. In some embodiments of a compound of Formula (II') or (II''), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{33} is -Cl. In some embodiments of a compound of Formula (II') or (II''), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{33} is -F. In some embodiments of a compound of Formula (II') or (II''), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{33} is -Br.

[0188] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II') or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{21} is -F. In some embodiments of a compound of Formula (II), (IIa), (IIb),

(IIc), (II'), or (II''), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{21} is -Cl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (I') or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{21} is -Br.

[0189] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{21} is 

. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Y^{11} is -O- and Y^{12} is -CH_2-. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Y^{11} is -NH- and Y^{12} is -CH_2-. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Y^{12} is -O- and Y^{11} is -CH_2-. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Y^{12} is -NH- and Y^{11} is -CH_2-.

[0190] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A' is heteroaryl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A' is heteroaryl selected from azaindolyl, pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A' is heteroaryl selected from pyridinyl, isoxazolyl, thienyl, thiazolyl, pyrazolyl, pyrimidinyl, furyl, and oxazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A' is pyridinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A' is isoxazolyl. In

some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A' is thienyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A' is thiazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A' is pyrazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A' is pyrimidinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A' is furyl.In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A' is oxazolyl.

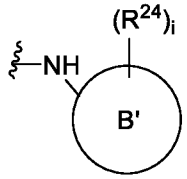
[0191] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A' is cycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A' is C_3-C_6 cycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A' is cyclopropyl and cyclobutyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A' is cyclohexyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A' is cyclopropyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A' is cyclobutyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A' is cyclopentyl.

[0192] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A' is heterocycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A' is heterocycloalkyl selected

from pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, oxazolidinonyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, aziridinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, pyrrolin-2-yl, pyrrolin-3-yl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl, indolin-2-onyl, isoindolin-1-onyl, isoindoline-1,3-dionyl, 3,4-dihydroisoquinolin-1(2H)-onyl, 3,4-dihydroquinolin-2(1H)-onyl, isoindoline-1,3-dithionyl, benzo[d]oxazol-2(3H)-onyl, 1H-benzo[d]imidazol-2(3H)-onyl, benzo[d]thiazol-2(3H)-onyl, and quinolizinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A' is heterocycloalkyl selected from tetrahydrofuranyl, piperazinyl, oxetanyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, imidazolinyl,and quinolizinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring A' is oxetanyl.

[0193] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof h is 1. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof h is 2. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof h is 3. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{23} is hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{23} is hydrogen, methyl, or –F. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{23} is hydrogen. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{23} is methyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{23} is a halogen. In

some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{23} is -Cl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{23} is -F. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{23} is -Br.

[0194] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{21} is 

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[0195] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, Ring B' is aryl.

[0196] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II''), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, Ring B' is phenyl.

[0197] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II') or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, wherein: Ring B' is naphthyl.

[0198] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B' is heteroaryl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, Ring B' is heteroaryl selected from azaindolyl, pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl.

[0199] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, Ring B' is heteroaryl selected from pyridinyl, isoxazolyl, thienyl, thiazolyl, pyrazolyl, pyrimidinyl, furyl, and oxazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, Ring B' is pyridinyl. In some embodiments of a

compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, Ring B' is isoxazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II''), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B' is thienyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B' is thiazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B' is pyrazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B' is pyrimidinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B' is furyl.

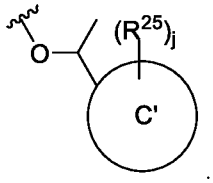
[0200] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B' is cycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B' is C_3-C_6 cycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B' is cyclopropyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B' is cyclobutyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B' is cyclopentyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B' is cyclohexyl.

[0201] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B' is heterocycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, Ring B' is heterocycloalkyl selected from pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, oxazolidinonyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, aziridinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, pyrrolin-2-yl, pyrrolin-3-yl, indolinyl,

2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl, indolin-2-onyl, isoindolin-1-onyl, isoindoline-1,3-dionyl, 3,4-dihydroisoquinolin-1(2H)-onyl, 3,4-dihydroquinolin-2(1H)-onyl, isoindoline-1,3-dithionyl, benzo[d]oxazol-2(3H)-onyl, 1H-benzo[d]imidazol-2(3H)-onyl, benzo[d]thiazol-2(3H)-onyl, and quinolizinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B' is heterocycloalkyl selected from tetrahydrofuranyl, piperazinyl, oxetanyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, imidazolinyl,and quinolizinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring B' is oxetanyl.

[0202] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II''), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof i is 1. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof i is 2. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof i is 3. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{24} is hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{24} is hydrogen, methyl, or –F. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{24} is hydrogen. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{24} is methyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{24} is a halogen. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{24} is -Cl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of

stereoisomers, or an isotopic variant thereof R^{24} is -F. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof, R^{24} is -Br.

[0203] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{21} is 

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[0204] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C' is aryl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C' is phenyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C' is naphthyl.

[0205] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C' is heteroaryl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C' is heteroaryl selected from azaindolyl, pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl.

[0206] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C' is heteroaryl selected from pyridinyl, isoxazolyl, thienyl, thiazolyl, pyrazolyl, pyrimidinyl, furyl, and oxazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C' is pyridinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C' is isoxazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C' is thienyl. In some embodiments of a compound of Formula (II), (IIa),

(IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C' is thiazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C' is pyrazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C' is pyrimidinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C' is furyl.

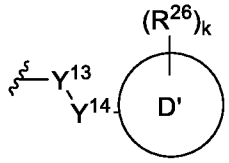
[0207] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C' is cycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C' is C_3-C_6 cycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C' is cyclopropyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C' is cyclobutyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C' is cyclopentyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C' is cyclohexyl.

[0208] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C' is heterocycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C' is heterocycloalkyl selected from pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, oxazolidinonyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, aziridinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, pyrrolin-2-yl, pyrrolin-3-yl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl, indolin-2-onyl, isoindolin-1-onyl, isoindoline-1,3-dionyl, 3,4-dihydroisoquinolin-1(2H)-onyl, 3,4-dihydroquinolin-2(1H)-onyl, isoindoline-1,3-dithionyl, benzo[d]oxazol-2(3H)-onyl, 1H-benzo[d]imidazol-2(3H)-onyl, benzo[d]thiazol-2(3H)-onyl, and

quinolizinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C' is heterocycloalkyl selected from tetrahydrofuranyl, piperazinyl, oxetanyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, imidazolinyl,and quinolizinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring C' is oxetanyl.

[0209] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof j is 1. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof j is 2. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof j is 3. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{25} is hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{25} is hydrogen, methyl, or -F. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{25} is hydrogen. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{25} is methyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{25} is a halogen. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{25} is -Cl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{25} is -F. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{25} is -Br.

[0210] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or

an isotopic variant thereof R^{21} is  . In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof wherein Y^{13} is S and Y^{14} is $-CH_2-$. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof wherein Y^{13} is $-CH_2-$ and Y^{14} is -S-.

[0211] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D' is aryl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D' is phenyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D' is naphthyl.

[0212] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D' is heteroaryl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D' is heteroaryl selected from azaindolyl, pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl.

[0213] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D' is heteroaryl selected from pyridinyl, isoxazolyl, thienyl, thiazolyl, pyrazolyl, pyrimidinyl, furyl, and oxazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D' is pyridinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D' is isoxazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D' is thienyl. In some embodiments of a compound of Formula (II), (IIa),

(IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D' is thiazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D' is pyrazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D' is pyrimidinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D' is furyl.

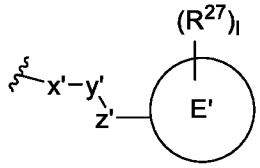
[0214] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D' is cycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D' is C_3-C_6 cycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D' is cyclopropyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D' is cyclobutyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D' is cyclopentyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D' is cyclohexyl.

[0215] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D' is heterocycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D' is heterocycloalkyl selected from pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, oxazolidinonyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, aziridinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, pyrrolin-2-yl, pyrrolin-3-yl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl, indolin-2-onyl, isoindolin-1-onyl, isoindoline-1,3-dionyl, 3,4-dihydroisoquinolin-1(2H)-onyl, 3,4-dihydroquinolin-2(1H)-onyl, isoindoline-1,3-dithionyl, benzo[d]oxazol-2(3H)-onyl, 1H-benzo[d]imidazol-2(3H)-onyl, benzo[d]thiazol-2(3H)-onyl, and

quinolizinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D' is heterocycloalkyl selected from tetrahydrofuranyl, piperazinyl, oxetanyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, imidazolinyl,and quinolizinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring D' is oxetanyl.

[0216] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof k is 1. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof k is 2. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof k is 3. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{26} is hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{26} is hydrogen, methyl, or -F. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{26} is hydrogen. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{26} is methyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{26} is a halogen. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{26} is -Cl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{26} is -F. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{26} is -Br.

[0217] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or

an isotopic variant thereof R^{21} is  . In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof x' is O; y' is $-CH_2-$; and z' is $-CH_2-$. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof x' is $-CH_2-$; y' is -O-; and z' is $-CH_2-$. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof x' is $-CH_2-$; y' is $-CH_2-$; and z' is -O-.

[0218] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E' is aryl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E' is phenyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E' is naphthyl.

[0219] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E' is heteroaryl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E' is heteroaryl selected from azaindolyl, pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl.

[0220] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E' is heteroaryl selected from pyridinyl, isoxazolyl, thienyl, thiazolyl, pyrazolyl, pyrimidinyl, furyl, and oxazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E' is pyridinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E' is

isoxazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E' is thienyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E' is thiazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E' is pyrazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E' is pyrimidinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E' is furyl.

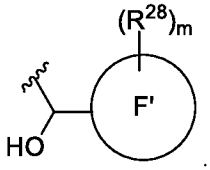
[0221] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E' is cycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E' is C_3-C_6 cycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E' is cyclopropyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E' is cyclobutyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E' is cyclopentyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E' is cyclohexyl.

[0222] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E' is heterocycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E' is heterocycloalkyl selected from pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, oxazolidinonyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, aziridinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, pyrrolin-2-yl, pyrrolin-3-yl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl,

3-azabicyclo[4.1.0]heptanyl, 3H-indolyl, indolin-2-onyl, isoindolin-1-onyl, isoindoline-1,3-dionyl, 3,4-dihydroisoquinolin-1(2H)-onyl, 3,4-dihydroquinolin-2(1H)-onyl, isoindoline-1,3-dithionyl, benzo[d]oxazol-2(3H)-onyl, 1H-benzo[d]imidazol-2(3H)-onyl, benzo[d]thiazol-2(3H)-onyl, and quinolizinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E' is heterocycloalkyl selected from tetrahydrofuranyl, piperazinyl, oxetanyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, imidazolinyl,and quinolizinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring E' is oxetanyl.

[0223] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof l is 1. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof l is 2. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof l is 3. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{27} is hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{27} is hydrogen, methyl, or -F. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{27} is hydrogen. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{27} is methyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{27} is a halogen. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{27} is -Cl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{27} is -F. In some embodiments of a compound of Formula

(II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{27} is -Br.

[0224] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{21} is 

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[0225] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F' is aryl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F' is phenyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F' is naphthyl.

[0226] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F' is heteroaryl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F' is heteroaryl selected from azaindolyl, pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl.

[0227] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F' is heteroaryl selected from pyridinyl, isoxazolyl, thienyl, thiazolyl, pyrazolyl, pyrimidinyl, furyl, and oxazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F' is pyridinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F' is isoxazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F' is thienyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer,

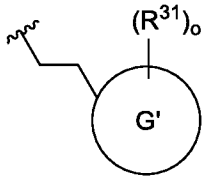
mixture of stereoisomers, or an isotopic variant thereof Ring F' is thiazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F' is pyrazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F' is pyrimidinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F' is furyl.

[0228] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F' is cycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F' is C_3-C_6 cycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F' is cyclopropyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F' is cyclobutyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F' is cyclopentyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F' is cyclohexyl.

[0229] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F' is heterocycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F' is heterocycloalkyl selected from pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, oxazolidinonyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, aziridinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, pyrrolin-2-yl, pyrrolin-3-yl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl, indolin-2-onyl, isoindolin-1-onyl, isoindoline-1,3-dionyl, 3,4-dihydroisoquinolin-1(2H)-onyl, 3,4-dihydroquinolin-2(1H)-onyl, isoindoline-1,3-dithionyl, benzo[d]oxazol-2(3H)-onyl, 1H-benzo[d]imidazol-2(3H)-onyl, benzo[d]thiazol-2(3H)-onyl, and quinolizinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a

pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F' is heterocycloalkyl selected from tetrahydrofuranyl, piperazinyl, oxetanyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, imidazolinyl,and quinolizinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring F' is oxetanyl.

[0230] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof m is 1. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof m is 2. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof m is 3. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{28} is hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{28} is hydrogen, methyl, or -F. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{28} is hydrogen. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{28} is methyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{28} is a halogen. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{28} is -Cl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{28} is -F. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{28} is -Br.

[0231] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{21} is 

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[0232] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring G' is aryl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring G' is phenyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring G' is naphthyl.

[0233] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring G' is heteroaryl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring G' is heteroaryl selected from azaindolyl, pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl.

[0234] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring G' is heteroaryl selected from pyridinyl, isoxazolyl, thienyl, thiazolyl, pyrazolyl, pyrimidinyl, furyl, and oxazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring G' is pyridinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring G' is isoxazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring G' is thienyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring G' is thiazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate,

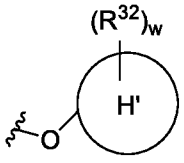
hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring G' is pyrazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring G' is pyrimidinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring G' is furyl.

[0235] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring G' is cycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring G' is C_3-C_6 cycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring G' is cyclopropyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring G' is cyclobutyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring G' is cyclopentyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring G' is cyclohexyl.

[0236] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring G' is heterocycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring G' is heterocycloalkyl selected from pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, oxazolidinonyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, aziridinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, pyrrolin-2-yl, pyrrolin-3-yl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl, indolin-2-onyl, isoindolin-1-onyl, isoindoline-1,3-dionyl, 3,4-dihydroisoquinolin-1(2H)-onyl, 3,4-dihydroquinolin-2(1H)-onyl, isoindoline-1,3-dithionyl, benzo[d]oxazol-2(3H)-onyl, 1H-benzo[d]imidazol-2(3H)-onyl, benzo[d]thiazol-2(3H)-onyl, and quinolizinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring G' is heterocycloalkyl selected from tetrahydrofuranyl, piperazinyl,

oxetanyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, imidazolinyl,and quinolizinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring G' is oxetanyl.

[0237] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof o is 1. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof o is 2. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof o is 3. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{31} is hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{31} is hydrogen, methyl, or -F. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{31} is hydrogen. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{31} is methyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{31} is a halogen. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{31} is -Cl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{31} is -F. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{31} is -Br.

[0238] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{21} is 

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[0239] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring H' is aryl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring H' is naphthyl.

[0240] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring H' is heteroaryl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring H' is heteroaryl selected from azaindolyl, pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl.

[0241] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring H' is heteroaryl selected from pyridinyl, isoxazolyl, thienyl, thiazolyl, pyrazolyl, pyrimidinyl, furyl, and oxazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring H' is pyridinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring H' is isoxazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring H' is thienyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring H' is thiazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring H' is pyrazolyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or

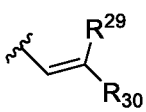
an isotopic variant thereof Ring H' is pyrimidinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring H' is furyl.

[0242] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring H' is cycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring H' is C_3-C_6 cycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring H' is cyclopropyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring H' is cyclobutyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring H' is cyclopentyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring H' is cyclohexyl.

[0243] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring H' is heterocycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring H' is heterocycloalkyl selected from pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, oxazolidinonyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, aziridinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, pyrrolin-2-yl, pyrrolin-3-yl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl, indolin-2-onyl, isoindolin-1-onyl, isoindoline-1,3-dionyl, 3,4-dihydroisoquinolin-1(2H)-onyl, 3,4-dihydroquinolin-2(1H)-onyl, isoindoline-1,3-dithionyl, benzo[d]oxazol-2(3H)-onyl, 1H-benzo[d]imidazol-2(3H)-onyl, benzo[d]thiazol-2(3H)-onyl, and quinolizinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring H' is heterocycloalkyl selected from tetrahydrofuranyl, piperazinyl, oxetanyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, imidazolinyl,and quinolizinyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II'') or a

pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring H' is oxetanyl.

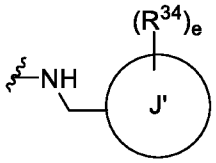
[0244] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof w is 1. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof w is 2. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof w is 3. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{32} is hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{32} is hydrogen, methyl, or -F. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{32} is hydrogen. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{32} is methyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{32} is a halogen. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{32} is -Cl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{32} is -F. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{32} is -Br.

[0245] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II') or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{21} is 

. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II') or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{29} is hydrogen and R^{30} is

hydrogen. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II') or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{29} is hydrogen and R^{30} is hydrogen. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II') or (II"), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{29} is C_1-C_6 alkyl and R^{30} is hydrogen. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II') or (II"), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{29} is C_1-C_6 alkyl and R^{30} is C_1-C_6 alkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II') or (II"), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{29} is hydrogen and R^{30} is C_1-C_6 alkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II') or (II"), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{29} is hydrogen and R^{30} is cycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II') or (II"), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{29} is hydrogen and R^{30} is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II') or (II"), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{30} is hydrogen and R^{29} is cycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II') or (II"), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{30} is hydrogen and R^{29} is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

[0246] In some embodiments a compound of Formula (II), (IIa), (IIb), (IIc), (II') or (II"), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof

acceptable salt, solvate, tautomer, or stereoisomer thereof R^{21} is 

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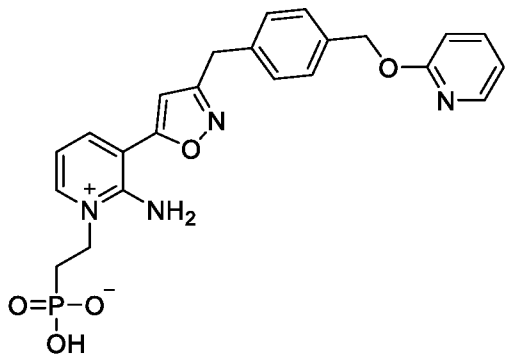
[0247] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II') or (II"), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring J' is aryl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II') or (II"), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring J' is phenyl. In some embodiments of a compound of Formula Formula (II), (IIa), (IIb), (IIc), (II') or (II"), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof Ring J' is naphthyl.

[0248] In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or

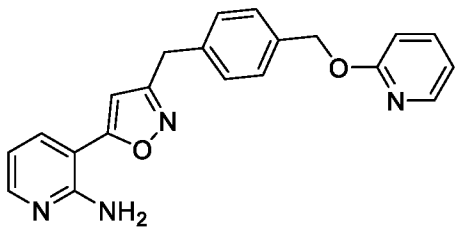
an isotopic variant thereof e is 1. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof e is 2. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II'), or (II") or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof e is 3. In some embodiments of a compound of Formula Formula (II), (IIa), (IIb), (IIc), (II') or (II"), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{34} is hydrogen, methyl, or –F. In some embodiments of a compound of Formula Formula (II), (IIa), (IIb), (IIc), (II') or (II"), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{34} is hydrogen. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II') or (II"), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{34} is methyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II') or (II"), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{33} is a halogen. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II') or (II"), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{34} is -Cl. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II') or (II"), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{34} is -F. In some embodiments of a compound of Formula (II), (IIa), (IIb), (IIc), (II') or (II"), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof R^{34} is -Br.

[0249] In some embodiments, the compound of Formula (III) is not hydrogen (2-(2-amino-3-(3-(4-((pyridin-2-yloxy)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)ethyl)phosphonate or a compound having structural formula:



Compound 1.

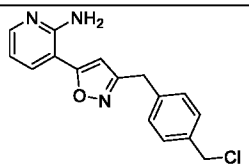
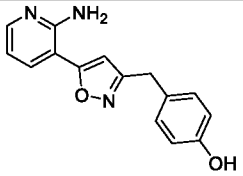
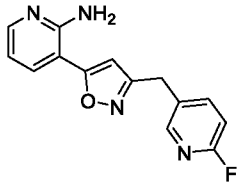
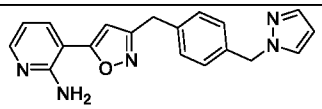
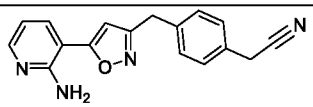
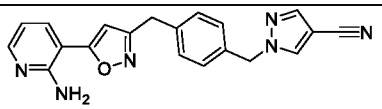
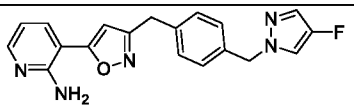
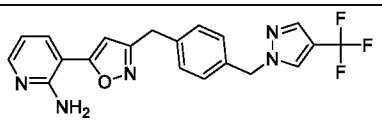
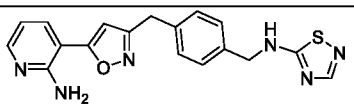
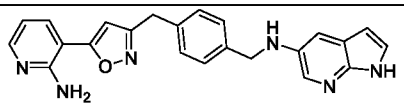
[0250] In some embodiments, the compound of Formula (III) is not 3-(3-(4-((pyridin-2-yloxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine or a compound having structural formula:

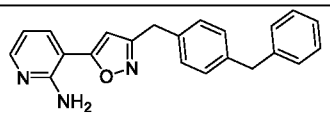
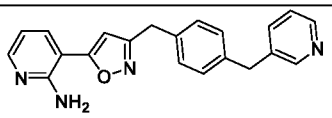
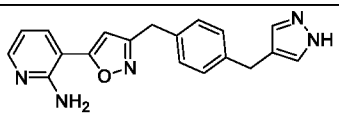
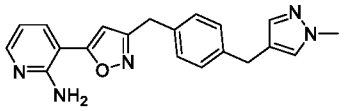
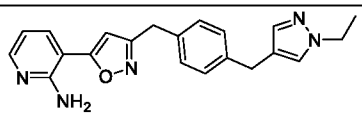
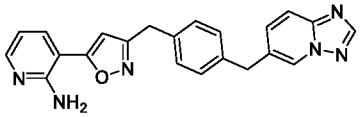
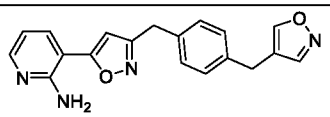
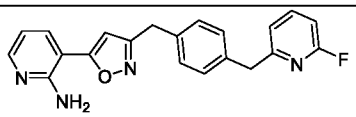
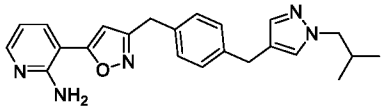
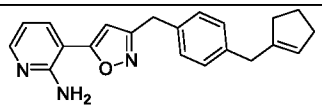
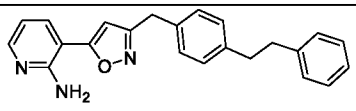
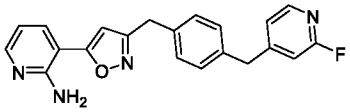
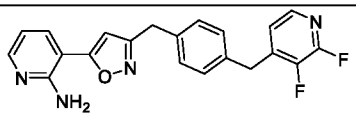
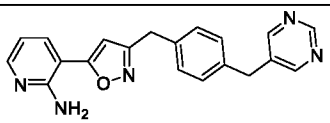


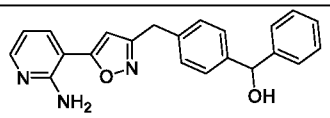
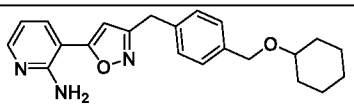
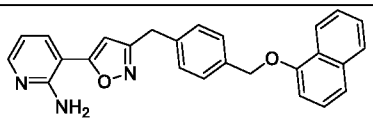
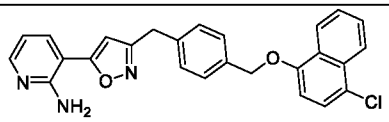
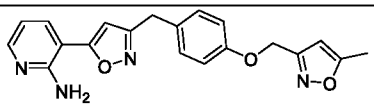
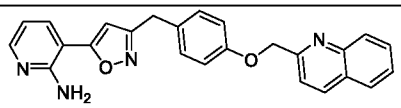
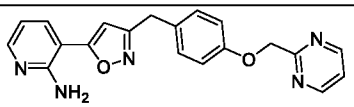
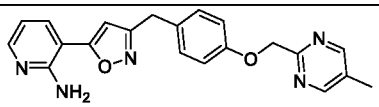
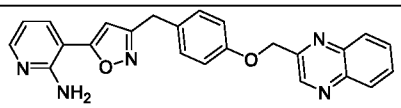
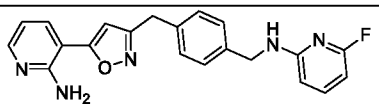
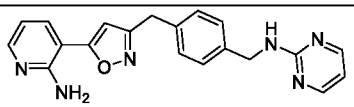
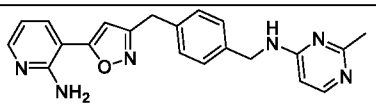
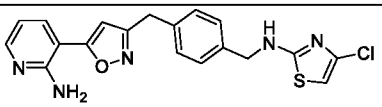
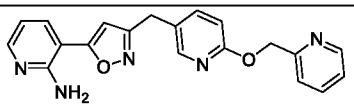
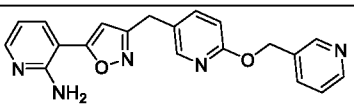
Compound 2.

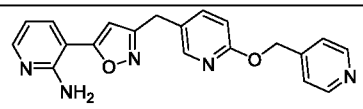
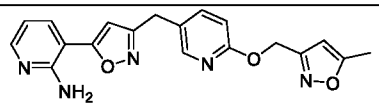
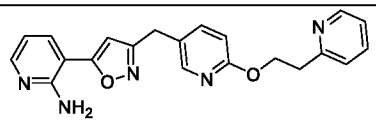
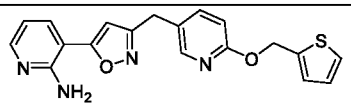
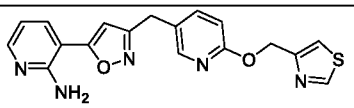
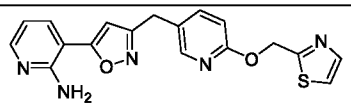
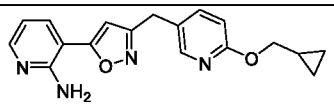
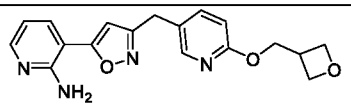
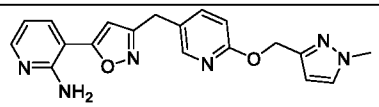
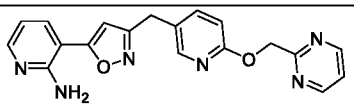
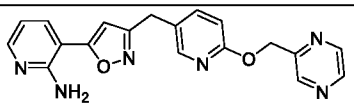
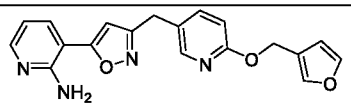
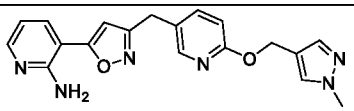
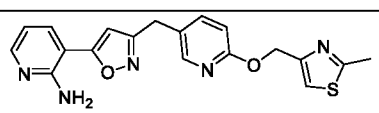
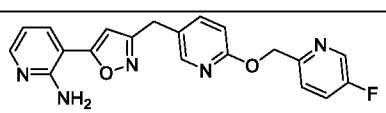
[0251] In some embodiments, there is a compound, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, having a structure selected from the compounds in **Table 1**.

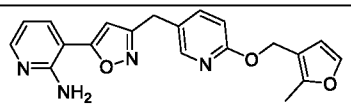
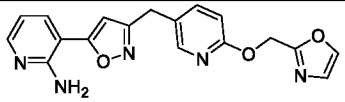
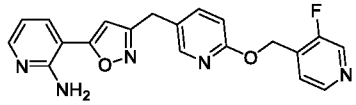
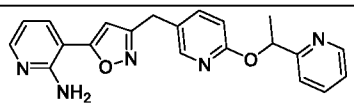
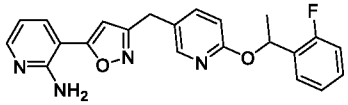
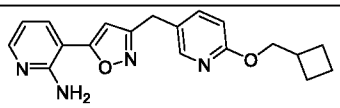
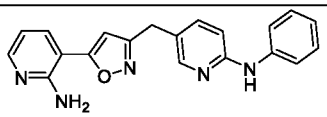
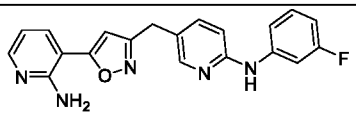
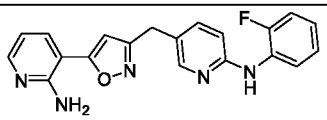
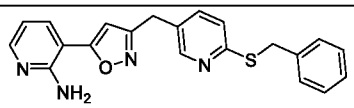
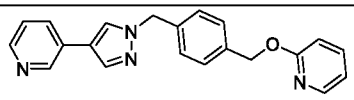
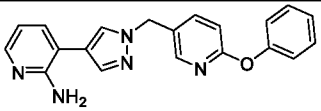
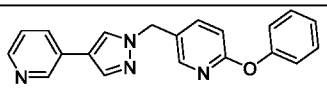
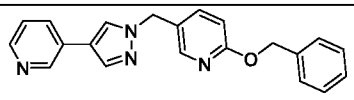
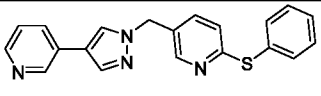
Table 1.

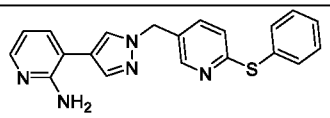
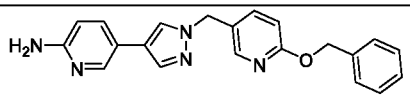
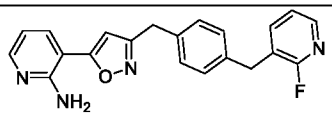
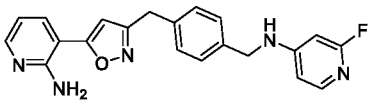
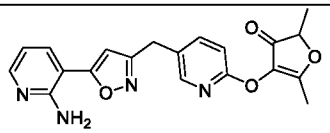
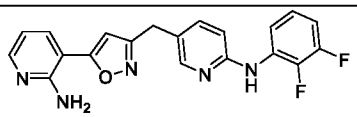
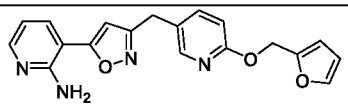
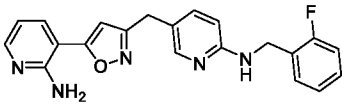
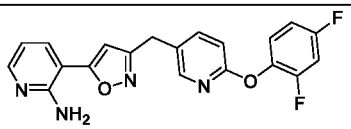
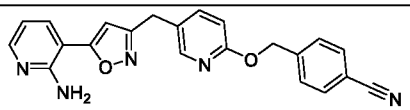
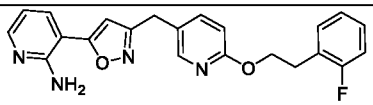
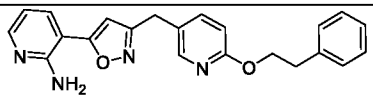
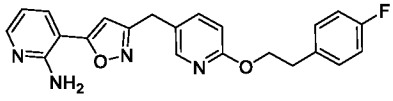
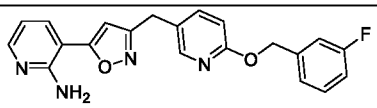
Ex.	Structure	Name
B		3-(3-(4-(chloromethyl)benzyl)isoxazol-5-yl)pyridin-2-amine
C		4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenol
E		3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
1		3-(3-(4-((1H-pyrazol-1-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
2		2-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenyl)acetonitrile
3		1-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)-1H-pyrazole-4-carbonitrile
4		3-(3-(4-((4-fluoro-1H-pyrazol-1-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
5		3-(3-(4-((4-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
6		N-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)-1,2,4-thiadiazol-5-amine
7		N-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)-1H-pyrrolo[2,3-b]pyridin-5-amine

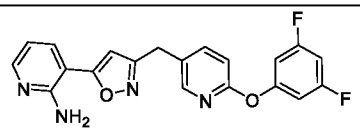
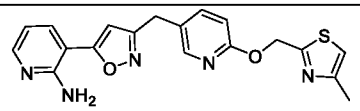
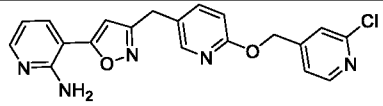
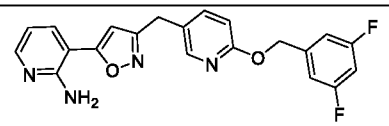
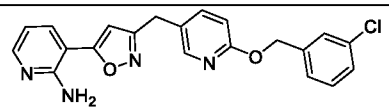
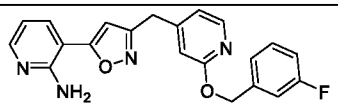
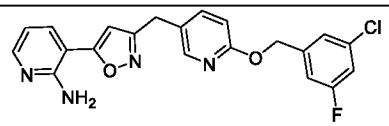
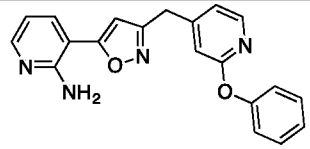
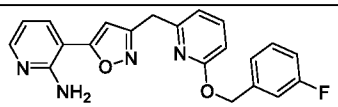
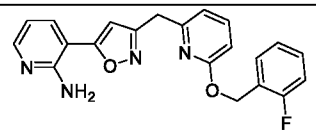
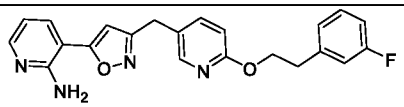
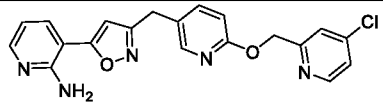
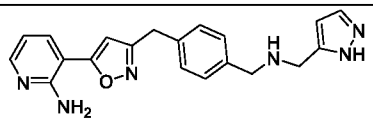
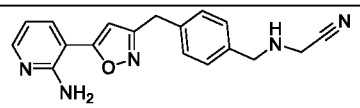
Ex.	Structure	Name
8		3-(3-(4-benzylbenzyl)isoxazol-5-yl)pyridin-2-amine
9		3-(3-(4-(pyridin-3-ylmethyl)benzyl)isoxazol-5-yl)pyridin-2-amine
10		3-(3-(4-((1H-pyrazol-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
11		3-(3-(4-((1-methyl-1H-pyrazol-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
12		3-(3-(4-((1-ethyl-1H-pyrazol-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
13		3-(3-(4-([1,2,4]triazolo[1,5-a]pyridin-6-ylmethyl)benzyl)isoxazol-5-yl)pyridin-2-amine
14		3-(3-(4-(isoxazol-4-ylmethyl)benzyl)isoxazol-5-yl)pyridin-2-amine
15		3-(3-(4-((6-fluoropyridin-2-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
16		3-(3-(4-((1-isobutyl-1H-pyrazol-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
17		3-(3-(4-(cyclopent-1-en-1-ylmethyl)benzyl)isoxazol-5-yl)pyridin-2-amine
18		3-(3-(4-phenethylbenzyl)isoxazol-5-yl)pyridin-2-amine
19		3-(3-(4-((2-fluoropyridin-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
20		3-(3-(4-((2,3-difluoropyridin-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
21		3-(3-(4-(pyrimidin-5-ylmethyl)benzyl)isoxazol-5-yl)pyridin-2-amine

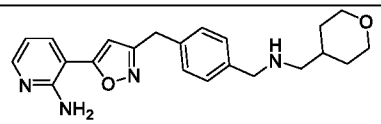
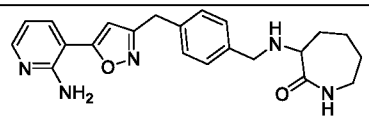
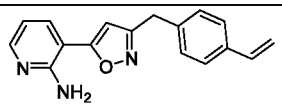
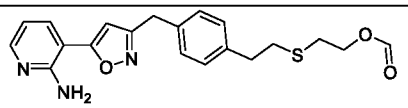
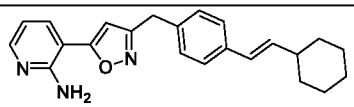
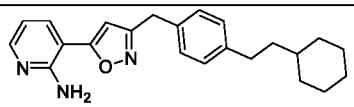
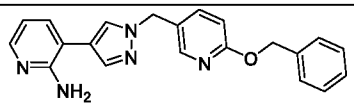
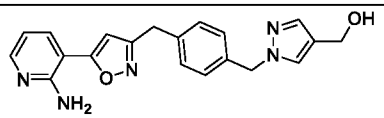
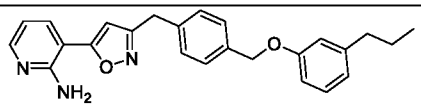
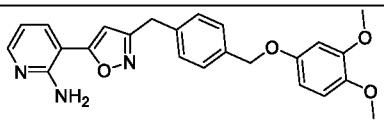
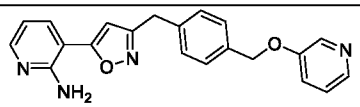
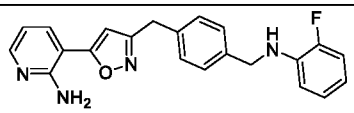
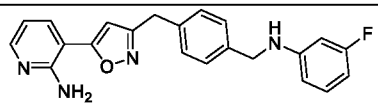
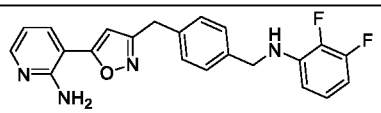
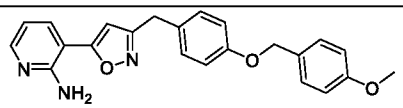
Ex.	Structure	Name
22		(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenyl)(phenyl)methanol
23		3-(3-(4-((cyclohexyloxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
24		3-(3-(4-((naphthalen-1-yloxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
25		3-(3-(4-(((4-chloronaphthalen-1-yl)oxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
26		3-(3-(4-((5-methylisoxazol-3-yl)methoxy)benzyl)isoxazol-5-yl)pyridin-2-amine
27		3-(3-(4-(quinolin-2-ylmethoxy)benzyl)isoxazol-5-yl)pyridin-2-amine
28		3-(3-(4-(pyrimidin-2-ylmethoxy)benzyl)isoxazol-5-yl)pyridin-2-amine
29		3-(3-(4-((5-methylpyrimidin-2-yl)methoxy)benzyl)isoxazol-5-yl)pyridin-2-amine
30		3-(3-(4-(quinoxalin-2-ylmethoxy)benzyl)isoxazol-5-yl)pyridin-2-amine
31		N-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)-6-fluoropyridin-2-amine
32		N-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)pyrimidin-2-amine
33		N-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)-2-methylpyrimidin-4-amine
34		N-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)-4-chlorothiazol-2-amine
35		3-(3-((6-(pyridin-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
36		3-(3-((6-(pyridin-3-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

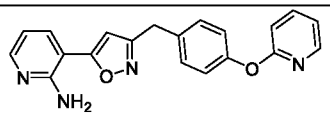
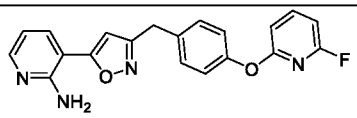
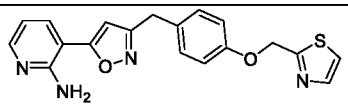
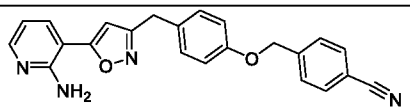
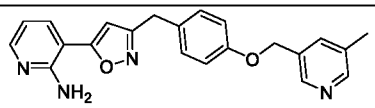
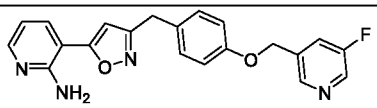
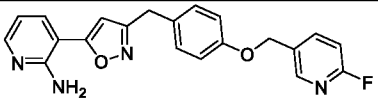
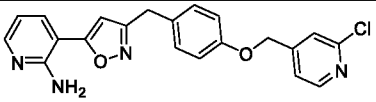
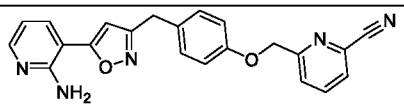
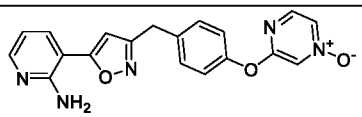
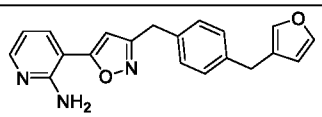
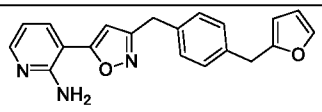
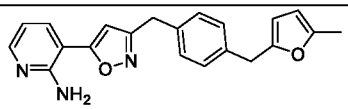
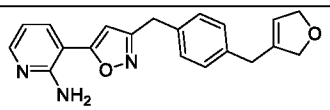
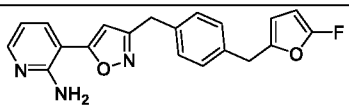
Ex.	Structure	Name
37		3-(3-((6-(pyridin-4-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
38		3-(3-((6-((5-methylisoxazol-3-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
39		3-(3-((6-(2-(pyridin-2-yl)ethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
40		3-(3-((6-(thiophen-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
41		3-(3-((6-(thiazol-4-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
42		3-(3-((6-(thiazol-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
43		3-(3-((6-(cyclopropylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
44		3-(3-((6-(oxetan-3-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
45		3-(3-((6-((1-methyl-1H-pyrazol-3-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
46		3-(3-((6-(pyrimidin-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
47		3-(3-((6-(pyrazin-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
48		3-(3-((6-(furan-3-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
49		3-(3-((6-((1-methyl-1H-pyrazol-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
50		3-(3-((6-((2-methylthiazol-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
51		3-(3-((6-((5-fluoropyridin-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

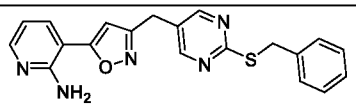
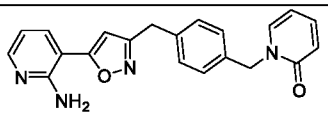
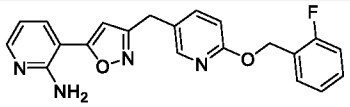
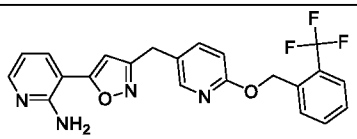
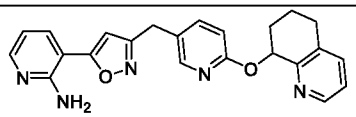
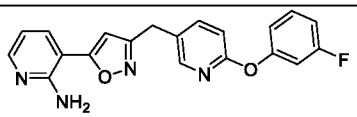
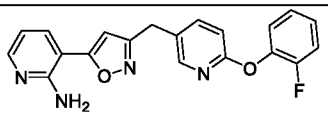
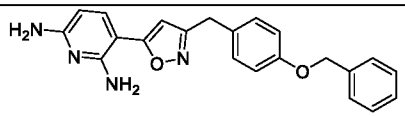
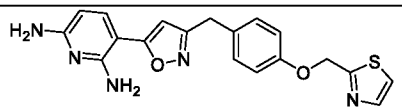
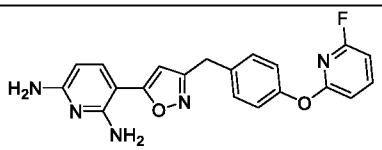
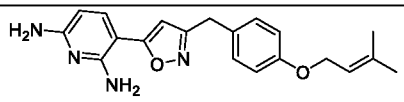
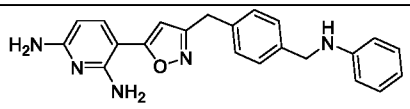
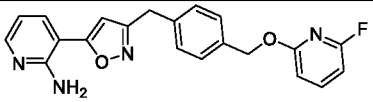
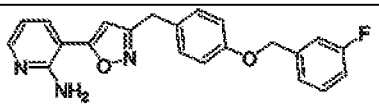
Ex.	Structure	Name
52		3-(3-((6-((2-methylfuran-3-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
53		3-(3-((6-(oxazol-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
54		3-(3-((6-((3-fluoropyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
55		3-(3-((6-(1-(pyridin-2-yl)ethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
56		3-(3-((6-(1-(2-fluorophenyl)ethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
57		3-(3-((6-(cyclobutylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
58		5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-phenylpyridin-2-amine
59		5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(3-fluorophenyl)pyridin-2-amine
60		5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(2-fluorophenyl)pyridin-2-amine
61		3-(3-((6-(benzylthio)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
62		2-((4-((4-(pyridin-3-yl)-1H-pyrazol-1-yl)methyl)benzyl)oxy)pyridine
63		3-(1-((6-phenoxypyridin-3-yl)methyl)-1H-pyrazol-4-yl)pyridin-2-amine
64		2-phenoxy-5-((4-(pyridin-3-yl)-1H-pyrazol-1-yl)methyl)pyridine
65		2-(benzyloxy)-5-((4-(pyridin-3-yl)-1H-pyrazol-1-yl)methyl)pyridine
66		2-(phenylthio)-5-((4-(pyridin-3-yl)-1H-pyrazol-1-yl)methyl)pyridine

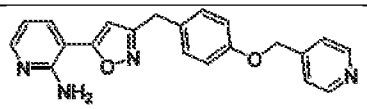
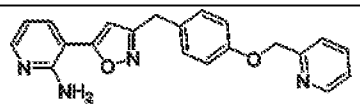
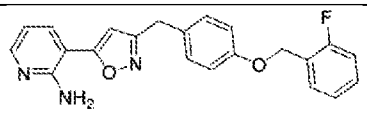
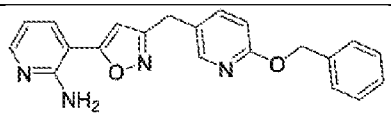
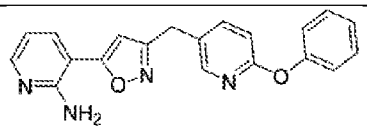
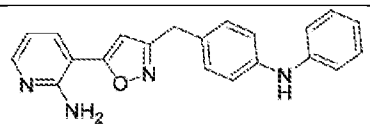
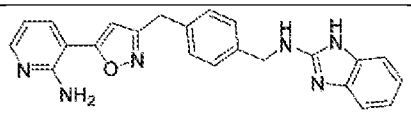
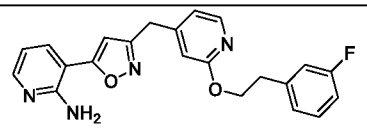
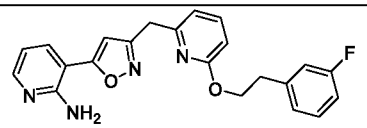
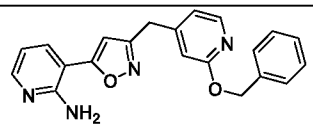
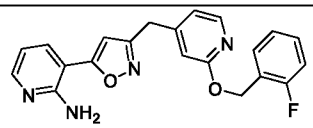
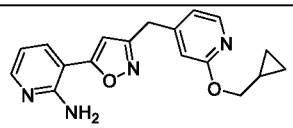
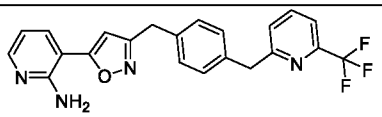
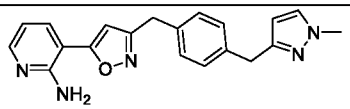
Ex.	Structure	Name
67		3-(1-((6-(phenylthio)pyridin-3-yl)methyl)-1H-pyrazol-4-yl)pyridin-2-amine
68		5-(1-((6-(benzyloxy)pyridin-3-yl)methyl)-1H-pyrazol-4-yl)pyridin-2-amine
69		3-(3-(4-((2-fluoropyridin-3-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
70		3-(3-(4-(((2-fluoropyridin-4-yl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
71		4-((5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)pyridin-2-yl)oxy)-2,5-dimethylfuran-3(2H)-one
72		5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(2,3-difluorophenyl)pyridin-2-amine
73		3-(3-((6-(furan-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
74		5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(2-fluorobenzyl)pyridin-2-amine
75		3-(3-((6-(2,4-difluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
76		4-(((5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)pyridin-2-yl)oxy)methyl)benzonitrile
77		3-(3-((6-(2-fluorophenethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
78		3-(3-((6-phenethoxypyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
79		3-(3-((6-(4-fluorophenethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
80		3-(3-((6-((3-fluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

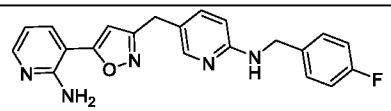
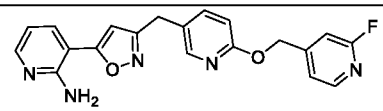
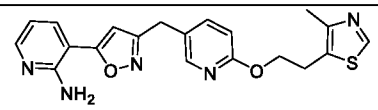
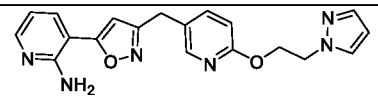
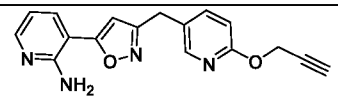
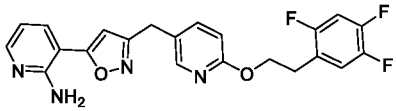
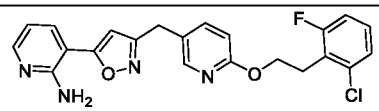
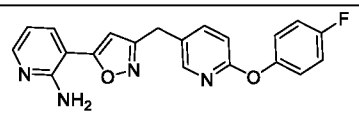
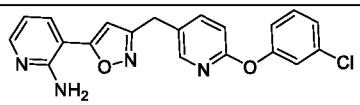
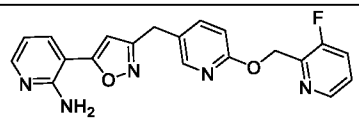
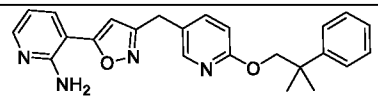
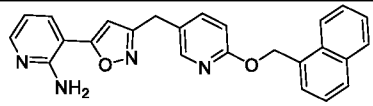
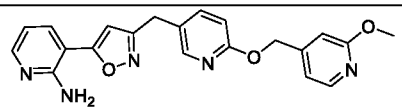
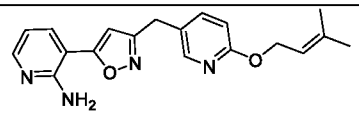
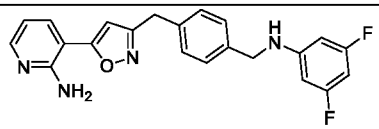
Ex.	Structure	Name
81		3-(3-((6-(3,5-difluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
82		3-(3-((6-((4-methylthiazol-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
83		3-(3-((6-((2-chloropyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
84		3-(3-((6-((3,5-difluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
85		3-(3-((6-((3-chlorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
86		3-(3-((2-((3-fluorobenzyl)oxy)pyridin-4-yl)methyl)isoxazol-5-yl)pyridin-2-amine
87		3-(3-((6-((3-chloro-5-fluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
88		3-(3-((2-((phenoxypyridin-4-yl)methyl)isoxazol-5-yl)pyridin-2-amine
89		3-(3-((6-((3-fluorobenzyl)oxy)pyridin-2-yl)methyl)isoxazol-5-yl)pyridin-2-amine
90		3-(3-((6-((2-fluorobenzyl)oxy)pyridin-2-yl)methyl)isoxazol-5-yl)pyridin-2-amine
91		3-(3-((6-(3-fluorophenethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
92		3-(3-((6-((4-chloropyridin-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
93		3-(3-(4-((((1H-pyrazol-5-yl)methyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
94		2-((4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)amino)acetonitrile

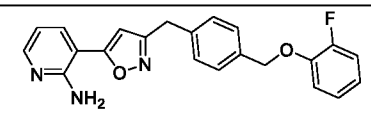
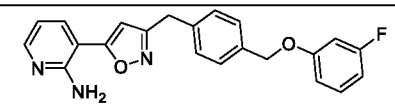
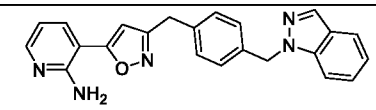
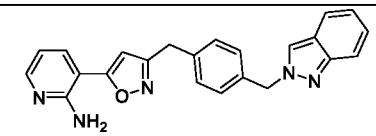
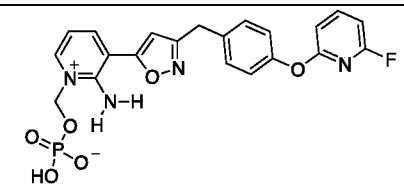
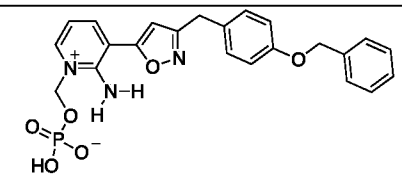
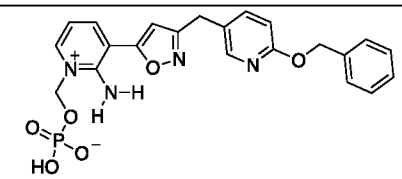
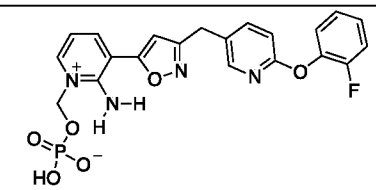
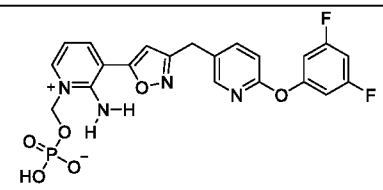
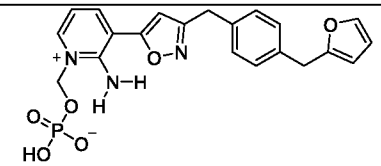
Ex.	Structure	Name
95		3-(3-(4-((((tetrahydro-2H-pyran-4-yl)methyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
96		3-((4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)amino)azepan-2-one
97		3-(3-(4-Vinylbenzyl)isoxazol-5-yl)pyridin-2-amine
98		2-((4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenethyl)thio)ethyl formate
99		(E)-3-(3-(4-(2-cyclohexylvinyl)benzyl)isoxazol-5-yl)pyridin-2-amine
100		3-(3-(4-(2-cyclohexylethyl)benzyl)isoxazol-5-yl)pyridin-2-amine
101		3-(1-((6-(benzyloxy)pyridin-3-yl)methyl)-1H-pyrazol-4-yl)pyridin-2-amine
102		(1-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)-1H-pyrazol-4-yl)methanol
103		3-(3-(4-((3-propylphenoxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
104		3-(3-(4-((3,4-dimethoxyphenoxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
105		3-(3-(4-((pyridin-3-yloxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
106		3-(3-(4-(((2-fluorophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
107		3-(3-(4-(((3-fluorophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
108		3-(3-(4-(((2,3-difluorophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
109		3-(3-(4-((4-methoxybenzyl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine

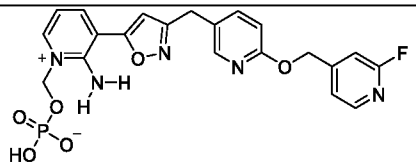
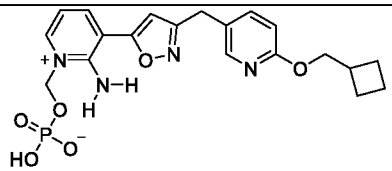
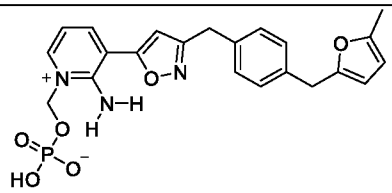
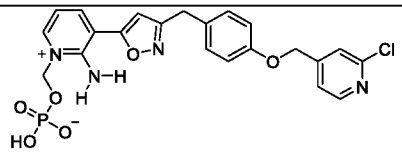
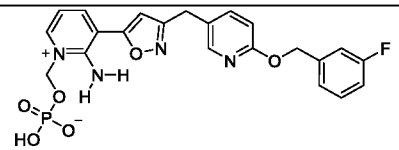
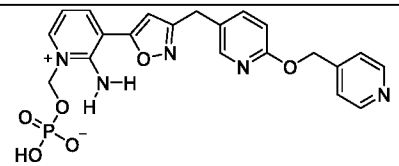
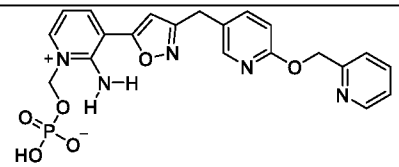
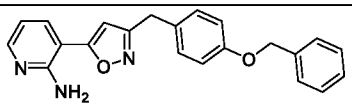
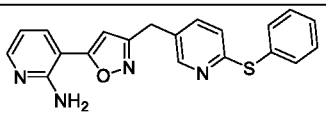
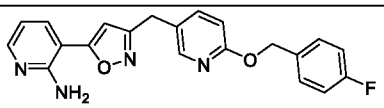
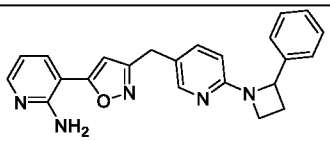
Ex.	Structure	Name
110		3-(3-(4-(pyridin-2-yloxy)benzyl)isoxazol-5-yl)pyridin-2-amine
111		3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine
112		3-(3-(4-(thiazol-2-ylmethoxy)benzyl)isoxazol-5-yl)pyridin-2-amine
113		4-((4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenoxy)methyl)benzonitrile
114		3-(3-(4-((5-methylpyridin-3-yl)methoxy)benzyl)isoxazol-5-yl)pyridin-2-amine
115		3-(3-(4-((5-fluoropyridin-3-yl)methoxy)benzyl)isoxazol-5-yl)pyridin-2-amine
116		3-(3-(4-((6-fluoropyridin-3-yl)methoxy)benzyl)isoxazol-5-yl)pyridin-2-amine
117		3-(3-(4-((2-chloropyridin-4-yl)methoxy)benzyl)isoxazol-5-yl)pyridin-2-amine
118		6-((4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenoxy)methyl)picolinonitrile
119		3-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenoxy)pyrazine 1-oxide
120		3-(3-(4-(furan-3-ylmethyl)benzyl)isoxazol-5-yl)pyridin-2-amine
121		3-(3-(4-(furan-2-ylmethyl)benzyl)isoxazol-5-yl)pyridin-2-amine
122		3-(3-(4-((5-methylfuran-2-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
123		3-(3-(4-((2,5-dihydrofuran-3-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
124		3-(3-(4-((5-fluorofuran-2-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine

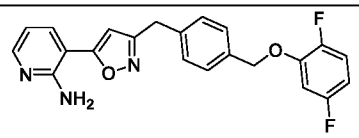
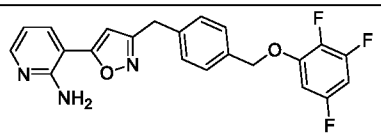
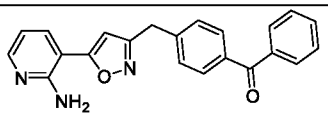
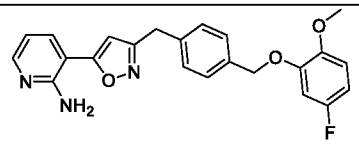
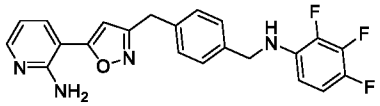
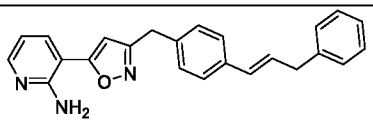
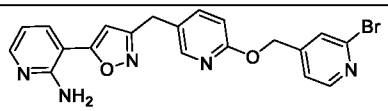
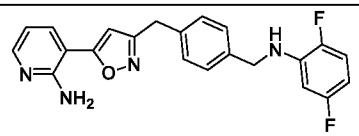
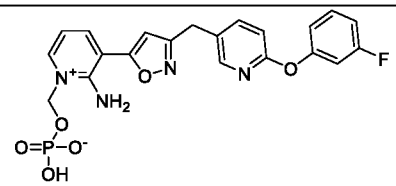
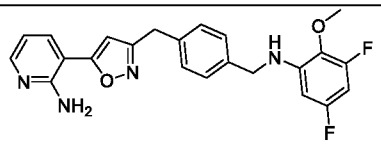
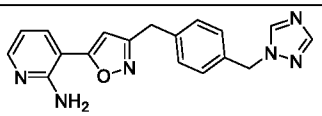
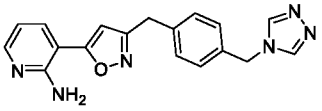
Ex.	Structure	Name
125		3-(3-((2-(benzylthio)pyrimidin-5-yl)methyl)isoxazol-5-yl)pyridin-2-amine
126		1-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)pyridin-2(1H)-one
127		3-(3-((6-((2-fluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
128		3-(3-((6-((2-(trifluoromethyl)benzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
129		3-(3-((6-((5,6,7,8-tetrahydroquinolin-8-yl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
130		3-(3-((6-(3-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
131		3-(3-((6-(2-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
132		3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridine-2,6-diamine
133		3-(3-(4-(thiazol-2-ylmethoxy)benzyl)isoxazol-5-yl)pyridine-2,6-diamine
134		3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridine-2,6-diamine
135		3-(3-(4-((3-methylbut-2-en-1-yl)oxy)benzyl)isoxazol-5-yl)pyridine-2,6-diamine
136		3-(3-(4-((phenylamino)methyl)benzyl)isoxazol-5-yl)pyridine-2,6-diamine
137		3-(3-(4-(((6-fluoropyridin-2-yl)oxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
138		3-(3-(4-((3-fluorobenzyl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine

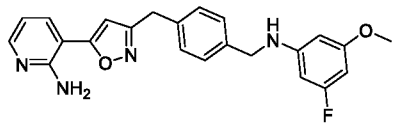
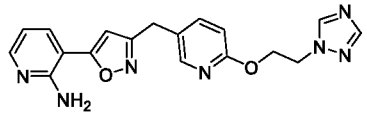
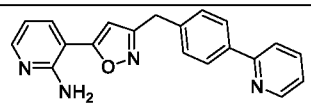
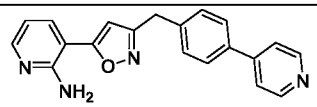
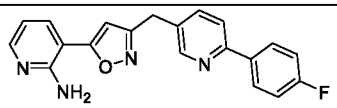
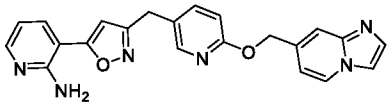
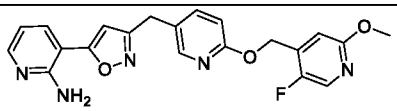
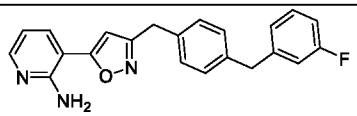
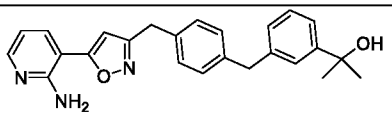
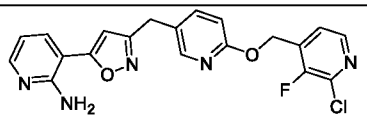
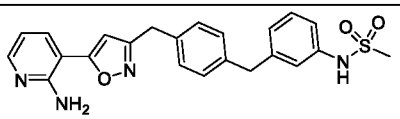
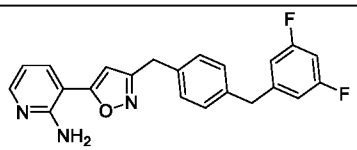
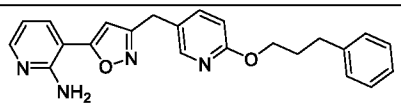
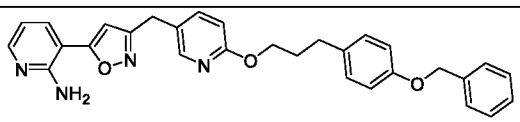
Ex.	Structure	Name
139		3-(3-(4-(pyridin-4-ylmethoxy)benzyl)isoxazol-5-yl)pyridin-2-amine
140		3-(3-(4-(pyridin-2-ylmethoxy)benzyl)isoxazol-5-yl)pyridin-2-amine
141		3-(3-(4-((2-fluorobenzyl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine
142		3-(3-((6-(benzyloxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
143		3-(3-((6-phenoxypyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
144		3-(3-(4-(phenylamino)benzyl)isoxazol-5-yl)pyridin-2-amine
145		N-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)-1H-benzo[d]imidazol-2-amine
146		3-(3-((2-(3-fluorophenethoxy)pyridin-4-yl)methyl)isoxazol-5-yl)pyridin-2-amine
147		3-(3-((6-(3-fluorophenethoxy)pyridin-2-yl)methyl)isoxazol-5-yl)pyridin-2-amine
148		3-(3-((2-(benzyloxy)pyridin-4-yl)methyl)isoxazol-5-yl)pyridin-2-amine
149		3-(3-((2-((2-fluorobenzyl)oxy)pyridin-4-yl)methyl)isoxazol-5-yl)pyridin-2-amine
150		3-(3-((2-(cyclopropylmethoxy)pyridin-4-yl)methyl)isoxazol-5-yl)pyridin-2-amine
151		3-(3-(4-((6-(trifluoromethyl)pyridin-2-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
152		3-(3-(4-((1-methyl-1H-pyrazol-3-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine

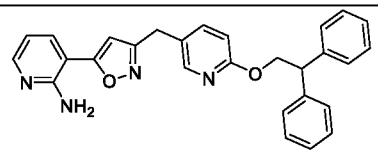
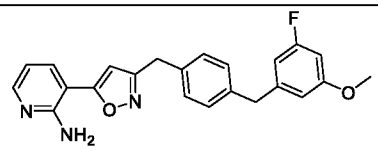
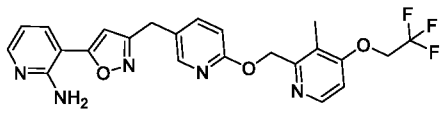
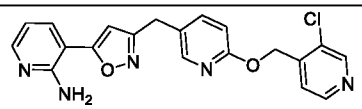
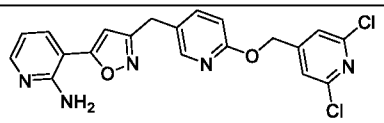
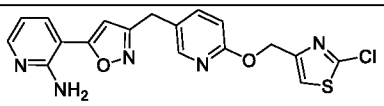
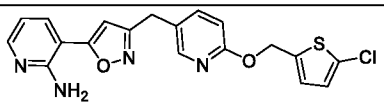
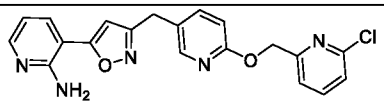
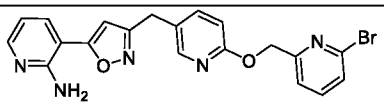
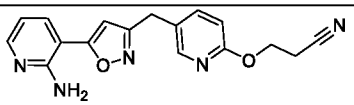
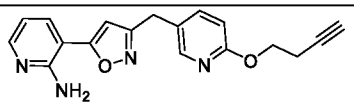
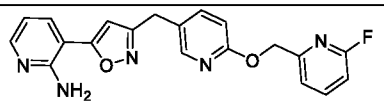
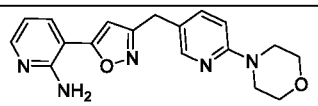
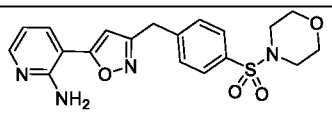
Ex.	Structure	Name
153		5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(4-fluorobenzyl)pyridin-2-amine
154		3-(3-((6-((2-fluoropyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
155		3-(3-((6-(2-(4-methylthiazol-5-yl)ethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
156		3-(3-((6-(2-(1H-pyrazol-1-yl)ethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
157		3-(3-((6-(prop-2-yn-1-yloxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
158		3-(3-((6-(2,4,5-trifluorophenethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
159		3-(3-((6-(2-chloro-6-fluorophenethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
160		3-(3-((6-(4-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
161		3-(3-((6-(3-chlorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
162		3-(3-((6-((3-fluoropyridin-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
163		3-(3-((6-(2-methyl-2-phenylpropoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
164		3-(3-((6-(naphthalen-1-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
165		3-(3-((6-((2-methoxypyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
166		3-(3-((6-((3-methylbut-2-en-1-yl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
167		3-(3-(4-(((3,5-difluorophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine

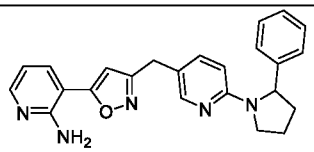
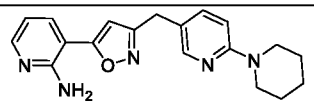
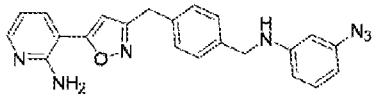
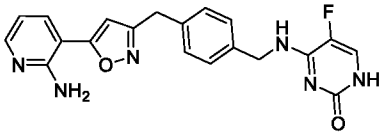
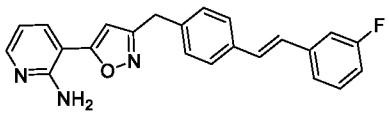
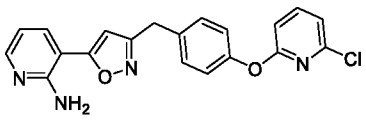
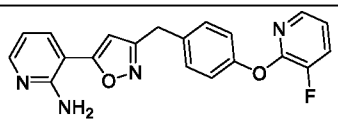
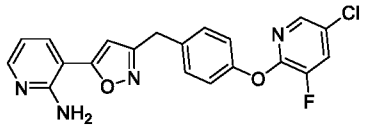
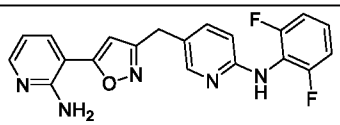
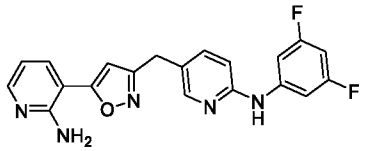
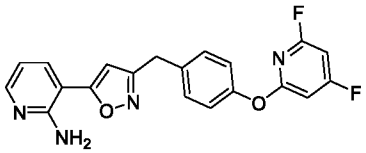
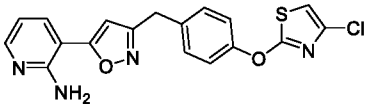
Ex.	Structure	Name
168		3-(3-(4-((2-fluorophenoxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
169		3-(3-(4-((3-fluorophenoxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
170		3-(3-(4-((1H-indazol-1-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
171		3-(3-(4-((2H-indazol-2-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
172		(2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
173		(2-amino-3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
174		(2-amino-3-(3-((6-(benzyloxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
175		(2-amino-3-(3-((6-(2-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
176		(2-amino-3-(3-((6-(3,5-difluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
177		(2-amino-3-(3-(4-(furan-2-ylmethyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

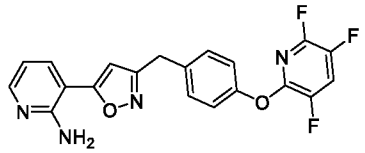
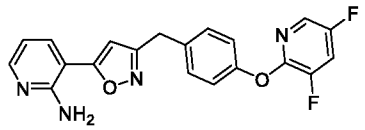
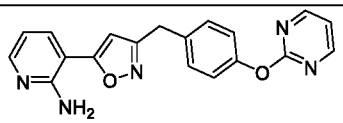
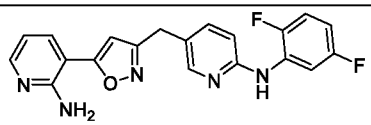
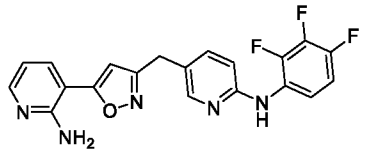
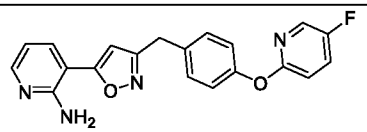
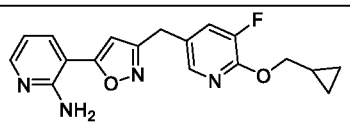
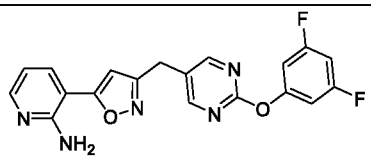
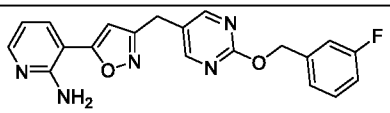
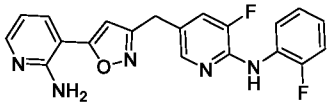
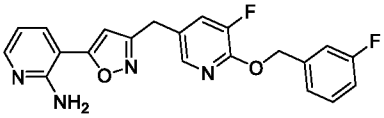
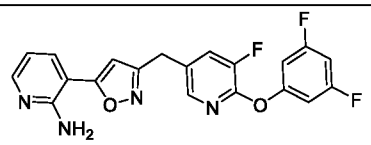
Ex.	Structure	Name
178		(2-amino-3-(3-((6-((2-fluoropyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
179		(2-amino-3-(3-((6-(cyclobutylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
180		(2-amino-3-(3-(4-((5-methylfuran-2-yl)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
181		(2-amino-3-(3-(4-((2-chloropyridin-4-yl)methoxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
182		(2-amino-3-(3-((6-((3-fluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
183		(2-amino-3-(3-((6-(pyridin-4-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
184		(2-amino-3-(3-((6-(pyridin-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
185		3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-2-amine
186		3-(3-((6-(phenylthio)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
187		3-(3-((6-((4-fluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
188		3-(3-((6-(2-phenylazetidin-1-yl)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

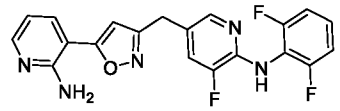
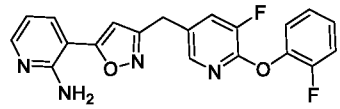
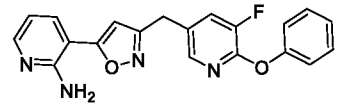
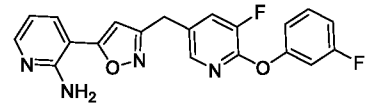
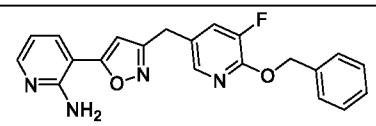
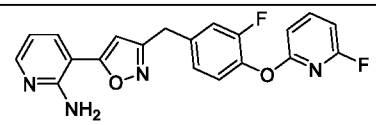
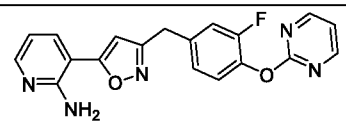
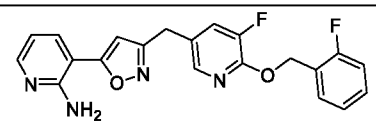
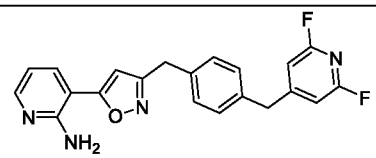
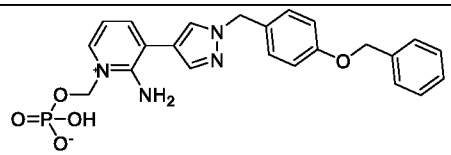
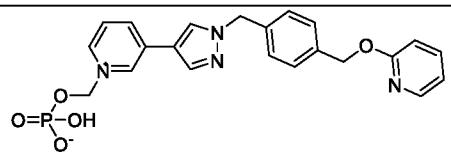
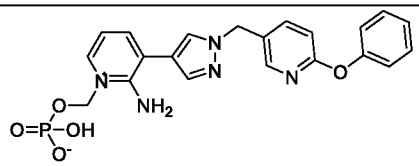
Ex.	Structure	Name
189		3-(3-(4-((2,5-difluorophenoxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
190		3-(3-(4-((2,3,5-trifluorophenoxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
191		(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenyl)(phenyl)methanone
192		3-(3-(4-((5-fluoro-2-methoxyphenoxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
193		3-(3-(4-(((2,3,4-trifluorophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
194		(E)-3-(3-(4-(3-phenylprop-1-en-1-yl)benzyl)isoxazol-5-yl)pyridin-2-amine
195		3-(3-((6-((2-bromopyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
196		3-(3-(4-(((2,5-difluorophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
197		(2-amino-3-(3-((6-(3-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
198		3-(3-(4-(((3,5-difluoro-2-methoxyphenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
199		3-(3-(4-((1H-1,2,4-triazol-1-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
200		3-(3-(4-((4H-1,2,4-triazol-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine

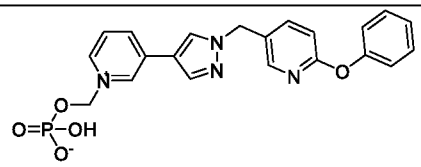
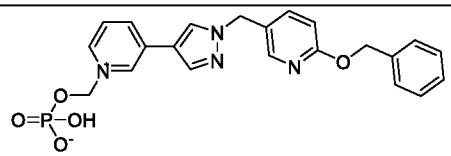
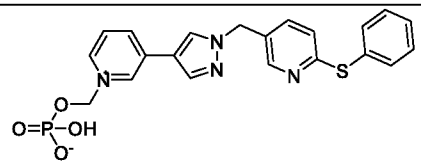
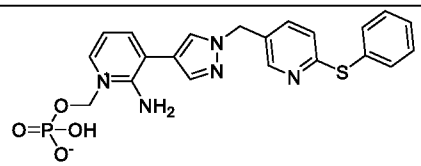
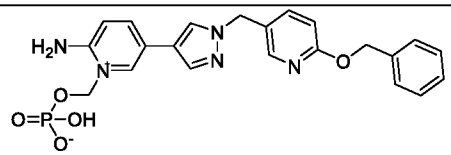
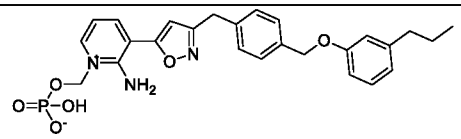
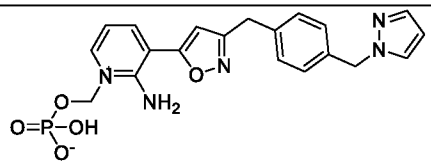
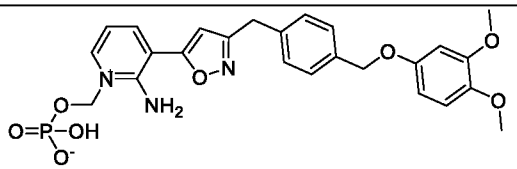
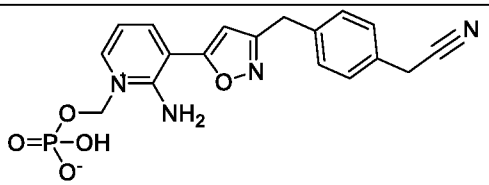
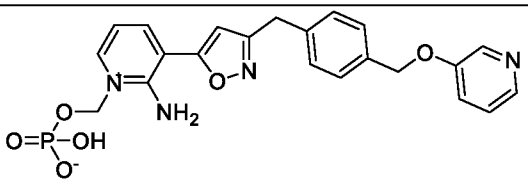
Ex.	Structure	Name
201		3-(3-(4-(((3-fluoro-5-methoxyphenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
202		3-(3-((6-(2-(1H-1,2,4-triazol-1-yl)ethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
203		3-(3-(4-(pyridin-2-yl)benzyl)isoxazol-5-yl)pyridin-2-amine
204		3-(3-(4-(pyridin-4-yl)benzyl)isoxazol-5-yl)pyridin-2-amine
205		3-(3-((6-(4-fluorophenyl)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
206		3-(3-((6-(imidazo[1,2-a]pyridin-7-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
207		3-(3-((6-((5-fluoro-2-methoxypyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
208		3-(3-(4-(3-fluorobenzyl)benzyl)isoxazol-5-yl)pyridin-2-amine
209		2-(3-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)phenyl)propan-2-ol
210		3-(3-((6-((2-chloro-3-fluoropyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
211		N-(3-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)phenyl)methanesulfonamide
212		3-(3-(4-(3,5-difluorobenzyl)benzyl)isoxazol-5-yl)pyridin-2-amine
213		3-(3-((6-(3-phenylpropoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
214		3-(3-((6-(3-(4-(benzyloxy)phenyl)propoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

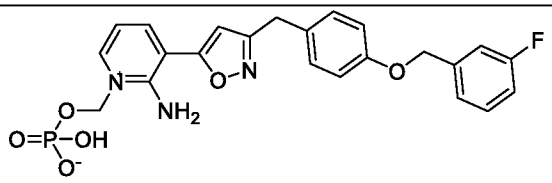
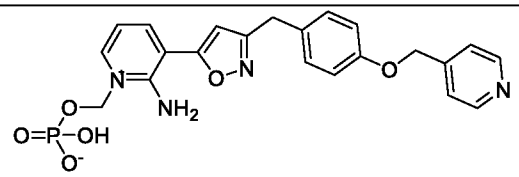
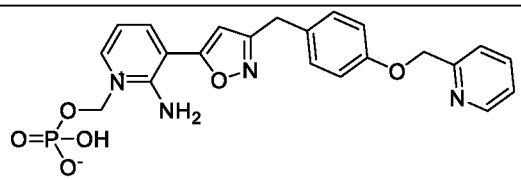
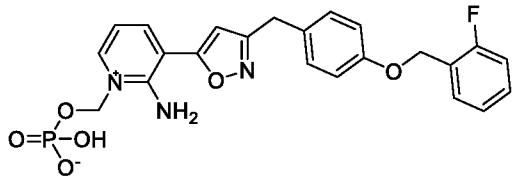
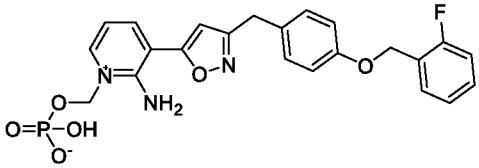
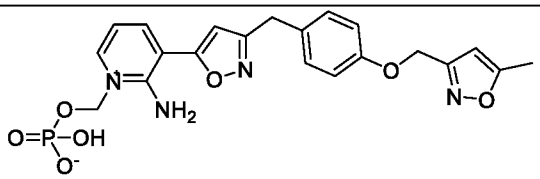
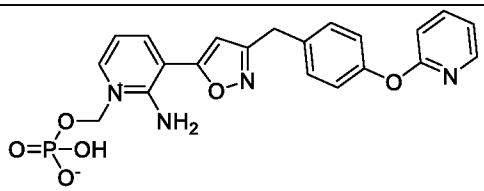
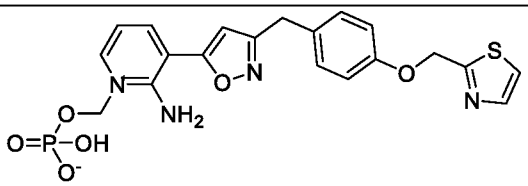
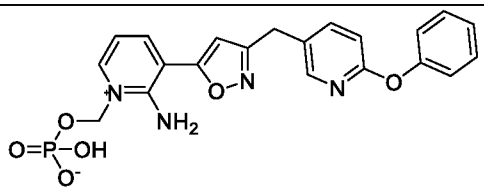
Ex.	Structure	Name
215		3-(3-((6-(2,2-diphenylethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
216		3-(3-(4-(3-fluoro-5-methoxybenzyl)benzyl)isoxazol-5-yl)pyridin-2-amine
217		3-(3-((6-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
218		3-(3-((6-((3-chloropyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
219		3-(3-((6-((2,6-dichloropyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
220		3-(3-((6-((2-chlorothiazol-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
221		3-(3-((6-((5-chlorothiophen-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
222		3-(3-((6-((6-chloropyridin-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
223		3-(3-((6-((6-bromopyridin-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
224		3-((5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)pyridin-2-yl)oxy)propanenitrile
225		3-(3-((6-(but-3-yn-1-yloxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
226		3-(3-((6-((6-fluoropyridin-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
227		3-(3-((6-morpholinopyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
228		3-(3-(4-(morpholinosulfonyl)benzyl)isoxazol-5-yl)pyridin-2-amine

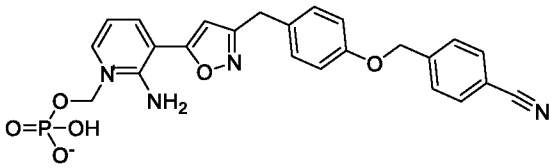
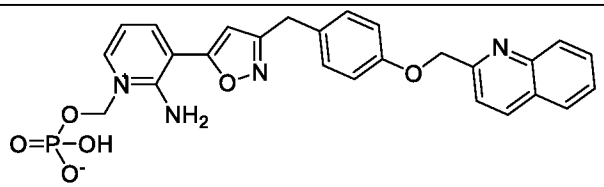
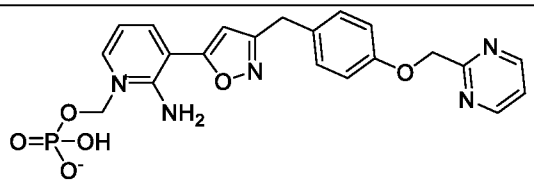
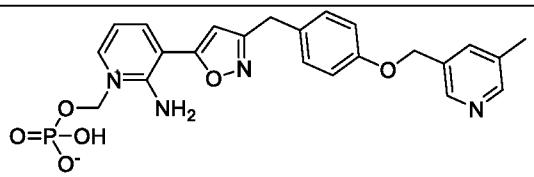
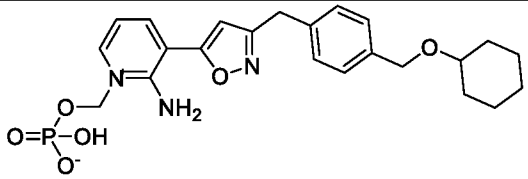
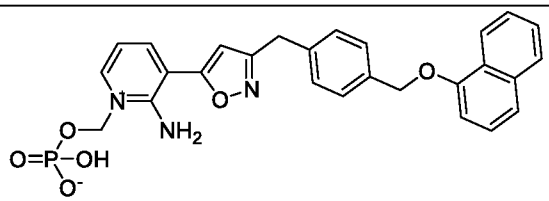
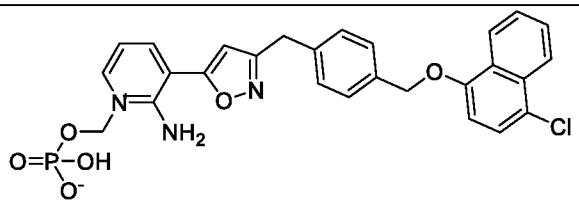
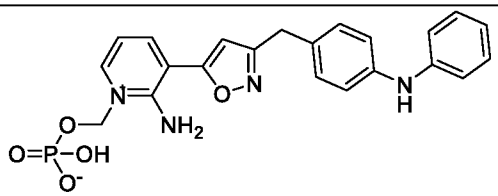
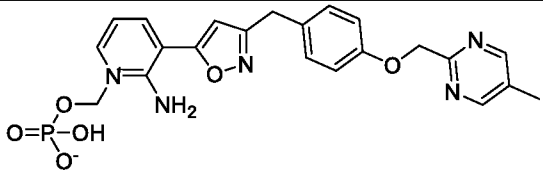
Ex.	Structure	Name
229		3-(3-((6-(2-phenylpyrrolidin-1-yl)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
230		3-(3-((6-(piperidin-1-yl)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
231		3-(3-(4-(((3-azidophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
232		4-((4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)amino)-5-fluoropyrimidin-2(1H)-one
233		(E)-3-(3-(4-(3-fluorostyryl)benzyl)isoxazol-5-yl)pyridin-2-amine
234		3-(3-(4-((6-chloropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine
235		3-(3-(4-((3-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine
236		3-(3-(4-((5-chloro-3-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine
237		5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(2,6-difluorophenyl)pyridin-2-amine
238		5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(3,5-difluorophenyl)pyridin-2-amine
239		3-(3-(4-((4,6-difluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine
240		3-(3-(4-((4-chlorothiazol-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine

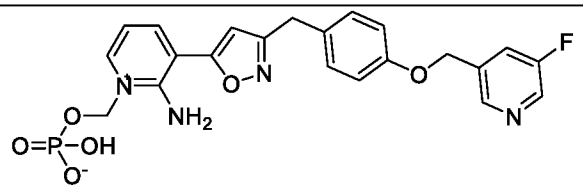
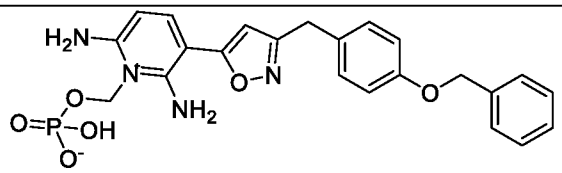
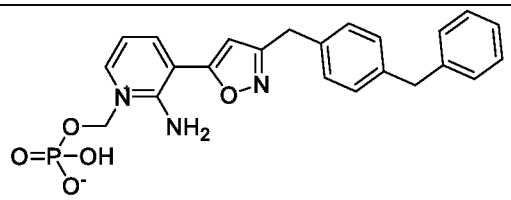
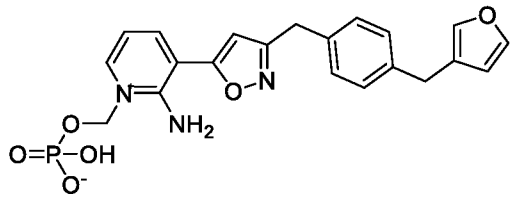
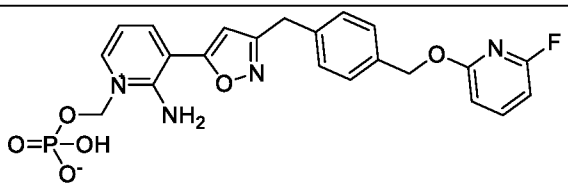
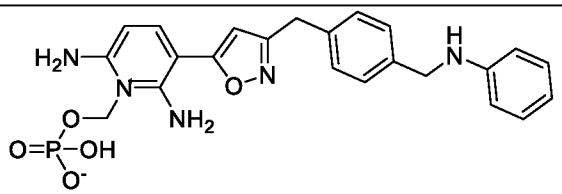
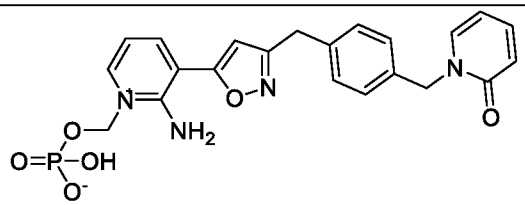
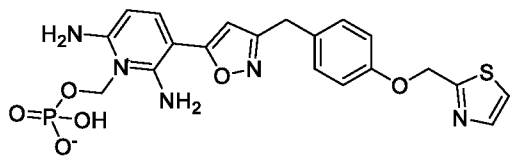
Ex.	Structure	Name
241		3-(3-(4-((3,5,6-trifluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine
242		3-(3-(4-((3,5-difluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine
243		3-(3-(4-(pyrimidin-2-yloxy)benzyl)isoxazol-5-yl)pyridin-2-amine
244		5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(2,5-difluorophenyl)pyridin-2-amine
245		5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(2,3,4-trifluorophenyl)pyridin-2-amine
246		3-(3-(4-((5-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine
247		3-(3-((6-(cyclopropylmethoxy)-5-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
248		3-(3-((2-(3,5-difluorophenoxy)pyrimidin-5-yl)methyl)isoxazol-5-yl)pyridin-2-amine
249		3-(3-((2-((3-fluorobenzyl)oxy)pyrimidin-5-yl)methyl)isoxazol-5-yl)pyridin-2-amine
250		5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-3-fluoro-N-(2-fluorophenyl)pyridin-2-amine
251		3-(3-((5-fluoro-6-((3-fluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
252		3-(3-((6-(3,5-difluorophenoxy)-5-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

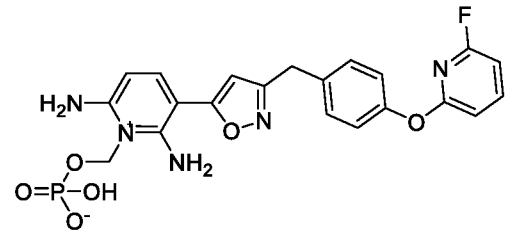
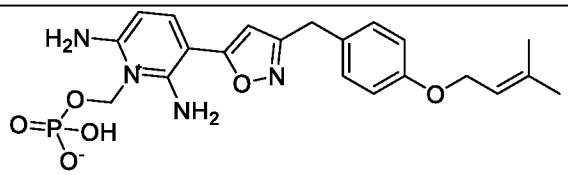
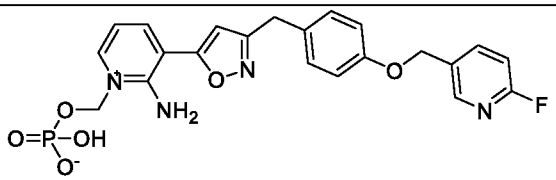
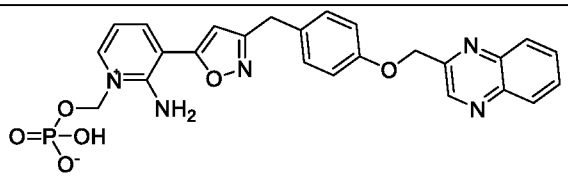
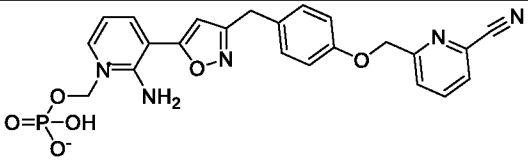
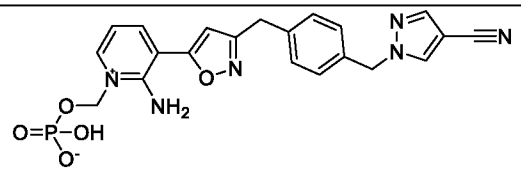
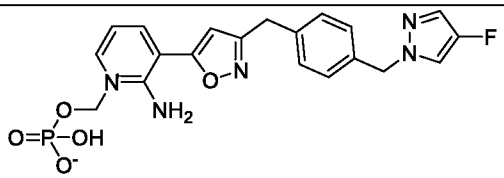
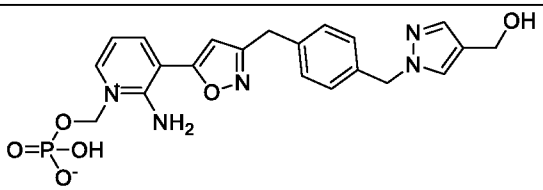
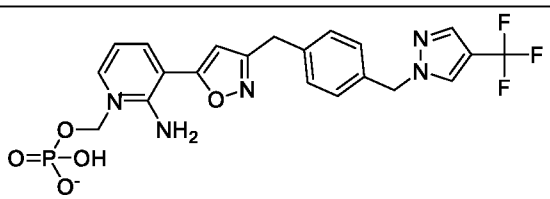
Ex.	Structure	Name
253		5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(2,6-difluorophenyl)-3-fluoropyridin-2-amine
254		3-(3-((5-fluoro-6-(2-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
255		3-(3-((5-fluoro-6-phenoxypyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
256		3-(3-((5-fluoro-6-(3-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
257		3-(3-((6-(benzyloxy)-5-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
258		3-(3-(3-fluoro-4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine
259		3-(3-(3-fluoro-4-(pyrimidin-2-yloxy)benzyl)isoxazol-5-yl)pyridin-2-amine
260		3-(3-((5-fluoro-6-((2-fluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine
261		3-(3-(4-((2,6-difluoropyridin-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine
262		(2-amino-3-(1-(4-(benzyloxy)benzyl)-1H-pyrazol-4-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
263		(3-(1-(4-((pyridin-2-yloxy)methyl)benzyl)-1H-pyrazol-4-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
264		(2-amino-3-(1-((6-phenoxypyridin-3-yl)methyl)-1H-pyrazol-4-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

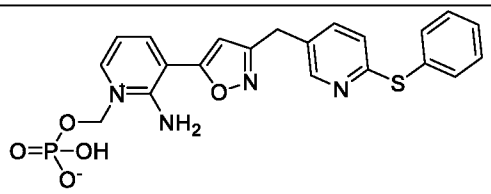
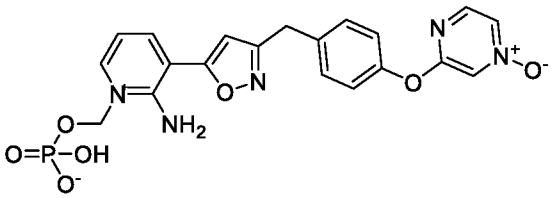
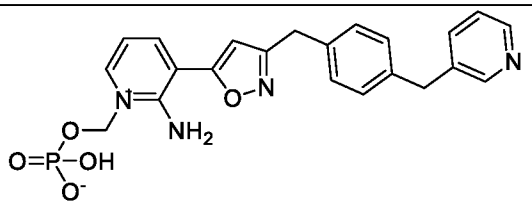
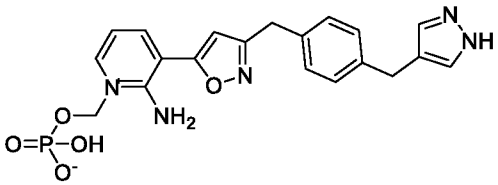
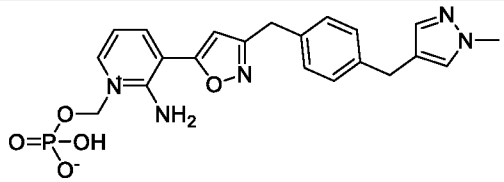
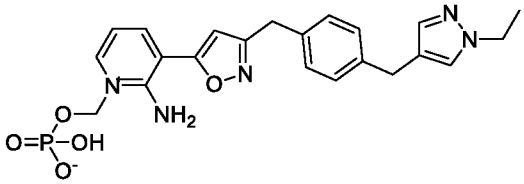
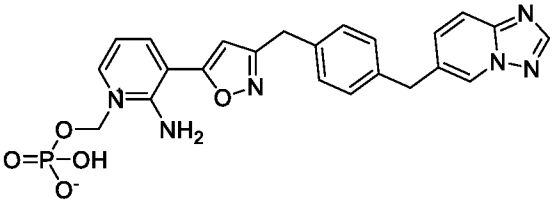
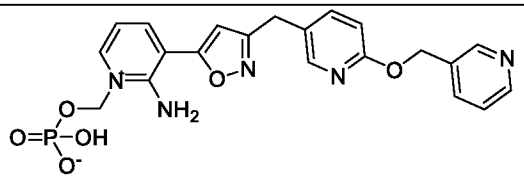
Ex.	Structure	Name
265		(3-(1-((6-phenoxypyridin-3-yl)methyl)-1H-pyrazol-4-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
266		(3-(1-((6-(benzyloxy)pyridin-3-yl)methyl)-1H-pyrazol-4-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
267		(3-(1-((6-(phenylthio)pyridin-3-yl)methyl)-1H-pyrazol-4-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
268		(2-amino-3-(1-((6-(phenylthio)pyridin-3-yl)methyl)-1H-pyrazol-4-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
269		(2-amino-5-(1-((6-(benzyloxy)pyridin-3-yl)methyl)-1H-pyrazol-4-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
270		(2-amino-3-(3-(4-((3-propylphenoxy)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
271		(3-(3-(4-((1H-pyrazol-1-yl)methyl)benzyl)isoxazol-5-yl)-2-aminopyridin-1-ium-1-yl)methyl hydrogen phosphate
272		(2-amino-3-(3-(4-((3,4-dimethoxyphenoxy)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
273		(2-amino-3-(3-(4-(cyanomethyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
274		(2-amino-3-(3-(4-((pyridin-3-yloxy)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

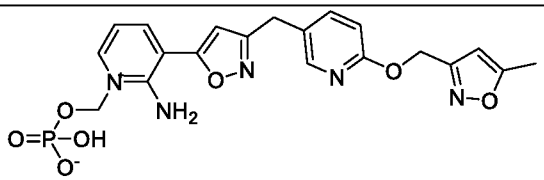
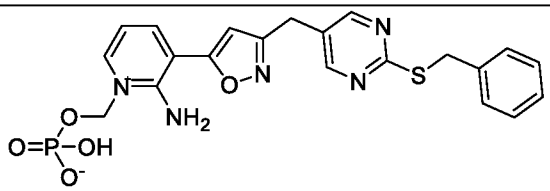
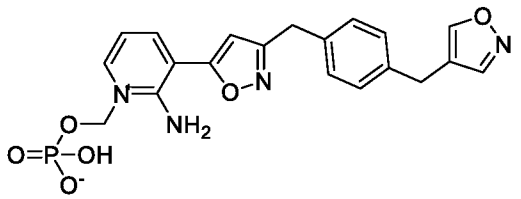
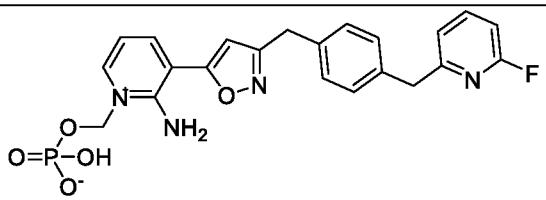
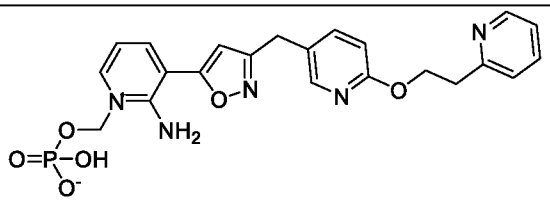
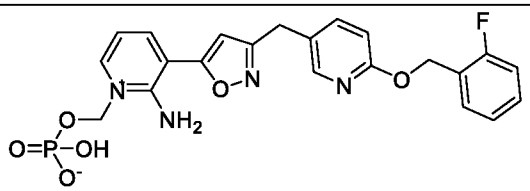
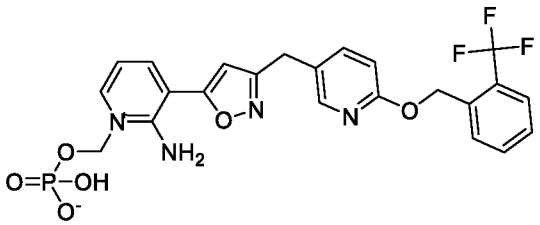
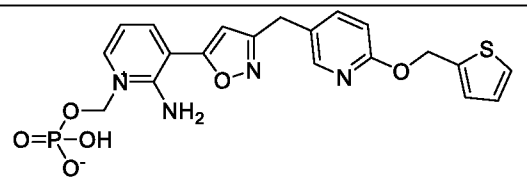
Ex.	Structure	Name
275		(2-amino-3-(3-(4-((3-fluorobenzyl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
276		(2-amino-3-(3-(4-(pyridin-4-ylmethoxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
277		(2-amino-3-(3-(4-(pyridin-2-ylmethoxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
278		(2-amino-3-(3-(4-((2-fluorobenzyl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
279		(2-amino-3-(3-(4-((4-methoxybenzyl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
280		(2-amino-3-(3-(4-((5-methylisoxazol-3-yl)methoxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
281		(2-amino-3-(3-(4-(pyridin-2-yloxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
282		(2-amino-3-(3-(4-(thiazol-2-ylmethoxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
283		(2-amino-3-(3-((6-phenoxypyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

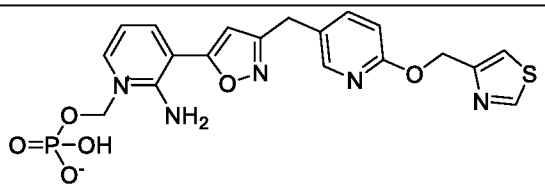
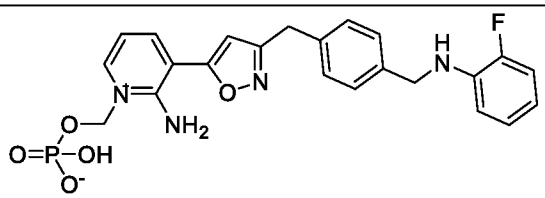
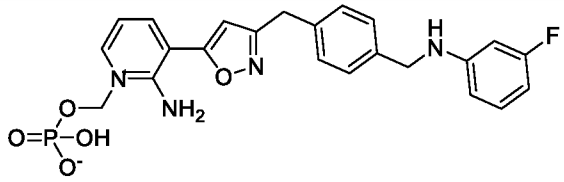
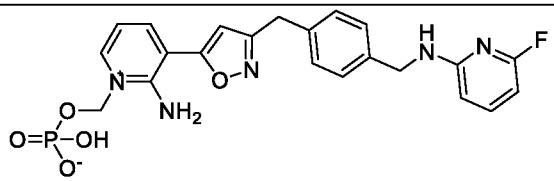
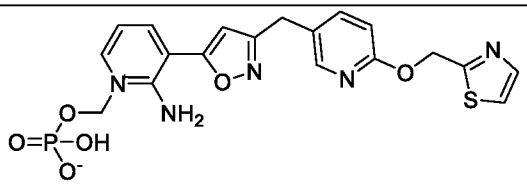
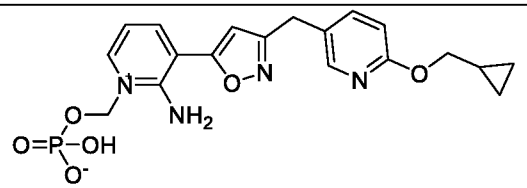
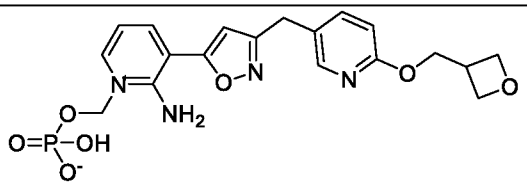
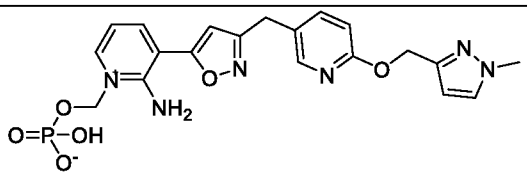
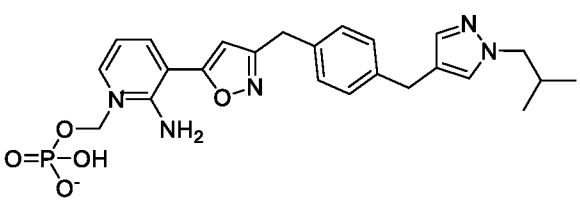
Ex.	Structure	Name
284		(2-amino-3-(3-(4-((4-cyanobenzyl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
285		(2-amino-3-(3-(4-(quinolin-2-ylmethoxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
286		(2-amino-3-(3-(4-(pyrimidin-2-ylmethoxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
287		(2-amino-3-(3-(4-((5-methylpyridin-3-yl)methoxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
288		(2-amino-3-(3-(4-((cyclohexyloxy)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
289		(2-amino-3-(3-(4-((naphthalen-1-yloxy)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
290		(2-amino-3-(3-(4-(((4-chloronaphthalen-1-yl)oxy)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
291		(2-amino-3-(3-(4-(phenylamino)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
292		(2-amino-3-(3-(4-((5-methylpyrimidin-2-yl)methoxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

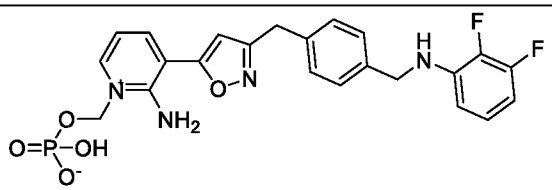
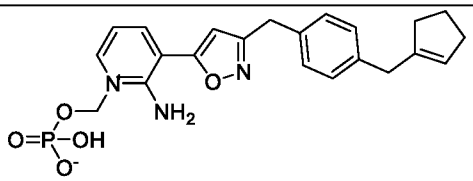
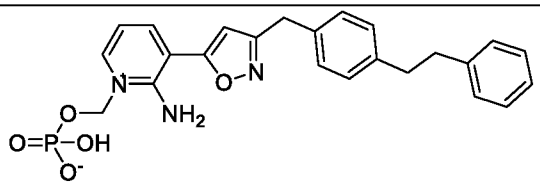
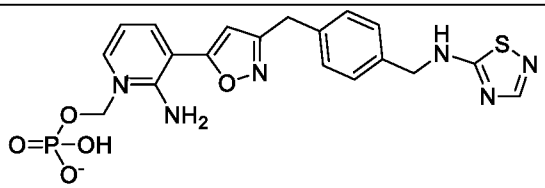
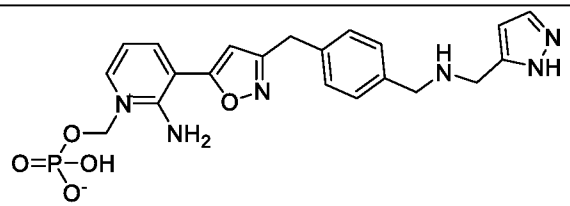
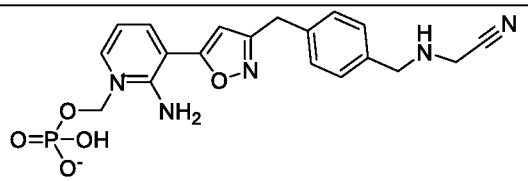
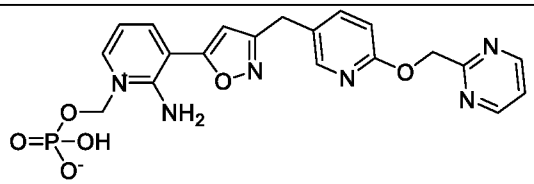
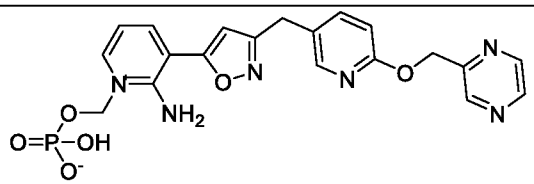
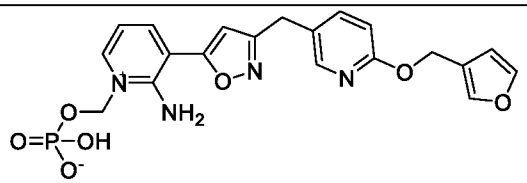
Ex.	Structure	Name
293		(2-amino-3-(3-(4-((5-fluoropyridin-3-yl)methoxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
294		(2,6-diamino-3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
295		(2-amino-3-(3-(4-benzylbenzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
296		(2-amino-3-(3-(4-(furan-3-ylmethyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
297		(2-amino-3-(3-(4-(((6-fluoropyridin-2-yl)oxy)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
298		(2,6-diamino-3-(3-(4-((phenylamino)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
299		(2-amino-3-(3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
300		(2,6-diamino-3-(3-(4-(thiazol-2-ylmethoxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

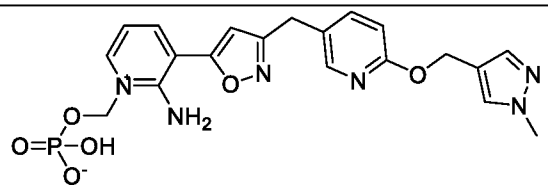
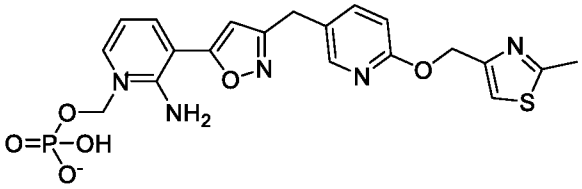
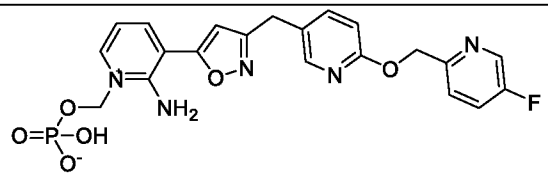
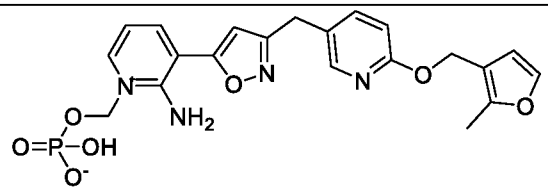
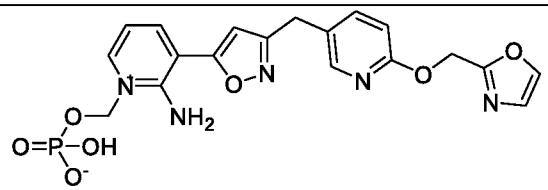
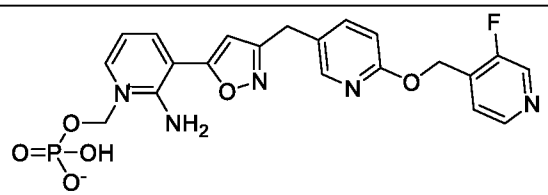
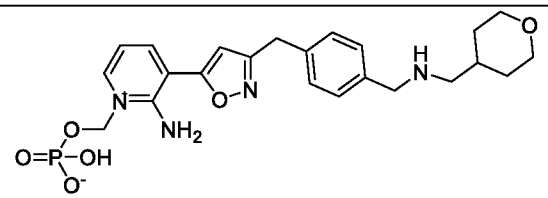
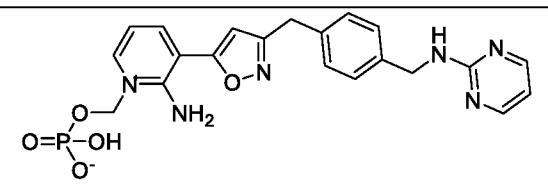
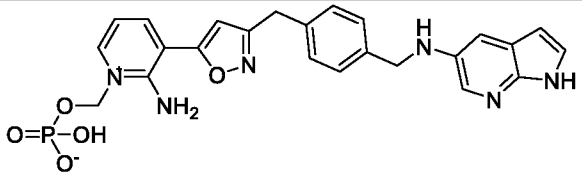
Ex.	Structure	Name
301		(2,6-diamino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
302		(2,6-diamino-3-(3-(4-((3-methylbut-2-en-1-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
303		(2-amino-3-(3-(4-((6-fluoropyridin-3-yl)methoxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
304		(2-amino-3-(3-(4-(quinoxalin-2-ylmethoxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
305		(2-amino-3-(3-(4-((6-cyanopyridin-2-yl)methoxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
306		(2-amino-3-(3-(4-((4-cyano-1H-pyrazol-1-yl)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
307		(2-amino-3-(3-(4-((4-fluoro-1H-pyrazol-1-yl)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
308		(2-amino-3-(3-(4-((4-(hydroxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
309		(2-amino-3-(3-(4-((4-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

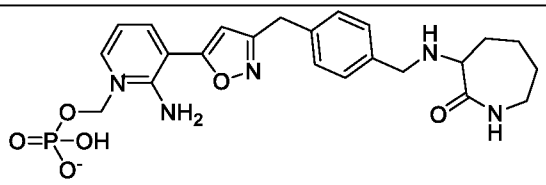
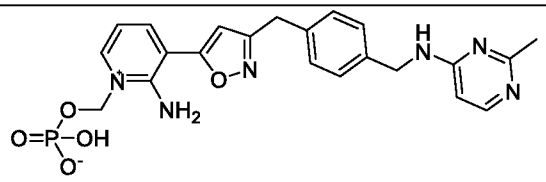
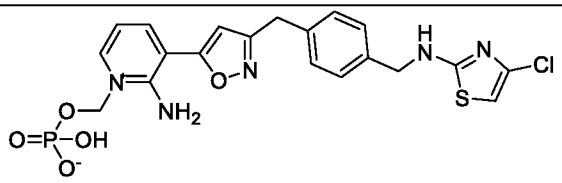
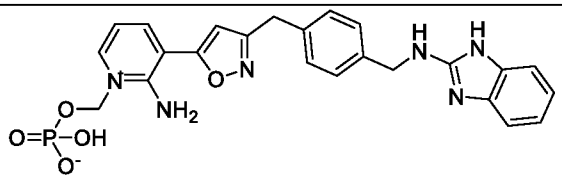
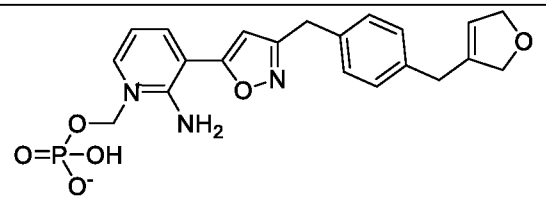
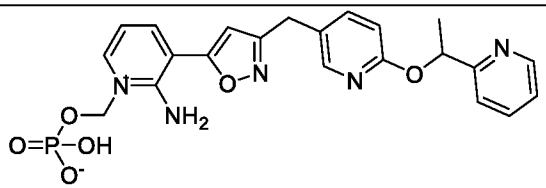
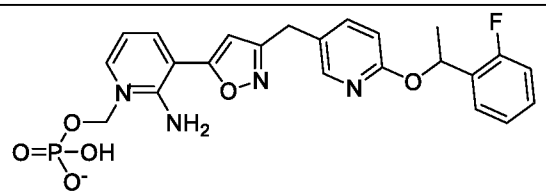
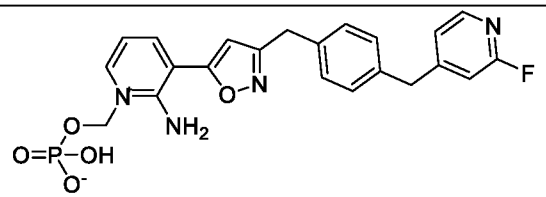
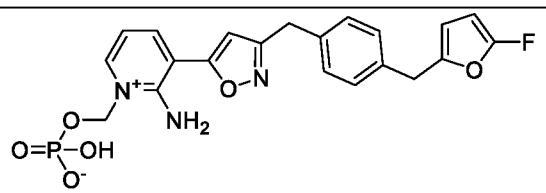
Ex.	Structure	Name
310		(2-amino-3-(3-((6-(phenylthio)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
311		(2-amino-3-(3-(4-((1-oxidopyrazin-3-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
312		(2-amino-3-(3-(4-(pyridin-3-ylmethyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
313		(3-(3-(4-((1H-pyrazol-4-yl)methyl)benzyl)isoxazol-5-yl)-2-aminopyridin-1-ium-1-yl)methyl hydrogen phosphate
314		(2-amino-3-(3-(4-((1-methyl-1H-pyrazol-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
315		(2-amino-3-(3-(4-((1-ethyl-1H-pyrazol-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
316		(3-(3-(4-([1,2,4]triazolo[1,5-a]pyridin-6-ylmethyl)benzyl)isoxazol-5-yl)-2-aminopyridin-1-ium-1-yl)methyl hydrogen phosphate
317		(2-amino-3-(3-((6-(pyridin-3-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

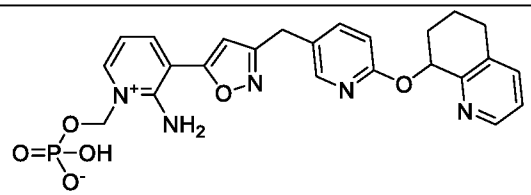
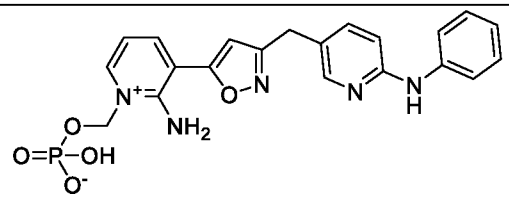
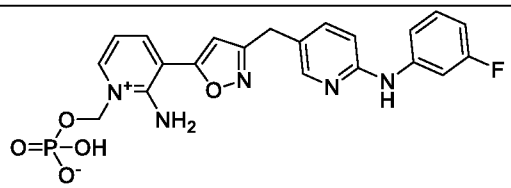
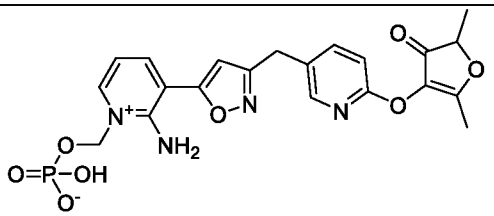
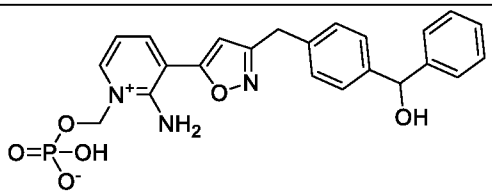
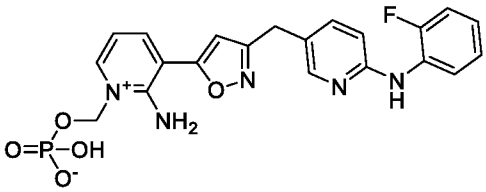
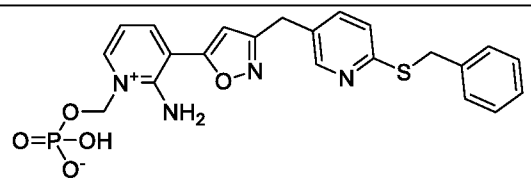
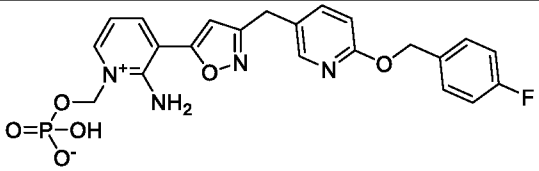
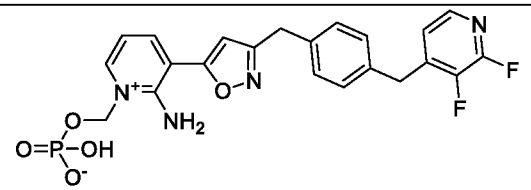
Ex.	Structure	Name
318		(2-amino-3-(3-((6-((5-methylisoxazol-3-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
319		(2-amino-3-(3-((2-(benzylthio)pyrimidin-5-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
320		(2-amino-3-(3-(4-(isoxazol-4-ylmethyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
321		(2-amino-3-(3-(4-((6-fluoropyridin-2-yl)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
322		(2-amino-3-(3-((6-(2-(pyridin-2-yl)ethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
323		(2-amino-3-(3-((6-((2-fluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
324		(2-amino-3-(3-((6-((2-(trifluoromethyl)benzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
325		(2-amino-3-(3-((6-(thiophen-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

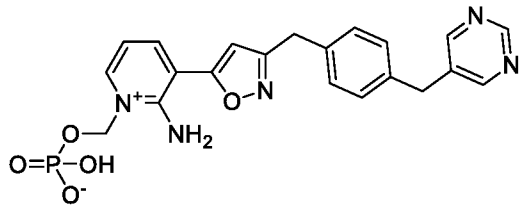
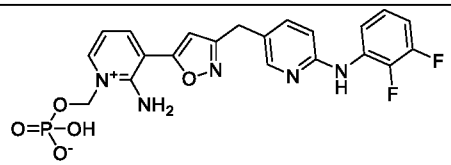
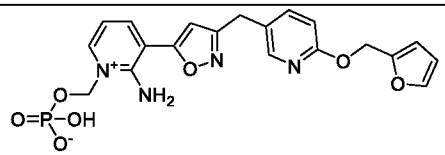
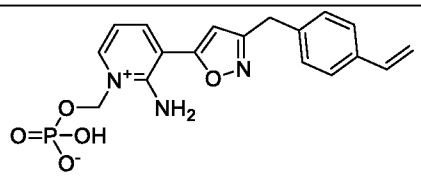
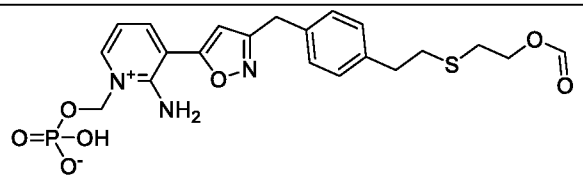
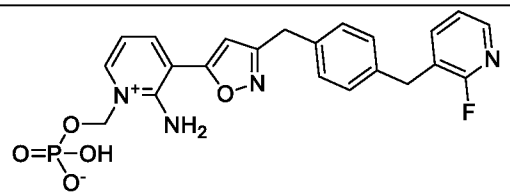
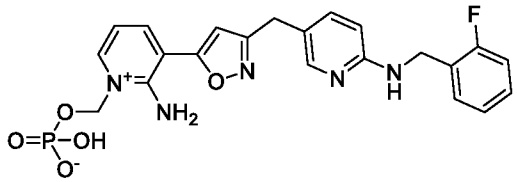
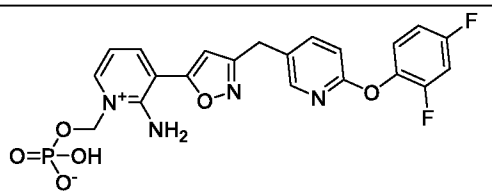
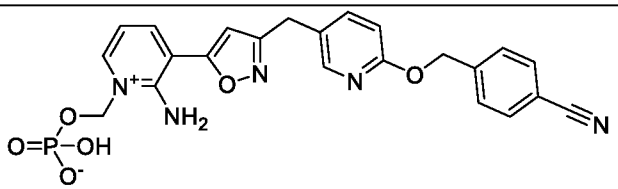
Ex.	Structure	Name
326		(2-amino-3-(3-((6-(thiazol-4-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
327		(2-amino-3-(3-(4-(((2-fluorophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
328		(2-amino-3-(3-(4-(((3-fluorophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
329		(2-amino-3-(3-(4-(((6-fluoropyridin-2-yl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
330		(2-amino-3-(3-((6-(thiazol-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
331		(2-amino-3-(3-((6-(cyclopropylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
332		(2-amino-3-(3-((6-(oxetan-3-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
333		(2-amino-3-(3-((6-((1-methyl-1H-pyrazol-3-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
334		(2-amino-3-(3-(4-((1-isobutyl-1H-pyrazol-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

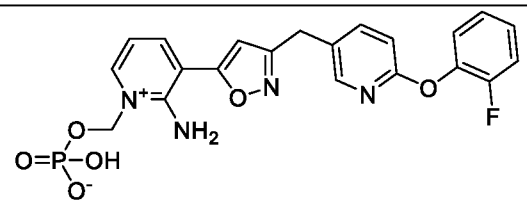
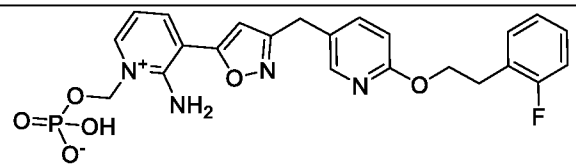
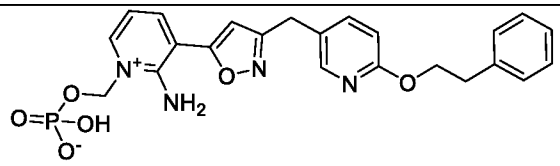
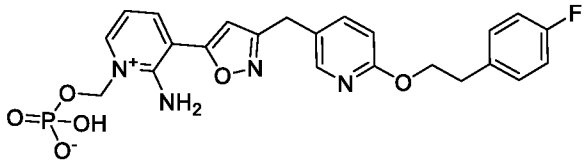
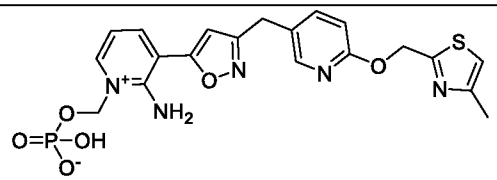
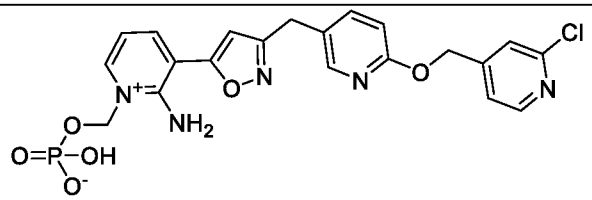
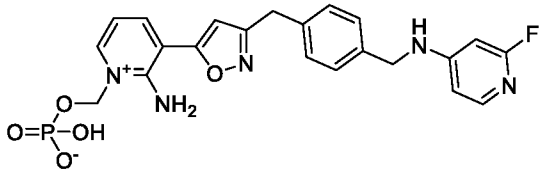
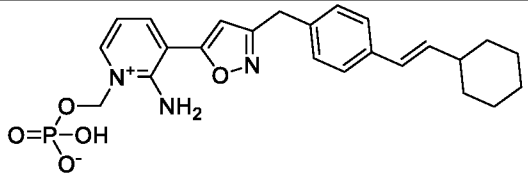
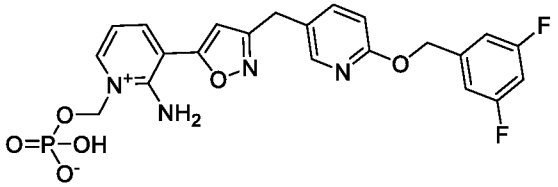
Ex.	Structure	Name
335		(2-amino-3-(3-(4-(((2,3-difluorophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
336		(2-amino-3-(3-(4-(cyclopent-1-en-1-ylmethyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
337		(2-amino-3-(3-(4-phenethylbenzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
338		(3-(3-(4-(((1,2,4-thiadiazol-5-yl)amino)methyl)benzyl)isoxazol-5-yl)-2-aminopyridin-1-ium-1-yl)methyl hydrogen phosphate
339		(3-(3-(4-((((1H-pyrazol-5-yl)methyl)amino)methyl)benzyl)isoxazol-5-yl)-2-aminopyridin-1-ium-1-yl)methyl hydrogen phosphate
340		(2-amino-3-(3-(4-(((cyanomethyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
341		(2-amino-3-(3-((6-(pyrimidin-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
342		(2-amino-3-(3-((6-(pyrazin-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
343		(2-amino-3-(3-((6-(furan-3-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

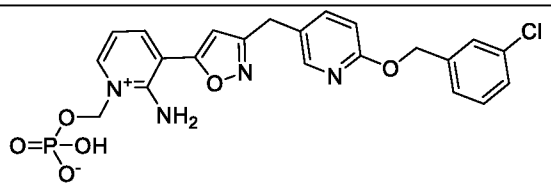
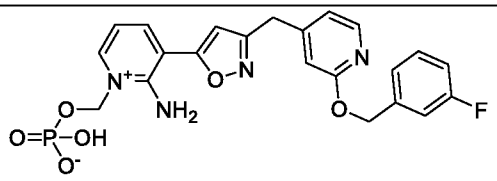
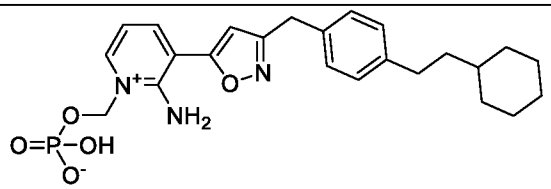
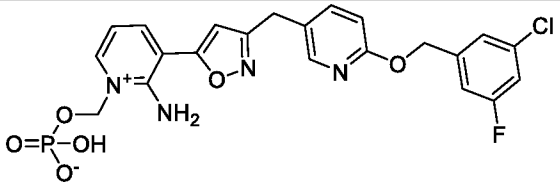
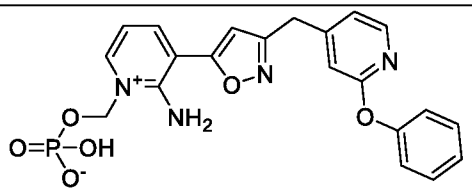
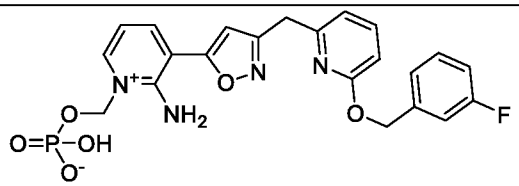
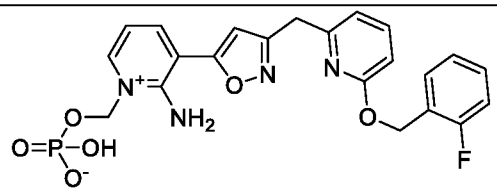
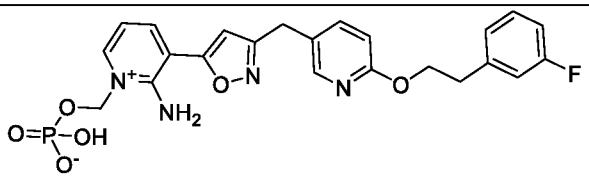
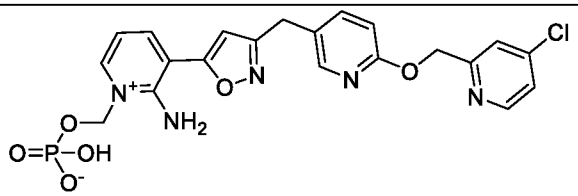
Ex.	Structure	Name
344		(2-amino-3-(3-((6-((1-methyl-1H-pyrazol-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
345		(2-amino-3-(3-((6-((2-methylthiazol-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
346		(2-amino-3-(3-((6-((5-fluoropyridin-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
347		(2-amino-3-(3-((6-((2-methylfuran-3-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
348		(2-amino-3-(3-((6-(oxazol-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
349		(2-amino-3-(3-((6-((3-fluoropyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
350		(2-amino-3-(3-(4-((((tetrahydro-2H-pyran-4-yl)methyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
351		(2-amino-3-(3-(4-((pyrimidin-2-ylamino)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
352		(3-(3-(4-(((1H-pyrrolo[2,3-b]pyridin-5-yl)amino)methyl)benzyl)isoxazol-5-yl)-2-aminopyridin-1-ium-1-yl)methyl hydrogen phosphate

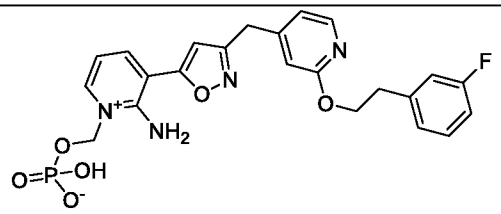
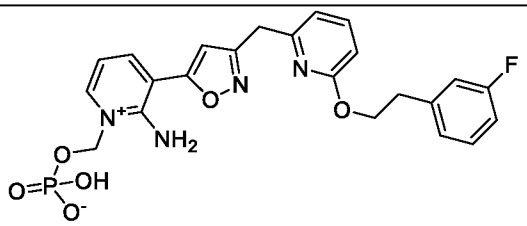
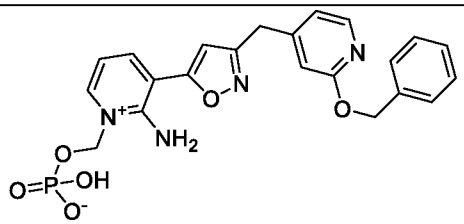
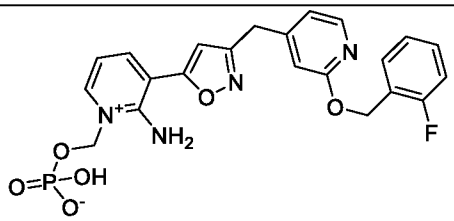
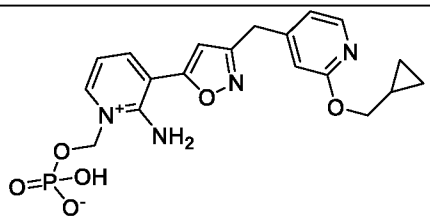
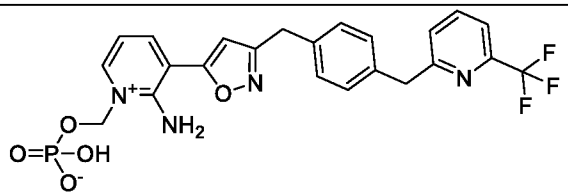
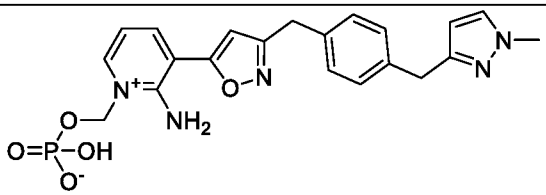
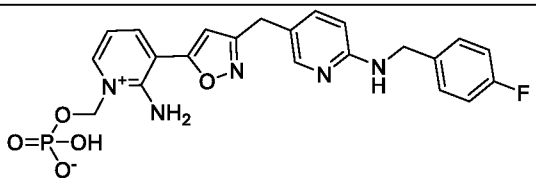
Ex.	Structure	Name
353		(2-amino-3-(3-(4-(((2-oxoazepan-3-yl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
354		(2-amino-3-(3-(4-(((2-methylpyrimidin-4-yl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
355		(2-amino-3-(3-(4-(((4-chlorothiazol-2-yl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
356		(3-(3-(4-(((1H-benzo[d]imidazol-2-yl)amino)methyl)benzyl)isoxazol-5-yl)-2-aminopyridin-1-ium-1-yl)methyl hydrogen phosphate
357		(2-amino-3-(3-(4-((2,5-dihydrofuran-3-yl)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
358		(2-amino-3-(3-((6-(1-(pyridin-2-yl)ethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
359		(2-amino-3-(3-((6-(1-(2-fluorophenyl)ethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
360		(2-amino-3-(3-(4-((2-fluoropyridin-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
361		(2-amino-3-(3-(4-((5-fluorofuran-2-yl)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

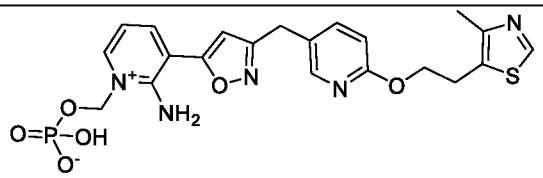
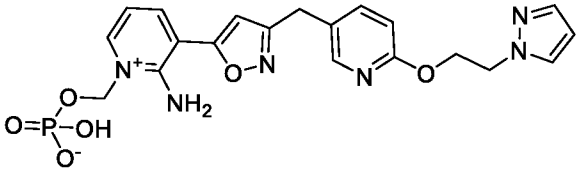
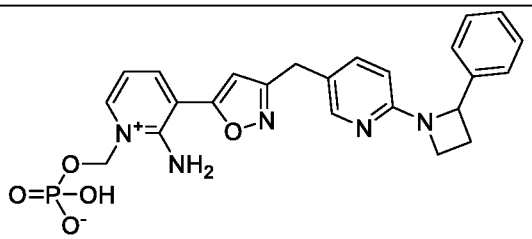
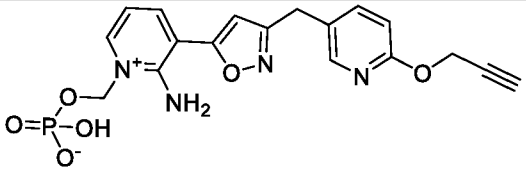
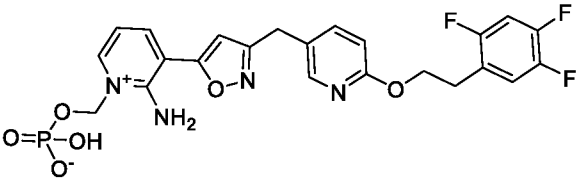
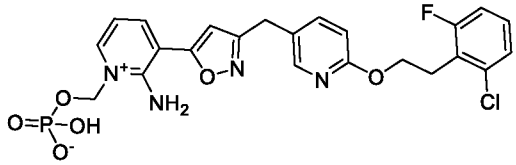
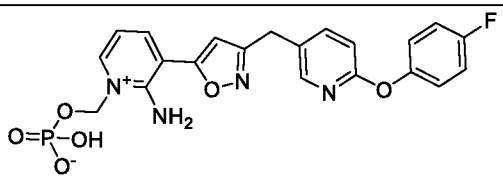
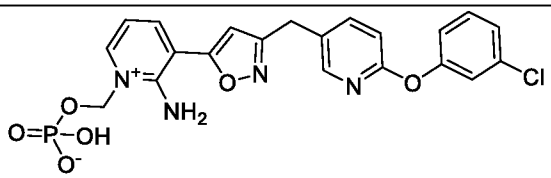
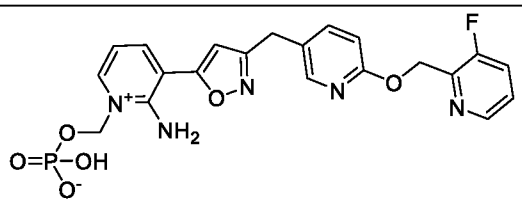
Ex.	Structure	Name
362		(2-amino-3-(3-((6-((5,6,7,8-tetrahydroquinolin-8-yl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
363		(2-amino-3-(3-((6-(phenylamino)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
364		(2-amino-3-(3-((6-((3-fluorophenyl)amino)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
365		(2-amino-3-(3-((6-((2,5-dimethyl-4-oxo-4,5-dihydrofuran-3-yl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
366		(2-amino-3-(3-(4-(hydroxy(phenyl)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
367		(2-amino-3-(3-((6-((2-fluorophenyl)amino)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
368		(2-amino-3-(3-((6-(benzylthio)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
369		(2-amino-3-(3-((6-((4-fluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
370		(2-amino-3-(3-(4-((2,3-difluoropyridin-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

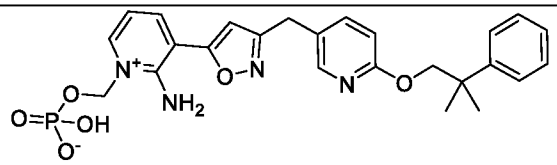
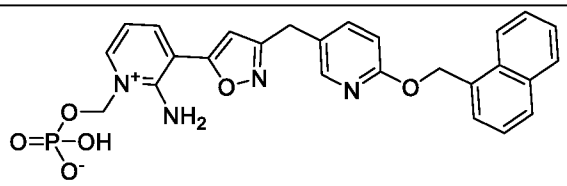
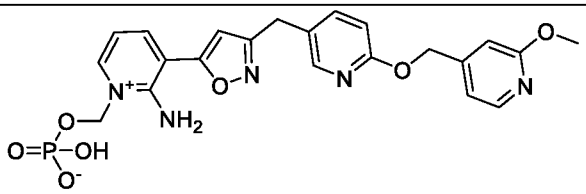
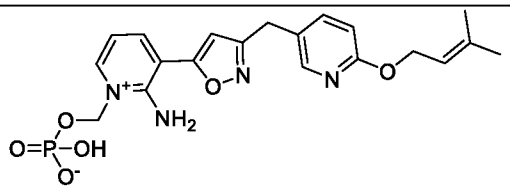
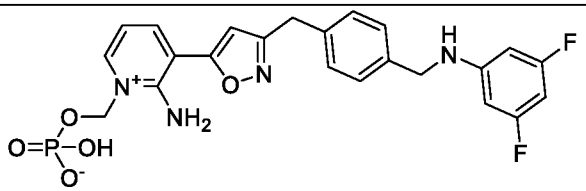
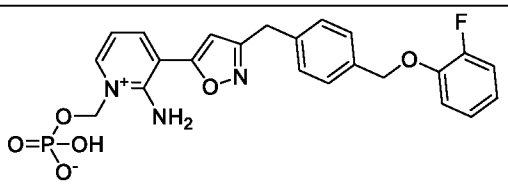
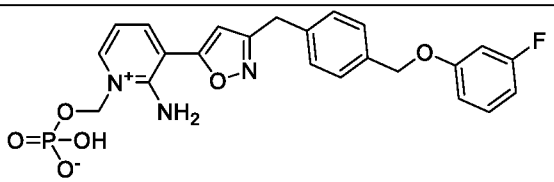
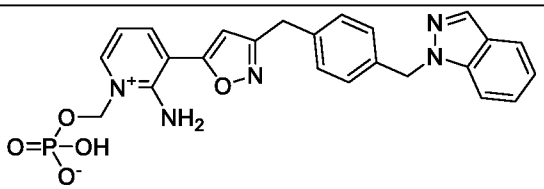
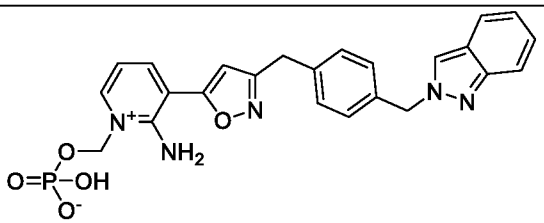
Ex.	Structure	Name
371		(2-amino-3-(3-(4-(pyrimidin-5-ylmethyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
372		(2-amino-3-(3-((6-((2,3-difluorophenyl)amino)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
373		(2-amino-3-(3-((6-(furan-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
374		(2-amino-3-(3-(4-vinylbenzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
375		(2-amino-3-(3-(4-(2-((2-(formyloxy)ethyl)thio)ethyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
376		(2-amino-3-(3-(4-((2-fluoropyridin-3-yl)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
377		(2-amino-3-(3-((6-((2-fluorobenzyl)amino)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
378		(2-amino-3-(3-((6-(2,4-difluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
379		(2-amino-3-(3-((6-((4-cyanobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

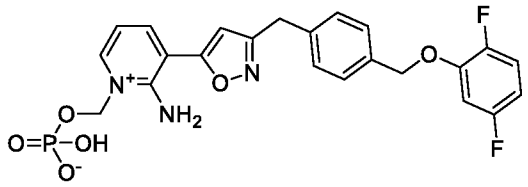
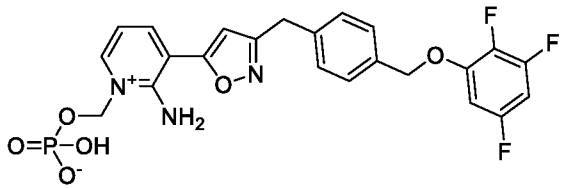
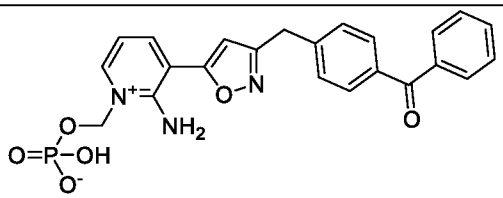
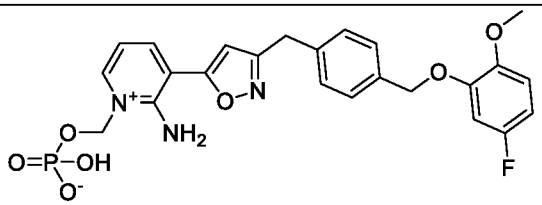
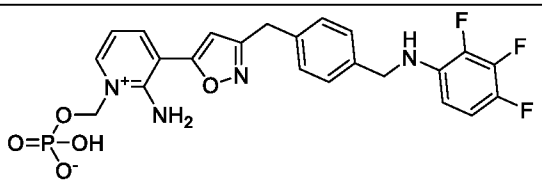
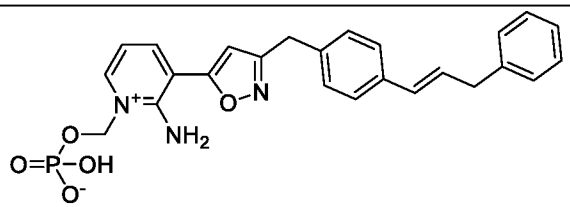
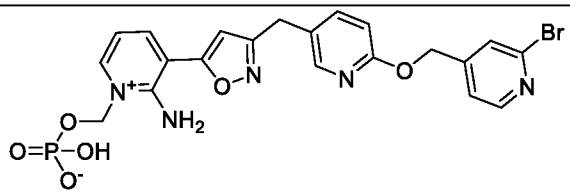
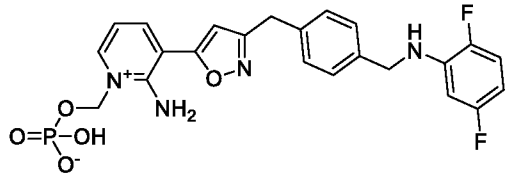
Ex.	Structure	Name
380		(2-amino-3-(3-((6-(2-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
381		(2-amino-3-(3-((6-(2-fluorophenethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
382		(2-amino-3-(3-((6-phenethoxypyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
383		(2-amino-3-(3-((6-(4-fluorophenethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
384		(2-amino-3-(3-((6-((4-methylthiazol-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
385		(2-amino-3-(3-((6-((2-chloropyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
386		(2-amino-3-(3-(4-(((2-fluoropyridin-4-yl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
387		(E)-(2-amino-3-(3-(4-(2-cyclohexylvinyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
388		(2-amino-3-(3-((6-((3,5-difluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

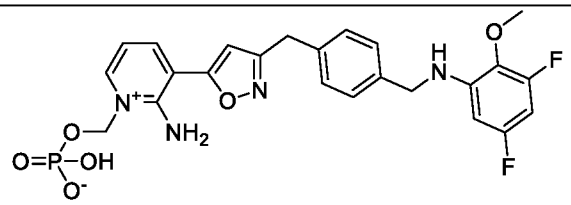
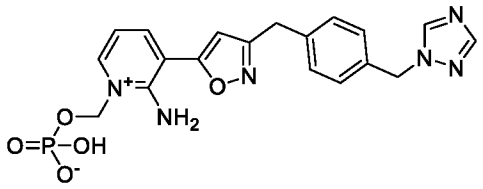
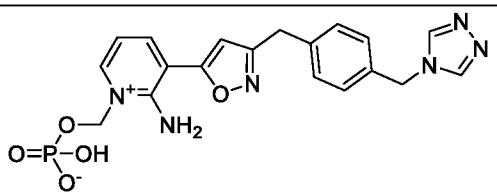
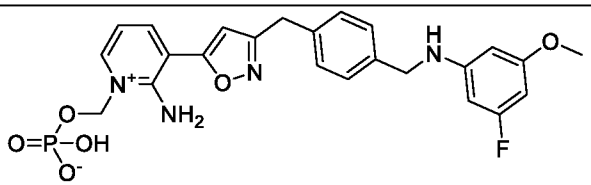
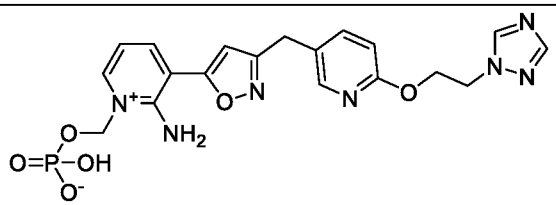
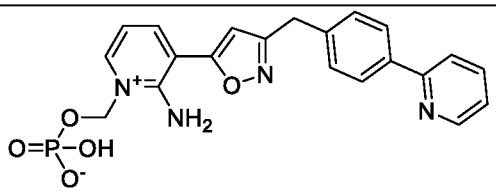
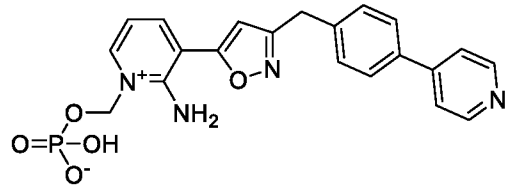
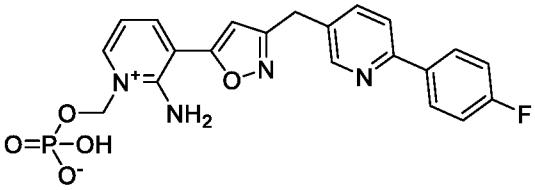
Ex.	Structure	Name
389		(2-amino-3-(3-((6-((3-chlorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
390		(2-amino-3-(3-((2-((3-fluorobenzyl)oxy)pyridin-4-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
391		(2-amino-3-(3-(4-(2-cyclohexylethyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
392		(2-amino-3-(3-((6-((3-chloro-5-fluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
393		(2-amino-3-(3-((2-phenoxypyridin-4-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
394		(2-amino-3-(3-((6-((3-fluorobenzyl)oxy)pyridin-2-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
395		(2-amino-3-(3-((6-((2-fluorobenzyl)oxy)pyridin-2-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
396		(2-amino-3-(3-((6-(3-fluorophenethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
397		(2-amino-3-(3-((6-((4-chloropyridin-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

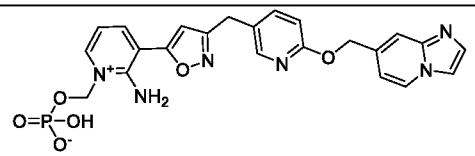
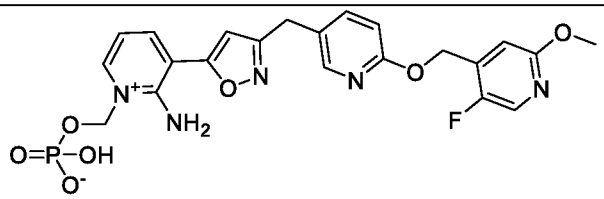
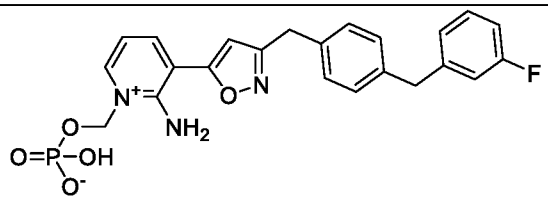
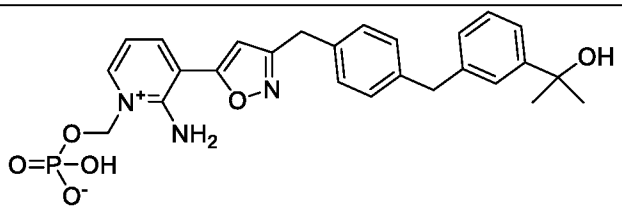
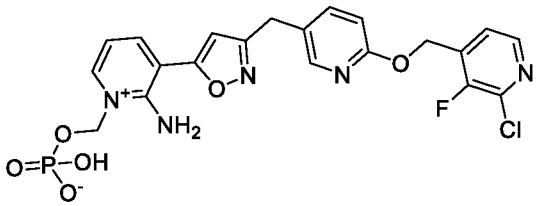
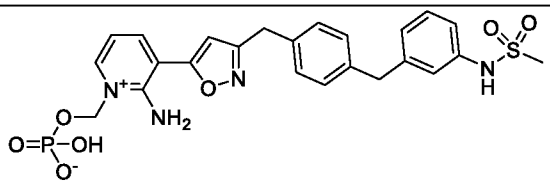
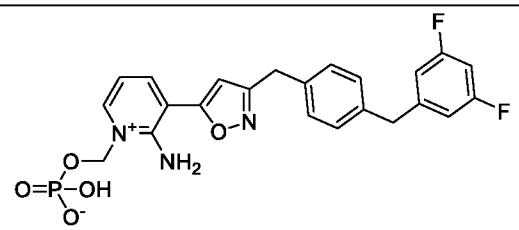
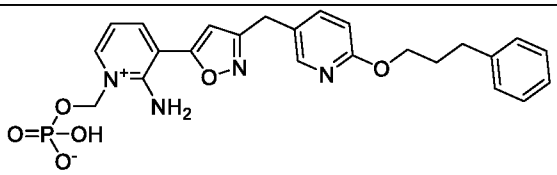
Ex.	Structure	Name
398		(2-amino-3-(3-((2-(3-fluorophenethoxy)pyridin-4-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
399		(2-amino-3-(3-((6-(3-fluorophenethoxy)pyridin-2-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
400		(2-amino-3-(3-((2-(benzyloxy)pyridin-4-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
401		(2-amino-3-(3-((2-((2-fluorobenzyl)oxy)pyridin-4-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
402		(2-amino-3-(3-((2-(cyclopropylmethoxy)pyridin-4-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
403		(2-amino-3-(3-(4-((6-(trifluoromethyl)pyridin-2-yl)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
404		(2-amino-3-(3-(4-((1-methyl-1H-pyrazol-3-yl)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
405		(2-amino-3-(3-((6-((4-fluorobenzyl)amino)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

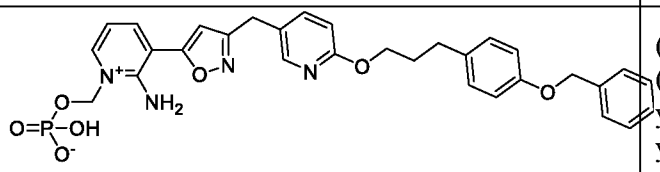
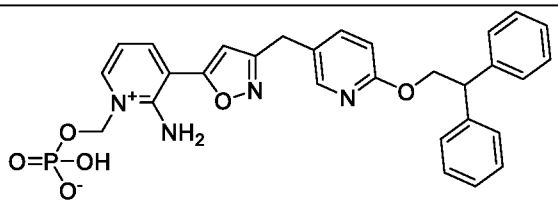
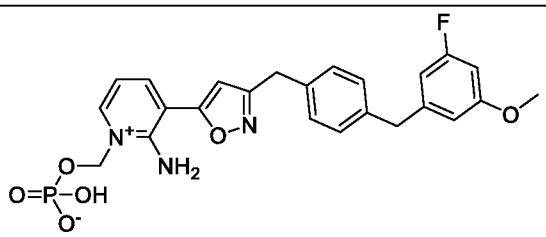
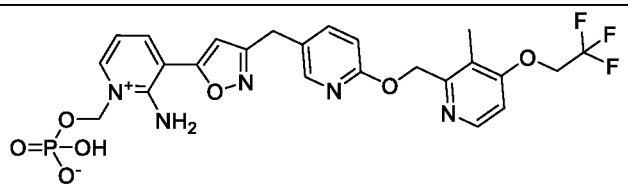
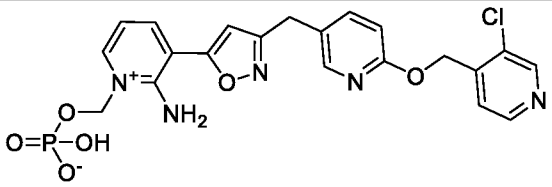
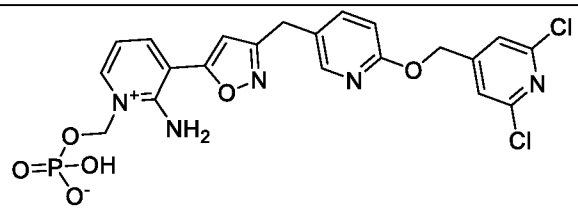
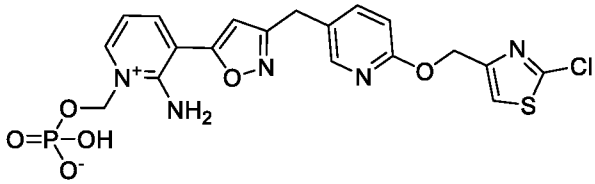
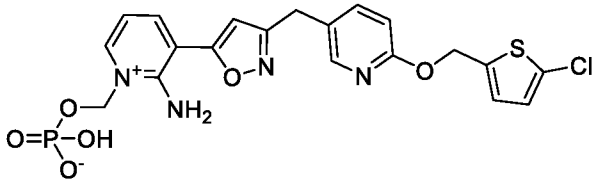
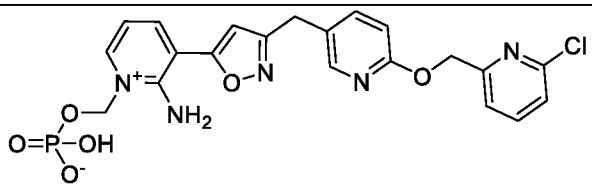
Ex.	Structure	Name
406		(2-amino-3-(3-((6-(2-(4-methylthiazol-5-yl)ethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
407		(3-(3-((6-(2-(1H-pyrazol-1-yl)ethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)-2-aminopyridin-1-ium-1-yl)methyl hydrogen phosphate
408		(2-amino-3-(3-((6-(2-phenylazetidin-1-yl)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
409		(2-amino-3-(3-((6-(prop-2-yn-1-yloxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
410		(2-amino-3-(3-((6-(2,4,5-trifluorophenethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
411		(2-amino-3-(3-((6-(2-chloro-6-fluorophenethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
412		(2-amino-3-(3-((6-(4-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
413		(2-amino-3-(3-((6-(3-chlorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
414		(2-amino-3-(3-((6-((3-fluoropyridin-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

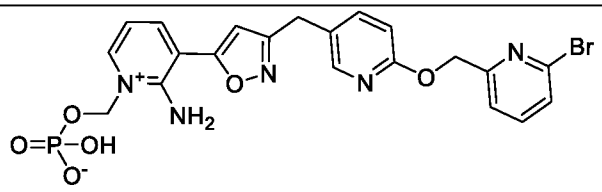
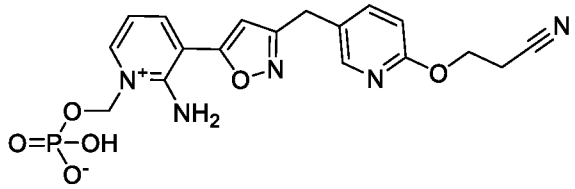
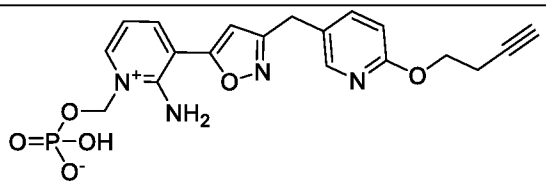
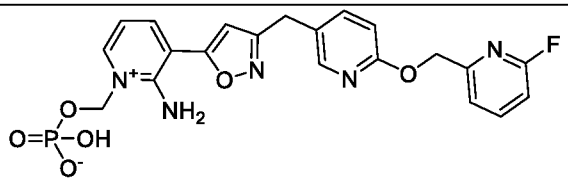
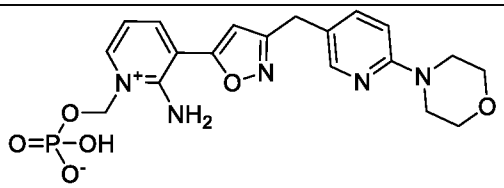
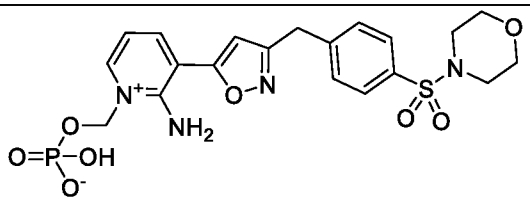
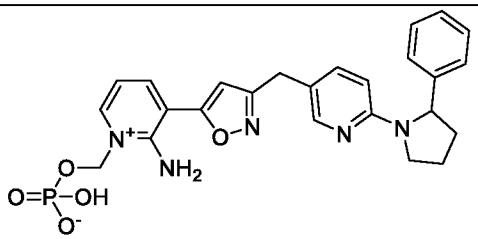
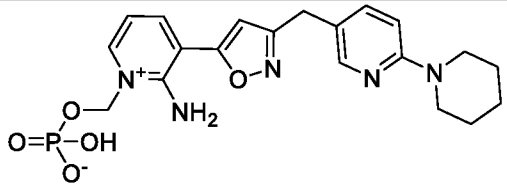
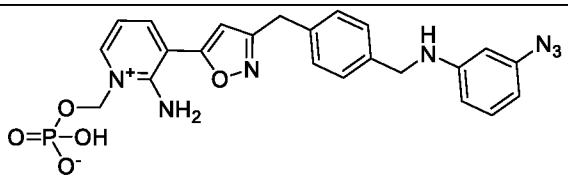
Ex.	Structure	Name
415		(2-amino-3-(3-((6-(2-methyl-2-phenylpropoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
416		(2-amino-3-(3-((6-(naphthalen-1-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
417		(2-amino-3-(3-((6-((2-methoxypyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
418		(2-amino-3-(3-((6-((3-methylbut-2-en-1-yl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
419		(2-amino-3-(3-(4-(((3,5-difluorophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
420		(2-amino-3-(3-(4-((2-fluorophenoxy)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
421		(2-amino-3-(3-(4-((3-fluorophenoxy)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
422		(3-(3-(4-((1H-indazol-1-yl)methyl)benzyl)isoxazol-5-yl)-2-aminopyridin-1-ium-1-yl)methyl hydrogen phosphate
423		(3-(3-(4-((2H-indazol-2-yl)methyl)benzyl)isoxazol-5-yl)-2-aminopyridin-1-ium-1-yl)methyl hydrogen phosphate

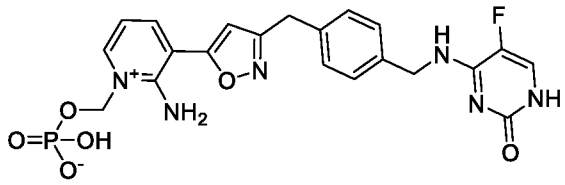
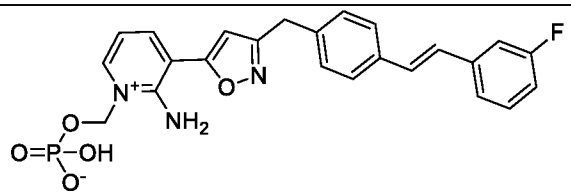
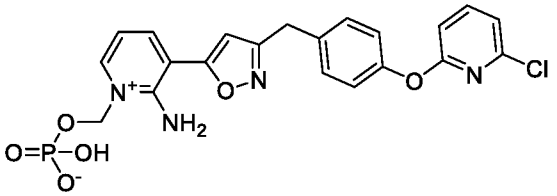
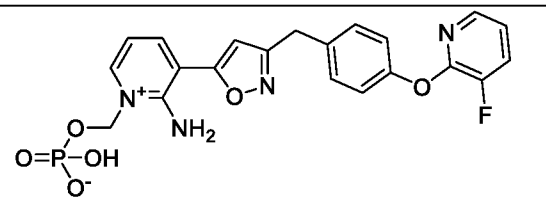
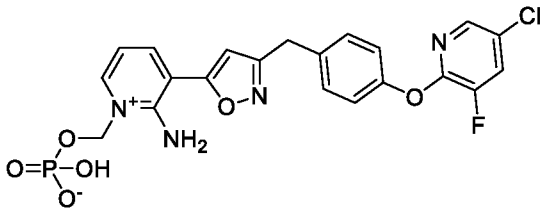
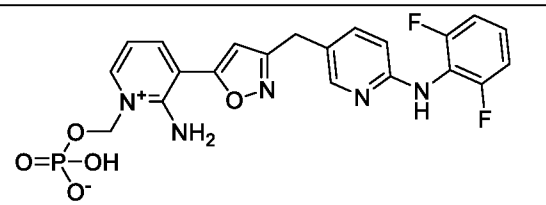
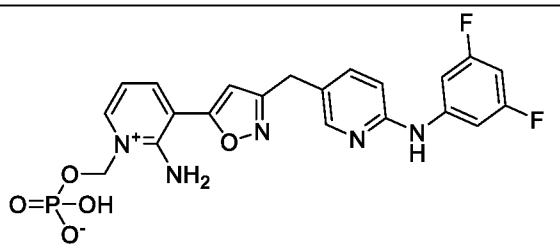
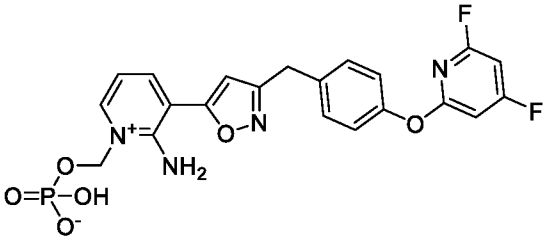
Ex.	Structure	Name
424		(2-amino-3-(3-(4-((2,5-difluorophenoxy)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
425		(2-amino-3-(3-(4-((2,3,5-trifluorophenoxy)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
426		(2-amino-3-(3-(4-benzoylbenzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
427		(2-amino-3-(3-(4-((5-fluoro-2-methoxyphenoxy)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
428		(2-amino-3-(3-(4-(((2,3,4-trifluorophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
429		(E)-(2-amino-3-(3-(4-(3-phenylprop-1-en-1-yl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
430		(2-amino-3-(3-((6-((2-bromopyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
431		(2-amino-3-(3-(4-(((2,5-difluorophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

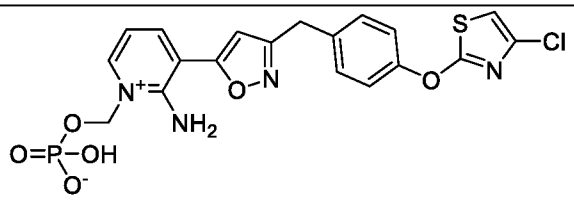
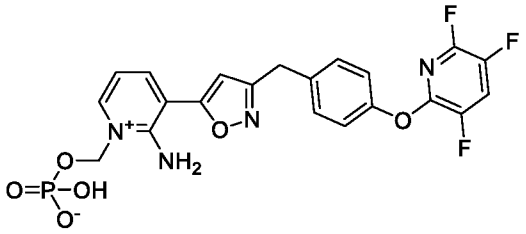
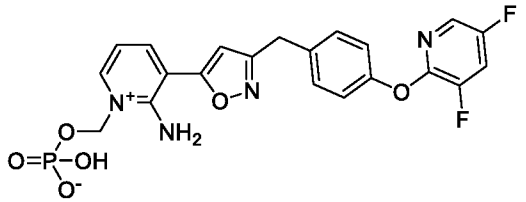
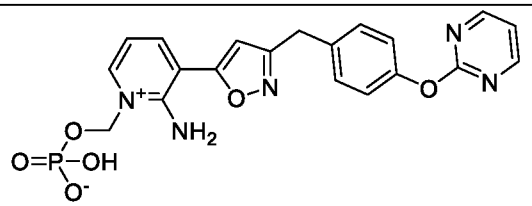
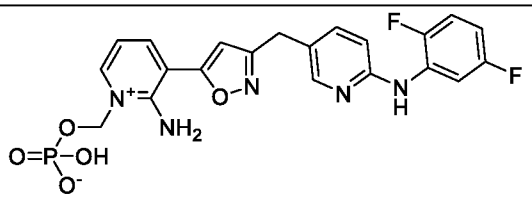
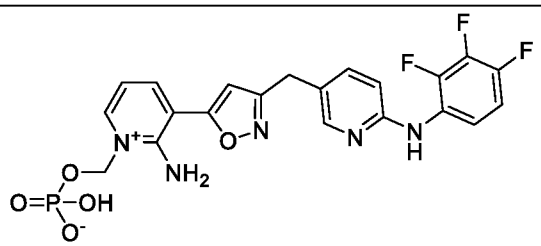
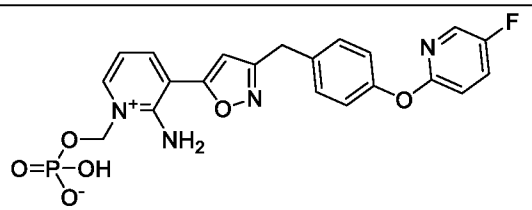
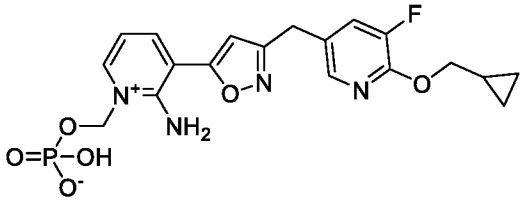
Ex.	Structure	Name
432		(2-amino-3-(3-(4-(((3,5-difluoro-2-methoxyphenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
433		(3-(3-(4-((1H-1,2,4-triazol-1-yl)methyl)benzyl)isoxazol-5-yl)-2-aminopyridin-1-ium-1-yl)methyl hydrogen phosphate
434		(3-(3-(4-((4H-1,2,4-triazol-4-yl)methyl)benzyl)isoxazol-5-yl)-2-aminopyridin-1-ium-1-yl)methyl hydrogen phosphate
435		(2-amino-3-(3-(4-(((3-fluoro-5-methoxyphenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
436		(3-(3-((6-(2-(1H-1,2,4-triazol-1-yl)ethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)-2-aminopyridin-1-ium-1-yl)methyl hydrogen phosphate
437		(2-amino-3-(3-(4-(pyridin-2-yl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
438		(2-amino-3-(3-(4-(pyridin-4-yl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
439		(2-amino-3-(3-((6-(4-fluorophenyl)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

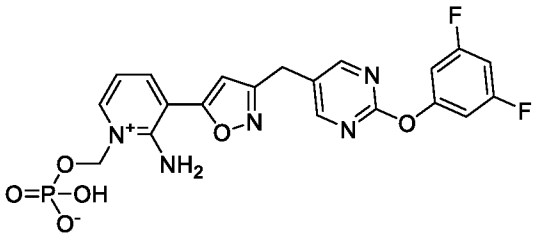
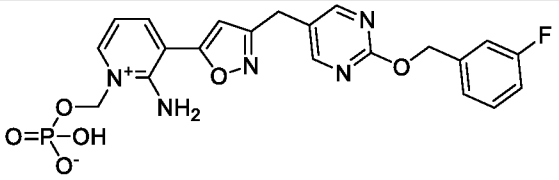
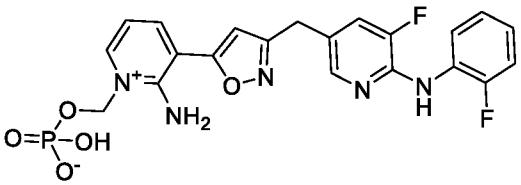
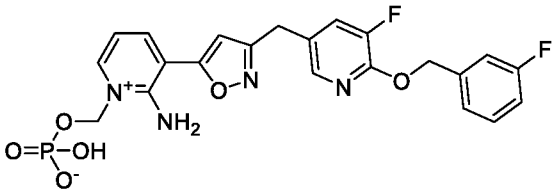
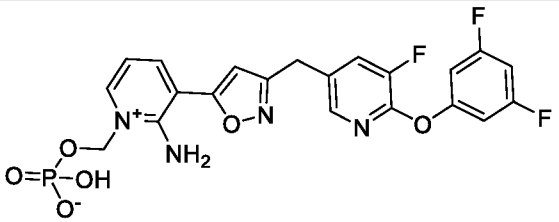
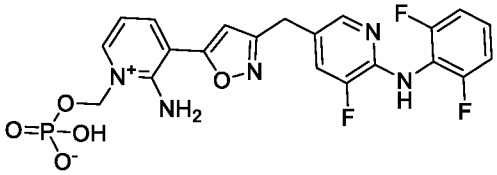
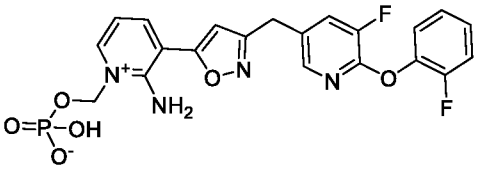
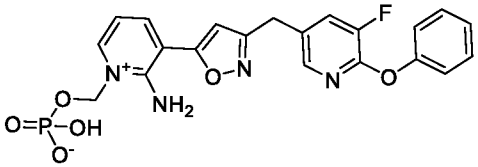
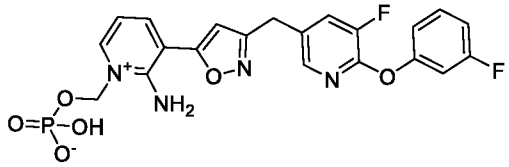
Ex.	Structure	Name
440		(2-amino-3-(3-((6-(imidazo[1,2-a]pyridin-7-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
441		(2-amino-3-(3-((6-((5-fluoro-2-methoxypyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
442		(2-amino-3-(3-(4-(3-fluorobenzyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
443		(2-amino-3-(3-(4-(3-(2-hydroxypropan-2-yl)benzyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
444		(2-amino-3-(3-((6-((2-chloro-3-fluoropyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
445		(2-amino-3-(3-(4-(3-(methylsulfonamido)benzyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
446		(2-amino-3-(3-(4-(3,5-difluorobenzyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
447		(2-amino-3-(3-((6-(3-phenylpropoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

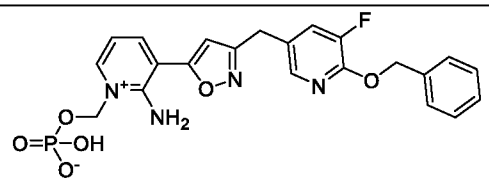
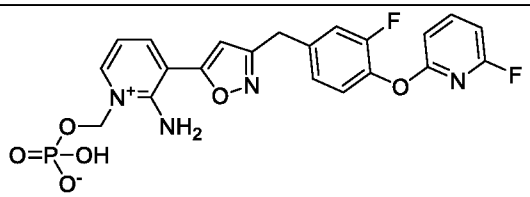
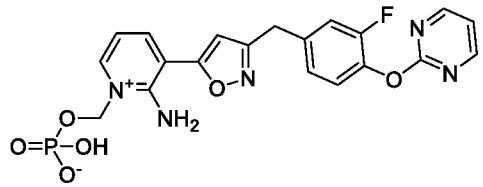
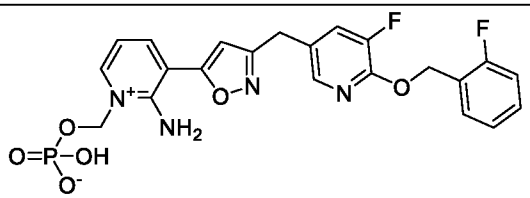
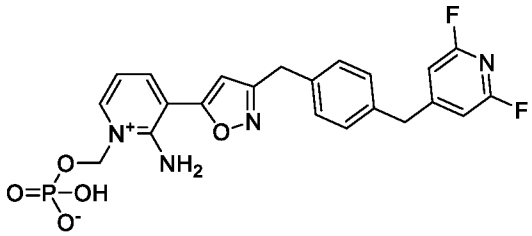
Ex.	Structure	Name
448		(2-amino-3-(3-((6-(3-(4-(benzyloxy)phenyl)propoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
449		(2-amino-3-(3-((6-(2,2-diphenylethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
450		(2-amino-3-(3-(4-(3-fluoro-5-methoxybenzyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
451		(2-amino-3-(3-((6-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
452		(2-amino-3-(3-((6-((3-chloropyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
453		(2-amino-3-(3-((6-((2,6-dichloropyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
454		(2-amino-3-(3-((6-((2-chlorothiazol-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
455		(2-amino-3-(3-((6-((5-chlorothiophen-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
456		(2-amino-3-(3-((6-((6-chloropyridin-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

Ex.	Structure	Name
457		(2-amino-3-(3-((6-((6-bromopyridin-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
458		(2-amino-3-(3-((6-(2-cyanoethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
459		(2-amino-3-(3-((6-(but-3-yn-1-yloxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
460		(2-amino-3-(3-((6-((6-fluoropyridin-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
461		(2-amino-3-(3-((6-morpholinopyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
462		(2-amino-3-(3-(4-(morpholinosulfonyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
463		(2-amino-3-(3-((6-(2-phenylpyrrolidin-1-yl)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
464		(2-amino-3-(3-((6-(piperidin-1-yl)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
465		(2-amino-3-(3-(4-(((3-azidophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

Ex.	Structure	Name
466		(2-amino-3-(3-(4-(((5-fluoro-2-oxo-1,2-dihydropyrimidin-4-yl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
467		(E)-(2-amino-3-(3-(4-(3-fluorostyryl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
468		(2-amino-3-(3-(4-((6-chloropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
469		(2-amino-3-(3-(4-((3-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
470		(2-amino-3-(3-(4-((5-chloro-3-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
471		(2-amino-3-(3-((6-((2,6-difluorophenyl)amino)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
472		(2-amino-3-(3-((6-((3,5-difluorophenyl)amino)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
473		(2-amino-3-(3-(4-((4,6-difluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

Ex.	Structure	Name
474		(2-amino-3-(3-(4-((4-chlorothiazol-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
475		(2-amino-3-(3-(4-((3,5,6-trifluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
476		(2-amino-3-(3-(4-((3,5-difluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
477		(2-amino-3-(3-(4-(pyrimidin-2-yloxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
478		(2-amino-3-(3-((6-((2,5-difluorophenyl)amino)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
479		(2-amino-3-(3-((6-((2,3,4-trifluorophenyl)amino)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
480		(2-amino-3-(3-(4-((5-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
481		(2-amino-3-(3-((6-(cyclopropylmethoxy)-5-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

Ex.	Structure	Name
482		(2-amino-3-(3-((2-(3,5-difluorophenoxy)pyrimidin-5-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
483		(2-amino-3-(3-((2-((3-fluorobenzyl)oxy)pyrimidin-5-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
484		(2-amino-3-(3-((5-fluoro-6-((2-fluorophenyl)amino)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
485		(2-amino-3-(3-((5-fluoro-6-((3-fluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
486		(2-amino-3-(3-((6-(3,5-difluorophenoxy)-5-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
487		(2-amino-3-(3-((6-((2,6-difluorophenyl)amino)-5-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
488		(2-amino-3-(3-((5-fluoro-6-(2-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
489		(2-amino-3-(3-((5-fluoro-6-phenoxypyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
490		(2-amino-3-(3-((5-fluoro-6-(3-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

Ex.	Structure	Name
491		(2-amino-3-(3-((6-(benzyloxy)-5-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
492		(2-amino-3-(3-(3-fluoro-4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
493		(2-amino-3-(3-(3-fluoro-4-(pyrimidin-2-yloxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
494		(2-amino-3-(3-((5-fluoro-6-((2-fluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate
495		(2-amino-3-(3-(4-((2,6-difluoropyridin-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

Further Forms of Compounds Disclosed Herein

Isomers/Stereoisomers

[0252] In some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds presented herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the corresponding mixtures thereof. In some situations, the compounds described herein possess one or more chiral centers and each center exists in the R configuration, or S configuration. The compounds described herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are useful for the applications described herein. In some embodiments, the compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. In some embodiments, dissociable complexes are preferred. In some embodiments, the diastereomers have distinct physical

properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In some embodiments, the diastereomers are separated by chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In some embodiments, the optically pure enantiomer is then recovered, along with the resolving agent.

Labeled compounds

[0253] In some embodiments, the compounds described herein exist in their isotopically-labeled forms. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds as pharmaceutical compositions. Thus, in some embodiments, the compounds disclosed herein include isotopically-labeled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of Formula (I), (II), or (III), or a solvate, or stereoisomer thereof, include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, and chloride, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, $^{18}0$, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds described herein, and the metabolites, pharmaceutically acceptable salts, esters, prodrugs, solvate, hydrates or derivatives thereof which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavy isotopes such as deuterium, *i.e.*, ^{2}H, produces certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements. In some embodiments, the isotopically labeled compound or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof is prepared by any suitable method.

[0254] In some embodiments, the compounds described herein are labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

Prodrugs

[0255] "Prodrug" is meant to indicate a compound that is, in some embodiments, converted under physiological conditions or by solvolysis to a biologically active compound described herein. Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. A prodrug is typically inactive when administered to a subject, but is converted *in vivo* to an active compound, for example, by hydrolysis. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (*see, e.g.,* Bundgard, H., Design of Prodrugs (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam). Prodrugs are delivered through any known methods described herein, including but not limited to orally, intravenously, intraperitoneal, or other method of administration known by those skilled in the art.

[0256] A discussion of prodrugs is provided in Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," A.C.S. Symposium Series, Vol. 14, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

[0257] The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of an active compound, as described herein, are prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent active compound. Prodrugs include compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. In some embodiments, prodrugs include any group bound to a heteroatom, such as the the nitrogen of a pyridine which is cleaved in-vivo to form the active compound or metabolite thereof. Examples of prodrugs include, but are not limited to, acetate, formate phosphate, and benzoate derivatives of alcohol or amine functional groups in the active compounds and the like.

[0258] In some embodiments, a prodrug is a salt. In some embodiments, a prodrug is a phosphate salt. In some embodiments, the prodrug is an alkyl phosphate salt. In some embodiments, the prodrug is an alkylated heteroaromatic salt. In some embodiments, the prodrug is a pyridinium salt. In some embodiments, the prodrug is a pyridinium alkylphosphate salt. In some embodiments, the prodrug is a pyridinium methylphosphate salt. In some embodiments, a prodrug comprises an alkyl phosphate bound to a heteroatom. In some embodiments, a prodrug comprises an alkyl phosphate bound to a heteroatom of a heterocycle.

[0259] The term "isotopic variant" refers to a compound that contains an unnatural proportion of an isotope at one or more of the atoms that constitute such a compound. In certain embodiments, an "isotopic variant" of a compound contains unnatural proportions of one or more isotopes, including, but not limited to, hydrogen (^{1}H), deuterium (^{2}H), tritium (^{3}H), carbon-11 (^{11}C), carbon-12 (^{12}C), carbon-13 (^{13}C), carbon-14 (^{14}C), nitrogen-13 (^{13}N), nitrogen-14 (^{14}N), nitrogen-15 (^{15}N), oxygen-14 (^{14}O), oxygen-15 (^{15}O), oxygen-16 (^{16}O), oxygen-17 (^{17}O), oxygen-18 (^{18}O), fluorine-17 (^{17}F), fluorine-18 (^{18}F), phosphorus-31 (^{31}P), phosphorus-32 (^{32}P), phosphorus-33 (^{33}P), sulfur-32 (^{32}S), sulfur-33 (^{33}S), sulfur-34 (^{34}S), sulfur-35 (^{35}S), sulfur-36 (^{36}S), chlorine-35 (^{35}Cl), chlorine-36 (^{36}Cl), chlorine-37 (^{37}Cl), bromine-79 (^{79}Br), bromine-81 (^{81}Br), iodine-123 (^{123}I), iodine-125 (^{125}I), iodine-127 (^{127}I), iodine-129 (^{129}I), and iodine-131 (^{131}I). In certain embodiments, an "isotopic variant" of a compound is in a stable form, that is, non-radioactive. In certain embodiments, an "isotopic variant" of a compound contains unnatural proportions of one or more isotopes, including, but not limited to, hydrogen (^{1}H), deuterium (^{2}H), carbon-12 (^{12}C), carbon-13 (^{13}C), nitrogen-14 (^{14}N), nitrogen-15 (^{15}N), oxygen-16 (^{16}O), oxygen-17 (^{17}O), oxygen-18 (^{18}O), fluorine-17 (^{17}F), phosphorus-31 (^{31}P), sulfur-32 (^{32}S), sulfur-33 (^{33}S), sulfur-34 (^{34}S), sulfur-36 (^{36}S), chlorine-35 (^{35}Cl), chlorine-37 (^{37}Cl), bromine-79 (^{79}Br), bromine-81 (^{81}Br), and iodine-127 (^{127}I). In certain embodiments, an "isotopic variant" of a compound is in an unstable form, that is, radioactive. In certain embodiments, an "isotopic variant" of a compound contains unnatural proportions

of one or more isotopes, including, but not limited to, tritium (^{3}H), carbon-11 (^{11}C), carbon-14 (^{14}C), nitrogen-13 (^{13}N), oxygen-14 (^{14}O), oxygen-15 (^{15}O), fluorine-18 (^{18}F), phosphorus-32 (^{32}P), phosphorus-33 (^{33}P), sulfur-35 (^{35}S), chlorine-36 (^{36}Cl), iodine-123 (^{123}I), iodine-125 (^{125}I), iodine-129 (^{129}I), and iodine-131 (^{131}I). It will be understood that, in a compound as provided herein, any hydrogen can be ^{2}H, for example, or any carbon can be ^{13}C, for example, or any nitrogen can be ^{15}N, for example, or any oxygen can be ^{18}O, for example, where feasible according to the judgment of one of skill. In certain embodiments, an "isotopic variant" of a compound contains unnatural proportions of deuterium (D).

Pharmaceutically acceptable salts

[0260] In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

[0261] In some embodiments, the compounds described herein possess acidic or basic groups and therefor react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. In some embodiments, these salts are prepared *in situ* during the final isolation and purification of the compounds disclosed herein, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

[0262] Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with a mineral, organic acid, or inorganic base, such salts including acetate, acrylate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, bisulfite, bromide, butyrate, butyn-1,4-dioate, camphorate, camphorsulfonate, caproate, caprylate, chlorobenzoate, chloride, citrate, cyclopentanepropionate, decanoate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hexyne-1,6-dioate, hydroxybenzoate, γ-hydroxybutyrate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isobutyrate, lactate, maleate, malonate, methanesulfonate, mandelate metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, 1-napthalenesulfonate, 2-napthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, pyrosulfate, pyrophosphate, propiolate, phthalate, phenylacetate, phenylbutyrate, propanesulfonate, salicylate, succinate, sulfate, sulfite, succinate, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylateundeconate, and xylenesulfonate.

[0263] Further, the compounds described herein can be prepared as pharmaceutically acceptable salts formed by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, including, but not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid metaphosphoric acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, p-toluenesulfonic acid, tartaric

acid, trifluoroacetic acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, arylsulfonic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, and muconic acid.

[0264] In some embodiments, those compounds described herein which comprise a free acid group react with a suitable base, such as the hydroxide, carbonate, bicarbonate, sulfate, of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, tertiary, or quaternary amine. Representative salts include the alkali or alkaline earth salts, like lithium, sodium, potassium, calcium, and magnesium, and aluminum salts and the like. Illustrative examples of bases include sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, $N^+(C_{1-4}$ alkyl$)_4$, and the like.

[0265] Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, and the like. It should be understood that the compounds described herein also include the quaternization of any basic nitrogen-containing groups they contain. In some embodiments, water or oil-soluble or dispersible products are obtained by such quaternization.

Solvates

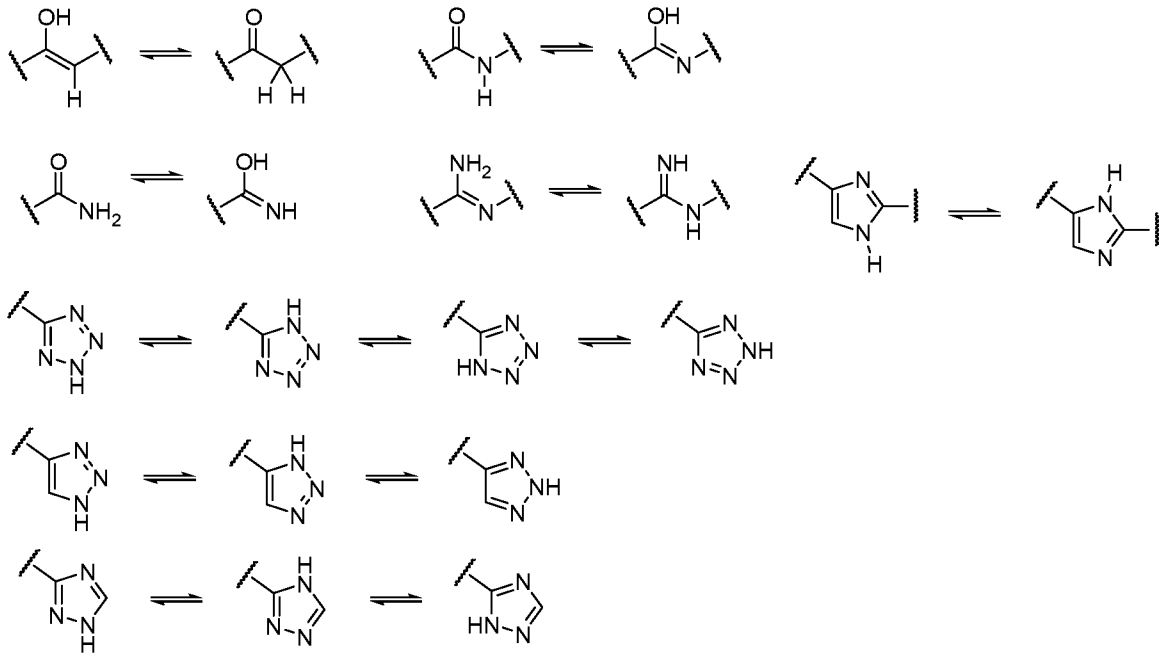
[0266] In some embodiments, the compounds described herein exist as solvates. The invention provides for methods of treating diseases by administering such solvates. The invention further provides for methods of treating diseases by administering such solvates as pharmaceutical compositions.

[0267] Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and, in some embodiments, are formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of the compounds described herein can be conveniently prepared or formed during the processes described herein. By way of example only, hydrates of the compounds described herein can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents including, but not limited to, dioxane, tetrahydrofuran, or methanol. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

Tautomers

[0268] In some situations, compounds exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein. Tautomers are compounds that are interconvertible by migration of a hydrogen atom, accompanied by a switch of a single bond and adjacent double bond. In bonding arrangements where tautomerization is possible, a chemical equilibrium of the tautomers will exist. All tautomeric forms of the compounds disclosed herein are contemplated. The

exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Some examples of tautomeric interconversions include:



Pharmaceutical Compositions

[0269] In certain embodiments, the compound of Formula (I), (Ia), (II), (IIa), (IIb), (IIc), (II'), (II''), (III), (IIIa), or (III-B) as described herein is administered as a pure chemical. In some embodiments, the compound of Formula (I), (Ia), (II), (IIa), (IIb), (IIc), (II'), (II''), (III), (IIIa), or (III-B) described herein is combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable (or acceptable) excipient, physiologically suitable (or acceptable) excipient, or physiologically suitable (or acceptable) carrier) selected on the basis of a chosen route of administration and standard pharmaceutical practice as described, for example, in *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)).

[0270] Accordingly, provided herein is a pharmaceutical composition comprising at least one compound of Formula (I), (Ia), (II), (IIa), (IIb), (IIc), (II'), (II''), (III), (IIIa), or (III-B) described herein, or a pharmaceutically acceptable salt, solvate, or steroisomer thereof, together with one or more pharmaceutically acceptable carriers. The carrier(s) (or excipient(s)) is acceptable or suitable if the carrier is compatible with the other ingredients of the composition and not deleterious to the recipient (*i.e.,* the subject) of the composition.

[0271] One embodiment provides a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula (I), (Ia), (II), (IIa), (IIb), (IIc), (II'), (II''), (III), (IIIa), or (III-B) or a pharmaceutically acceptable salt, solvate, or steroisomer thereof.

[0272] In certain embodiments, the compound of Formula (I), (Ia), (II), (IIa), (IIb), (IIc), (II'), (II''), (III), (IIIa), or (III-B) provided herein is substantially pure, in that it contains less than about 5%, or less than about 1%, or less than about 0.1%, of other organic small molecules, such as unreacted intermediates or synthesis by-products that are created, for example, in one or more of the steps of a synthesis method.

[0273] Pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (*e.g.*, an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity. Optimal doses are generally determined using experimental models and/or clinical trials. The optimal dose depends upon the body mass, weight, sex, age, renal status, hepatic status, or blood volume of the patient.

[0274] Oral doses typically range from about 1.0 mg to about 1000 mg, one to four times, or more, per day, or one to four times per week

[0275] In some embodiments, the compounds contemplated by the present disclosure may be administered (e.g., orally) at dosage levels of about 0.01 mg/kg to about 1000 mg/kg, or about 1 mg/kg to about 50 mg/kg, of subject body weight per day, one, two, three, four or more times a day, to obtain the desired therapeutic effect. For administration of an oral agent, the compositions can be provided in the form of tablets, capsules and the like containing from 0.05 to 1000 milligrams of the active ingredient, particularly 0.05, 0.1, 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 5.0, 7.5, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 125.0, 150.0, 175.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient. Pharmaceutically acceptable carrier(s), diluent(s) and/or excipient(s) may be present in an amount of from about 0.1 g to about 2.0 g.

Methods of Treatment

[0276] Disclosed herein, in certain embodiments, are methods for treating a fungal disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), (Ia), (II), (IIa), (IIb), (IIc), (II'), (II''), (III), (IIIa), or (III-B) at a frequency and for a duration sufficient to provide a beneficial effect to the subject.

[0277] Disclosed herein, in certain embodiments, are methods for treating a fungal disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a pharmaceutical composition, comprising compound of Formula (I), (Ia), (II), (IIa), (IIb), (IIc), (II'), (II''), (III), (IIIa), or (III-B), and at least one pharmaceutically acceptable excipient, at a frequency and for a duration sufficient to provide a beneficial effect to the subject.

Fungal Diseases

[0278] In some embodiments, the fungal disease is selected from the group consisting of aspergillosis, blastomycosis, candidiasis, coccidioidomycosis (Valley Fever), cryptococcosis, fungal eye infection, histoplasmosis, mucormycosis, *Pneumocystis* pneumonia (PCP), ringworm, sporotrichosis, and talaromycosis.

[0279] In some embodiments, the fungal disease is aspergillosis. In some embodiments, aspergillosis is allergic bronchopulmonary aspergillosis (abpa), allergic *aspergillus* sinusitis, chronic pulmonary

aspergillosis, invasive aspergillosis or cutaneous (skin) aspergillosis. In some embodiments, the subject has an aspergilloma.

[0280] In some embodiments, the fungal disease is blastomycosis.

[0281] In some embodiments, the fungal disease is candidiasis. In some embodiments, candidiasis is oropharyngeal candidiasis (thrush), vulvovaginal candidiasis (vaginal candidiasis), fungemia, or invasive candidiasis.

[0282] In some embodiments, the fungal disease is coccidioidomycosis (Valley Fever). In some embodiments, coccidioidomycosis is acute coccidioidomycosis (primary pulmonary coccidioidomycosis), chronic coccidioidomycosis, or disseminated coccidioidomycosis, including primary cutaneous coccidioidomycosis.

[0283] In some embodiments, the fungal disease is cryptococcosis. In some embodiments, cryptococcosis is wound or cutaneous cryptococcosis, pulmonary cryptococcosis, or cryptococcal meningitis.

[0284] In some embodiments, the fungal disease is a fungal eye infection. In some embodiments, the fungal eye infection is fungal keratitis, fungal exogenous endophthalmitis, or fungal endogenous endophthalmitis.

[0285] In some embodiments, the fungal disease is histoplasmosis. In some embodiments, histoplasmosis is acute histoplamosis. In some embodiments, histoplamosis is chronic histoplamosis.

[0286] In some embodiments, the fungal disease is mucormycosis. In some embodiments, mucormycosis is rhinocerebral (sinus and brain) mucormycosis, pulmonary (lung) mucormycosis, gastrointestinal mucormycosis, cutaneous (skin) mucormycosis, or disseminated mucormycosis.

[0287] In some embodiments, the fungal disease is *Pneumocystis* pneumonia (PCP).

[0288] In some embodiments, the fungal disease is ringworm. In some embodiments, the ringworm is tinea pedis, tinea cruris, tinea capitis, tinea barbae, tinea manuum, tinea unguium, or tinum corporis. In some embodiments, the ringworm is caused by a type of fungi including *Trichophyton, Microsporum*, or *Epidermophyton.*

[0289] In some embodiments, the fungal disease is sporotrichosis. In some embodiments, sporotrichosis is cutaneous (skin) sporotrichosis, pulmonary (lung) sporotrichosis, or disseminated sporotrichosis.

[0290] In some embodiments, the fungal disease is talaromycosis.

[0291] In some embodiments, the fungal disease is caused by a fungal species including, but not limited to, *Aspergillus fumigatus, Aspergillus flavus*, *Aspergillus niger, Aspergillus terreus*, *Blastomyces dermatitidis, Ajellomyces dermatitidis, Candida albicans, Candida auris, Candida glabrata*, *Candida parapsilosis, Candida rugosa*, *Candida tropicalis, Coccidioides immitis*, *Coccidioides posadasii, Cryptococcus neoformans*, *Cryptococcus gattii, Histoplasma capsulatum, Rhizopus stolonifer, Rhizopus arrhizus, Mucor indicus, Cunninghamella bertholletiae, Apophysomyces elegans, Absidia species, Saksenaea species, Rhizomucor pusillus, Entomophthora species, Conidiobolus species, Basidiobolus species, Sporothrix schenckii, Pneumocystis jirovecii*, *Talaromyces marneffei, Asclepias albicans*, *Fusarium solani, Scedosporium apiospermum,* and *Rhizomucor pusillus.*. In some embodiments, the

fungal disease is caused by the fungal species *Aspergillus fumigatus.* In some embodiments, the fungal disease is caused by the fungal species *Candida albicans.* In some embodiments, the fungal disease is caused by the fungal species *Fusarium solani.* In some embodiments, the fungal disease is caused by the fungal species *Mucor indicus.* In some embodiments, the fungal disease is caused by the fungal species *Scedosporium apiospermum.* In some embodiments, the fungal disease is caused by the fungal species *Cryptococcus neoformans.* In some embodiments, the fungal disease is caused by the fungal species *Cryptococcus gattii.* In some embodiments, the fungal disease is caused by the fungal species *Candida auris.*

[0292] In an aspect provided herein, there is a method of treating a fungal disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), (Ia), (II), (IIa), (IIb), (IIc), (II'), (II''), (III), (IIIa), or (III-B). In an aspect provided herein, there is a method of treating a fungal disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising compound of Formula (I), (Ia), (II), (IIa), (IIb), (IIc), (II'), (II''), (III), (IIIa), or (III-B) and at least one pharmaceutically acceptable excipient.

[0293] In some embodiments of the methods disclosed herein, the fungal disease is selected from the group consisting of aspergillosis, blastomycosis, candidiasis, coccidioidomycosis (Valley Fever), cryptococcosis, fungal eye infection, histoplasmosis, mucormycosis, *Pneumocystis* pneumonia (PCP), ringworm, sporotrichosis, and talaromycosis.

[0294] In some embodiments of the methods disclosed herein, the fungal disease is caused by a fungal species selected the group consisting of *Aspergillus fumigatus, Aspergillus flavus, Blastomyces dermatitidis, Ajellomyces dermatitidis, Candida albicans, Candida glabrata, Candida rugosa, Candida auris, Coccidioides immitis, Coccidioides posadasii, Cryptococcus neoformans, Cryptococcus gattii, Histoplasma capsulatum, Rhizopus stolonifer, Rhizopus arrhizus, Mucor indicus, Cunninghamella bertholletiae, Apophysomyces elegans, Absidia species, Saksenaea species, Rhizomucor pusillus, Entomophthora species, Conidiobolus species, Basidiobolus species, Sporothrix schenckii, Pneumocystis jirovecii, Talaromyces marneffei, Asclepias albicans, Fusarium solani, Scedosporium apiospermum, and Rhizomucor pusillus.*

[0295] In some embodiments of the methods disclosed herein, the subject is immunocompromised.

[0296] In some embodiments of the methods disclosed herein, the subject has received chemotherapy treatment.

[0297] In some embodiments of the methods disclosed herein, the subject is infected with HIV/AIDS.

[0298] In some embodiments of the methods disclosed herein, the fungal disease is caused by *Cryptococcus neoformans* or *Cryptococcus gattii.*

[0299] In some embodiments of the methods disclosed herein, the compound is selected from the compounds in **Table 1**. In some embodiments of the methods disclosed herein, the compound is selected from the compounds in **Table 2**.

[0300] In some embodiments of the methods disclosed herein, the compound is selected from:

3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-(4-((6-chloropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-(4-((3-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-(4-((3,5-difluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-((6-(3-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-(4-((5-fluorofuran-2-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-((6-phenoxypyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-((6-((3-fluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine;

5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(2-fluorophenyl)pyridin-2-amine;

5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(2,6-difluorophenyl)pyridin-2-amine;

3-(3-(4-benzylbenzyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-(4-((6-fluoropyridin-2-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-((6-(2-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-((6-(3,5-difluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-((6-(cyclopropylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-(4-(3,5-difluorobenzyl)benzyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-((2-((3-fluorobenzyl)oxy)pyridin-4-yl)methyl)isoxazol-5-yl)pyridin-2-amine;

3-(3-(4-(3-fluorobenzyl)benzyl)isoxazol-5-yl)pyridin-2-amine; and

3-(3-(4-(((3-fluorophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof.

[0301] In some embodiments, a compound described herein is active against the fungal Gwt1 protein. This conserved enzyme catalyzes the glycosylphosphatidyl inositol (GPI) post-translational modification that anchors eukaryotic cell surface proteins to the cell membrane. In yeasts, GPI mediates cross-linking of cell wall mannoproteins to β-1,6-glucan. Inhibition of this enzyme in both *Candida albicans* and *Saccharomyces cerevisiae* has been shown to result in inhibition of maturation and localization of GPI-anchored mannoproteins thus demonstrating pleiotropic effects that include inhibition of fungal adherence to surfaces, inhibition of biofilm formation, inhibition of germ tube formation, severe growth defects, or lethality.

Subjects

[0302] In some embodiments, the subject is immunocompromised. In some embodiments, the subject is an immunocompromised human subject. In some embodiments, the human subject is under the age of 1 year. In some embodiments, the human subject is an infant under 1 month old. In some embodiments, the human subject is over the age of 70 years. In some embodiments, the subject is infected with HIV/AIDS. In some embodiments, the subject is undergoing or has undergone cancer chemotherapy treatment. In some embodiments, the subject is undergoing or has undergone corticosteroid treatment. In some embodiments, the subject is undergoing or has undergone TNF inhibitor treatment. In some embodiments, the subject is a transplant recipient. In some embodiments, the subject is a recipient of a

hematopoietic stem-cell transplant, bone marrow transplant, lung transplant, liver transplant, heart transplant, kidney transplant, pancreas transplant or a combination thereof. In some embodiments, the subject is a recipient of a hematopoietic stem-cell transplant. In some embodiments, the subject is a recipient of a bone marrow transplant. In some embodiments, the subject is a recipient of a lung transplant. In some embodiments, the subject is a recipient of a liver transplant. In some embodiments, the subject is a recipient of a heart transplant. In some embodiments, the subject is a recipient of a kidney transplant. In some embodiments, the subject is a recipient of a pancreas transplant.

[0303] In some embodiments, the subject is a vertebrate. In some embodiments, the vertebrate is a fish, an amphibian, a reptile, a bird, a marsupial, or a mammal. In some embodiments, the subject is a fish. In some embodiments, the subject is a mammal. In some embodiments, the mammal is a human. In some embodiments, the mammal is a dog. In some embodiments, the mammal is a cat. In some embodiments, the mammal is livestock. In some embodiments, the livestock is selected from the group consisting of cattle, sheep, goats, swine, poultry, bovine, and equine animals. In some embodiments, the subject is an invertebrate. In some embodiments, the invertebrate is an insect. In some embodiments, the invertebrate is a plant.

Combination Therapy

[0304] In certain instances, the compound of Formula (I), (Ia), (II), (IIa), (IIb), (IIc), (II'), (II''), (III), (IIIa), or (III-B) or a pharmaceutically acceptable salt, solvate, or steroisomer thereof, is administered in combination with a second therapeutic agent.

[0305] In some embodiments, the benefit experienced by a subject is increased by administering one of the compounds described herein with a second therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit.

[0306] In one specific embodiment, a compound of Formula (I), (Ia), (II), (IIa), (IIb), (IIc), (II'), (II''), (III), (IIIa), or (III-B) or a pharmaceutically acceptable salt, solvate, or steroisomer thereof, is co-administered with a second therapeutic agent, wherein the compound of Formula (I), (Ia), (II), (IIa), (IIb), (IIc), (II'), (II''), (III), (IIIa), or (III-B) or a pharmaceutically acceptable salt, solvate, or steroisomer thereof, and the second therapeutic agent modulate different aspects of the disease, disorder or condition being treated, thereby providing a greater overall benefit than administration of either therapeutic agent alone.

[0307] In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the subject is simply additive of the two therapeutic agents or the subject experiences a synergistic benefit.

[0308] In certain embodiments, different therapeutically-effective dosages of the compounds disclosed herein will be utilized in formulating a pharmaceutical composition and/or in treatment regimens when the compounds disclosed herein are administered in combination with a second therapeutic agent. Therapeutically-effective dosages of drugs and other agents for use in combination treatment regimens are optionally determined by means similar to those set forth hereinabove for the actives themselves. Furthermore, the methods of prevention/treatment described herein encompasses the use of metronomic

dosing, i.e., providing more frequent, lower doses in order to minimize toxic side effects. In some embodiments, a combination treatment regimen encompasses treatment regimens in which administration of a compound of Formula (I), (Ia), (II), (IIa), (IIb), (IIc), (II'), (II''), (III), (IIIa), or (III-B) or a pharmaceutically acceptable salt, solvate, or steroisomer thereof, is initiated prior to, during, or after treatment with a second agent described herein, and continues until any time during treatment with the second agent or after termination of treatment with the second agent. It also includes treatments in which a compound of Formula (I), (Ia), (II), (IIa), (IIb), (IIc), (II'), (II''), (III), (IIIa), or (III-B) or a pharmaceutically acceptable salt, solvate, or steroisomer thereof, and the second agent being used in combination are administered simultaneously or at different times and/or at decreasing or increasing intervals during the treatment period. Combination treatment further includes periodic treatments that start and stop at various times to assist with the clinical management of the patient.

[0309] It is understood that the dosage regimen to treat, prevent, or ameliorate the condition(s) for which relief is sought, is modified in accordance with a variety of factors (e.g. the disease, disorder or condition from which the subject suffers; the age, weight, sex, diet, and medical condition of the subject). Thus, in some instances, the dosage regimen actually employed varies and, in some embodiments, deviates from the dosage regimens set forth herein.

[0310] For combination therapies described herein, dosages of the co-administered compounds vary depending on the type of co-drug employed, on the specific drug employed, on the disease or condition being treated, and so forth. In additional embodiments, when co-administered with a second therapeutic agent, the compound provided herein is administered either simultaneously with the second therapeutic agent, or sequentially.

[0311] In combination therapies, the multiple therapeutic agents (one of which is one of the compounds described herein) are administered in any order or even simultaneously. If administration is simultaneous, the multiple therapeutic agents are, by way of example only, provided in a single, unified form, or in multiple forms (e.g., as a single pill or as two separate pills).

[0312] The compounds of Formula (I), (Ia), (II), (IIa), (IIb), (IIc), (II'), (II''), (III), (IIIa), or (III-B) or a pharmaceutically acceptable salt, solvate, or steroisomer thereof, as well as combination therapies, are administered before, during or after the occurrence of a disease or condition, and the timing of administering the composition containing a compound varies. Thus, in one embodiment, the compounds described herein are used as a prophylactic and are administered continuously to subjects with a propensity to develop conditions or diseases in order to prevent the occurrence of the disease or condition. In another embodiment, the compounds and compositions are administered to a subject during or as soon as possible after the onset of the symptoms. In specific embodiments, a compound described herein is administered as soon as is practicable after the onset of a disease or condition is detected or suspected, and for a length of time necessary for the treatment of the disease. In some embodiments, the length required for treatment varies, and the treatment length is adjusted to suit the specific needs of each subject. For example, in specific embodiments, a compound described herein or a formulation containing the compound is administered for at least 2 weeks, about 1 month to about 5 years.

[0313] In certain embodiments, the second therapeutic agent is antifungal agent. In some embodiments, the second therapeutic agent is an antifungal agent selected from the group consisting of: a polyene antifungal agent, an azole antifungal agent, an allylamine antifungal agent, and an echinocandin antifungal agent.

[0314] In some embodiments, the polyene antifungal agent is selected from the group consisting of: Amphotericin B, Candicidin, Filipin, Hamycin, Natamycin, Nystatin, and Rimocidin.

[0315] In some embodiments, the azole antifungal agent is selected from the group consisting of: an imidazole, a triazole, and a thiazole. In some embodiments, the imidazole is selected from the group consisting of: Bifonazole, Butoconazole, Clotrimazole, Econazole, Fenticonazole, Isoconazole, Ketoconazole, Luliconazole, Miconazole, Omoconazole, Oxiconazole, Sertaconazole, Sulconazole, and Tioconazole. In some embodiments, the triazole is selected from the group consisting of: Albaconazole, Efinaconazole, Epoxiconazole, Fluconazole, Isavuconazole, Itraconazole, Posaconazole, Propiconazole, Ravuconazole, Terconazole, and Voriconazole. In some embodiments, the thiazole is Abafungin.

[0316] In some embodiments, the allylamine antifungal agent is selected from the group consisting of: Amorolfin, Butenafine, Naftifine, and Terbinafine.

[0317] In some embodiments, the echinocandin antifungal agent is selected from the group consisting of: Anidulafungin, Caspofungin, Micafungin and Rezafungin.

[0318] In some embodiments, are methods for treating a subject with a fungal disease comprising administering to the subject a combination treatment of a compound of Formula (I), (Ia), (II), (IIa), (IIb), (IIc), (II'), (II''), (III), (IIIa), or (III-B) or a pharmaceutically acceptable salt, solvate, or steroisomer thereof, and fluconazole, wherein the subject is selected from the group consisting of cattle, sheep, goats, swine, poultry, bovine, and equine animals.

[0319] In some embodiments, are methods for treating a subject with a fungal disease comprising administering to the subject a combination treatment of a compound of Formula (I), (Ia), (II), (IIa), (IIb), (IIc), (II'), (II''), (III), (IIIa), or (III-B) or a pharmaceutically acceptable salt, solvate, or steroisomer thereof, and ketoconazole, wherein the subject is selected from the group consisting of cattle, sheep, goats, swine, poultry, bovine, and equine animals.

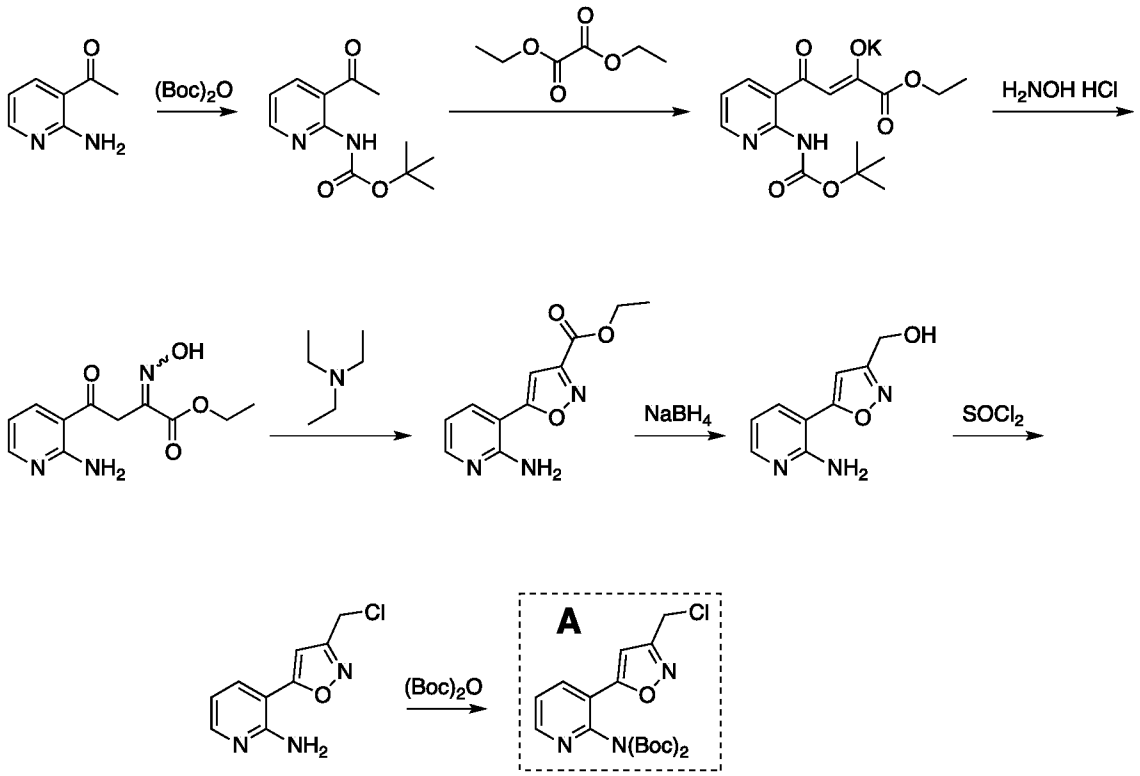
[0320] In some embodiments, are methods for treating a subject with a fungal disease comprising administering to the subject a combination treatment of a compound of Formula (I), (Ia), (II), (IIa), (IIb), (IIc), (II'), (II''), (III), (IIIa), or (III-B) or a pharmaceutically acceptable salt, solvate, or steroisomer thereof, and itraconazole, wherein the subject is selected from the group consisting of cattle, sheep, goats, swine, poultry, bovine, and equine animals.

EXAMPLES

Example I: Chemical Synthesis

[0321] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Anhydrous solvents and oven-dried glassware were used for synthetic transformations sensitive to moisture and/or oxygen. Yields were not optimized. Reaction times are approximate and were not optimized. Column chromatography and thin layer chromatography (TLC) were performed on silica gel unless otherwise noted.

Intermediate A: Synthesis of di-tert-butyl [3-(3-(chloromethyl)-1,2-oxazol-5-yl)pyridin-2-yl]imidodicarbonate



Step 1: *tert*-butyl (3-acetylpyridin-2-yl)carbamate:

[0322] 1-(2-Aminopyridin-3-yl)ethan-1-one (5 g, 37 mmol) was dissolved in *tert*-butyl alcohol (20 mL), and then di-*tert*-butyl dicarbonate (12 g) was added. The mixture was heated to 90 °C for 3 hours. The mixture was cooled to room temperature and evaporated under reduced pressure to give a dark-tan solid. The crude material was washed with a mixture of heptane and hexane, and then filtered. The solid was manually crushed, and again washed with heptane and hexane. The solid was air-dried, then extensively vacuum-dried to give the title compound as a tan solid (7.8 g, 90%). This material was taken forward without further purification.

Step 2: Ethyl 5-(2-aminopyridin-3-yl)isoxazole-3-carboxylate:

[0323] To a solution of t*ert*-butyl (3-acetylpyridin-2-yl)carbamate (7.7 g, 33 mmol) and diethyl oxalate (8.9 mL, 65 mmol) in toluene (65 mL) was added potassium *tert*-butoxide (7.3 g, 65 mmol) portion-wise at room temperature. The dark-purple heterogeneous mixture was stirred under nitrogen and began to form a thick precipitate. An additional 65 mL of toluene was added, and the mixture was stirred for another 2 hours before adding an additional 3.7 g of potassium *tert*-butoxide. After stirring another 1 hour, ethanol (130 mL) was added followed by hydroxylamine hydrochloride (6.8 g, 98 mmol). The

resulting burnt-orange-colored mixture was stirred for 2 hours, and then water (13 mL) was added. The solution briefly cleared somewhat, and then became a thick caramel-color. The mixture was stirred for 16 hours and gradually became a yellowish color. Another 400 mL of water was added and 500 mL of ethyl acetate. The layers were separated. The organic phase was washed with water (2x150 mL). The combined aqueous phase was extracted with ethyl acetate (2x250 mL). The combined organic phase was washed with brine, dried over sodium sulfate, and evaporated under reduced pressure to give an orange solid. To the solid product was added DMF (65 mL) and triethylamine (4.5 mL, 33 mmol). The solution was stirred at 80 °C for 6 hours, and then allowed to gradually reach room temperature overnight. Water (300 mL) was added and the solution was extracted with ethyl acetate, and then evaporated to give an orange oily solid. The crude material was treated with warm hexane/acetone (15:1) which resulted in a deep orange solution over a solid material. The solid was collected by filtering through a sintered glass funnel and washed with copious amounts of hexane. This gave the title compound as a free-flowing tannish pale-orange solid (4 g, 53%) which was taken forward without further purification.

Step 3: (5-(2-Aminopyridin-3-yl)isoxazol-3-yl)methanol:

[0324] To a suspension of ethyl 5-(2-aminopyridin-3-yl)isoxazole-3-carboxylate (0.50 g, 2.1 mmol) in a 1:1 mixture of THF/ethanol (10 mL) at 0 °C was added sodium borohydride (0.24 g, 6.4 mmol) in portions. The cold bath was removed, and the mixture was stirred at room temperature for 19 hours with occasional monitoring by TLC. Another 0.5 equivalents of sodium borohydride (0.040 g, 1.0 mmol) was added to the mixture. After stirring briefly the mixture was quenched by pouring into ice followed by slow cautious addition of aqueous 5N HCl solution (2 mL) – *vigorous reaction*. The acidic solution (pH 3) was stirred for 10 min, then basified to pH 9 with aqueous 5N NaOH solution. The basic mixture was extracted three times with ethyl acetate. The combined organic phase was washed with brine, dried over sodium sulfate, and evaporated under reduced pressure to give the title compound as a yellow solid (0.32 g, 77%). This material was taken forward without further purification.

Step 4: 3-(3-(Chloromethyl)isoxazol-5-yl)pyridin-2-amine:

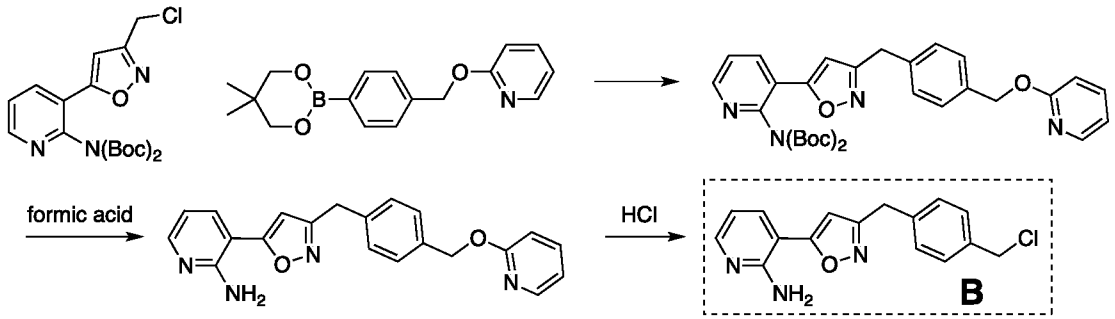
[0325] To a mixture of (5-(2-aminopyridin-3-yl)isoxazol-3-yl)methanol (0.31 g, 1.6 mmol) in N,N-dimethylacetamide (1.6 mL) at 0 °C was added a cold mixture of thionyl chloride (0.24 mL, 3.3 mmol) and benzotriazole (0.43 g, 3.6 mmol) in tetrahydrofuran. The cold bath was removed, and the mixture was stirred at room temperature. TLC after 30 min indicated complete reaction. The mixture was quenched by pouring into ice followed by basification to pH 8 with aqueous 5N NaOH. The mixture was then extracted three times with ethyl acetate. The combined organic phase was washed with brine, dried over sodium sulfate, and evaporated under reduced pressure to give the title compound as an oil which will be taken forward without further purification.

Step 5: Di-tert-butyl [3-(3-(chloromethyl)-1,2-oxazol-5-yl)pyridin-2-yl]imidodicarbonate:

[0326] To a solution of 3-(3-(chloromethyl)isoxazol-5-yl)pyridin-2-amine (0.34 g, 1.6 mmol, *based on theoretical yield of previous reaction*) in tetrahydrofuran was added N,N-dimethylaminopyridine (0.020 g, 0.16 mmol) and di-tert-butyl dicarbonate (0.75 g, 3.4 mmol). The homogeneous solution was stirred at room temperature and gradually changed color from orange to red. LCMS and TLC after 2h suggested

only partially completed conversion, and there was little improvement after 19h. Another 0.6 equivalents of di-tert-butyl dicarbonate (0.20 g, 0.92 mmol) was added and the mixture stirred for another 2h. The reaction was quenched with water and extracted three times with toluene. The combined organic phase was washed with diluted brine, dried over sodium sulfate, and evaporated under reduced pressure to give a red oil. The oil was further purified using Biotage normal-phase flash chromatography (50 g SNAP Ultra, 2-40% ethyl acetate in hexanes). The desired fractions were combined and evaporated to give the title compound as a white solid (0.53 g, 80% yield over two steps). 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.50 (dd, J = 4.8, 1.8 Hz, 1H), 8.18 (dd, J = 7.9, 1.8 Hz, 1H), 7.36 (dd, J = 7.9, 4.8 Hz, 1H), 6.56 (s, 1H), 4.52 (s, 2H), 1.21 (s, 18H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 165.7, 161.6, 150.2, 150.0, 148.5, 136.6, 123.6, 121.5, 102.4, 83.5, 35.2, 27.6 ppm. MS: 410.5 $[M+H]^+$.

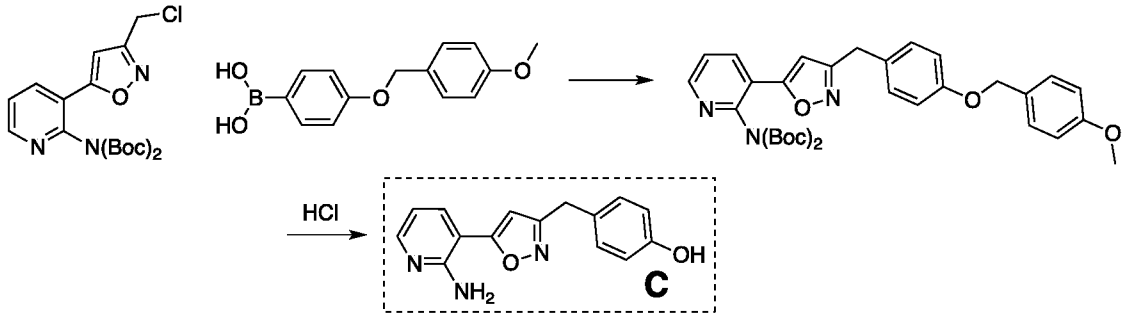
Intermediate B: Synthesis of 3-(3-(4-(chloromethyl)benzyl)isoxazol-5-yl)pyridin-2-amine



[0327] Di-tert-butyl [3-(3-(chloromethyl)-1,2-oxazol-5-yl)pyridin-2-yl]imidodicarbonate (Intermediate A, 1.00g, 2.44mmol) and 2-((4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzyl)oxy)pyridine (0.87g, 2.93mmol) were mixed in DME (15mL) in a sealable tube. A 2M solution of sodium carbonate in water (2.81mL, 5.62mmol) and palladium tetrakis triphenylphosphine (226mg, 0.195mmol) were added and the sealable tube was flushed with argon and sealed. The mixture was stirred for 4h at 100°C. The cooled reaction mixture was poured into ethyl acetate (400ml) and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to give the di-Boc protected coupling intermediate, to which was added formic acid (10mL). The resulting mixture was stirred for 8h at 21-25°C to complete the di-Boc de-protection. The mixture was poured into ice-water (150mL) containing K_3PO_4 (37g) and then extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude residue containing 3-(3-(4-((pyridin-2-yloxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine. The residue was dissolved in dioxane (10mL) and concentrated HCl (12M; 1ml, 12mmol) was added. The mixture was heated under reflux for 2h. The cooled mixture was poured into an ice-cold pH7 phosphate buffer solution (0.5M, 100mL) containing an additional amount of NaOH (480mg, 12mmol) to neutralize the excess of HCl. The resulting mixture was extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to yield 3-(3-(4-(chloromethyl)benzyl)isoxazol-5-

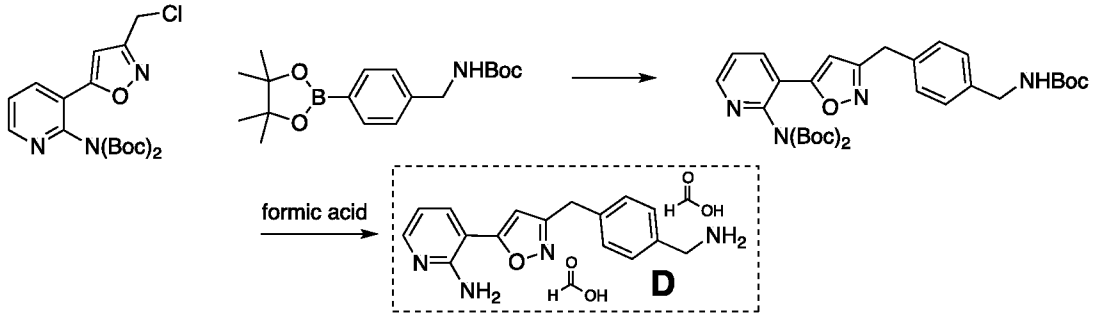
yl)pyridin-2-amine (280mg, 0.93mmol, 38% overall yield) as a white solid. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.13 (dd, J = 4.9, 1.8 Hz, 1H), 7.70 (dd, J = 7.7, 1.8 Hz, 1H), 7.40 – 7.32 (m, 2H), 7.32 – 7.25 (m, 2H), 6.70 (dd, J = 7.7, 4.9 Hz, 1H), 6.25 (s, 1H), 5.44 (s, 3H), 4.57 (s, 2H), 4.06 (s, 2H). MS: 300.4 $[M+H]^+$.

Intermediate C: Synthesis of 4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenol



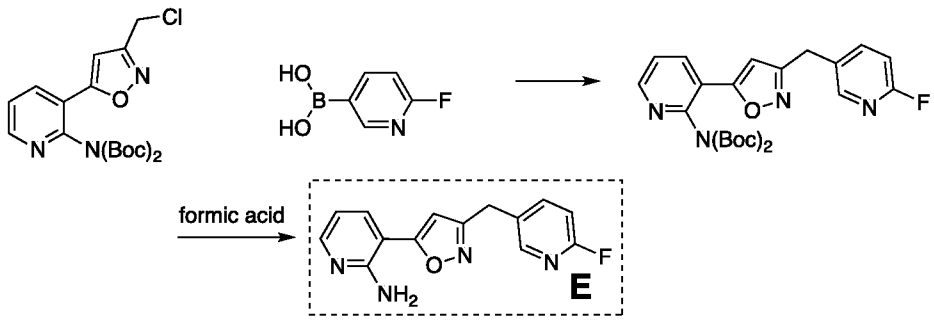
[0328] (4-((4-methoxybenzyl)oxy)phenyl)boronic acid (4.41g, 17.08mmol) was mixed with DME (70mL) in a sealable tube. A 2M solution of sodium carbonate in water (14.64mL, 29.28mmol) was added followed by a solution of di-tert-butyl [3-(3-(chloromethyl)-1,2-oxazol-5-yl)pyridin-2-yl]imidodicarbonate (Intermediate A, 5.00g, 12.20mmol) in DME (10mL). Palladium tetrakis triphenylphosphine (1.27g, 1.10mmol) was added and the sealable tube was flushed with argon and sealed. The mixture was stirred for 3h at 90°C. The cooled reaction mixture was poured into a stirring mixture of water (300mL) and warm ethyl acetate (500mL). The layers were separated the aqueous phase was further extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to give the di-Boc protected coupling intermediate (6.00g, 10.21mmol), which was dissolved in dioxane (60mL). To the resulting solution was added HCl (4M; 10mL, 40mmol) and the mixture was stirred for 3h at 50°C. THF (100mL) and toluene (100mL) were added and the pH was adjusted to 6-7 by the addition of an aqueous solution of K_3PO_4. The layers were separated the aqueous phase was further extracted with a mixture of ethyl acetate/THF/toluene = 1:1:1 (3×100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to yield 4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenol (2.30g, 8.60mmol, 84%) as a white solid. 400 MHz ^{1}H NMR (DMSO-d6) δ 9.30 (s, 1H), 8.08 (dd, J = 4.8, 1.8 Hz, 1H), 7.86 (dd, J = 7.7, 1.9 Hz, 1H), 7.15 – 7.07 (m, 2H), 6.80 – 6.65 (m, 4H), 6.26 (s, 2H), 3.90 (s, 2H). MS: 268.4 $[M+H]^+$.

Intermediate D: Synthesis of 3-(3-(4-(aminomethyl)benzyl)isoxazol-5-yl)pyridin-2-amine



[0329] Di-tert-butyl [3-(3-(chloromethyl)-1,2-oxazol-5-yl)pyridin-2-yl]imidodicarbonate (Intermediate A, 1.35g, 3.30mmol) and tert-butyl (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)carbamate (1.00g, 3.00mmol) were mixed in DME (15mL) in a sealable tube. A 2M solution of sodium carbonate in water (3.75mL, 7.50mmol) and palladium tetrakis triphenylphosphine (277mg, 0.240mmol) were added and the sealable tube was flushed with argon and sealed. The mixture was stirred for 4h at 100°C. The cooled reaction mixture was poured into ethyl acetate (400mL) and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to give the Boc protected coupling intermediate to which was added formic acid (8mL). The resulting mixture was stirred for 13h at 21-25°C to complete the global Boc de-protection, and then added dropwise to a rapidly stirring mixture of diethyl ether and hexane. The precipitated product in form of its formate salt was collected by filtration and dried under vacuum to yield 3-(3-(4-(aminomethyl)benzyl)isoxazol-5-yl)pyridin-2-amine formate (811mg, 2.49mmol, 83%) as a white solid. 500 MHz ^{1}H NMR (DMSO-d6) δ 8.32 (s, 2H), 8.09 (dd, J = 4.8, 1.8 Hz, 1H), 7.86 (dd, J = 7.7, 1.8 Hz, 1H), 7.44 – 7.34 (m, 4H), 6.81 (s, 1H), 6.70 (dd, J = 7.7, 4.8 Hz, 1H), 6.26 (s, 2H), 4.05 (s, 2H), 3.96 (s, 2H). MS: 281.4 $[M+H]^+$.

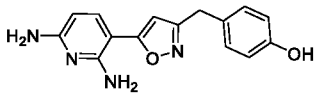
Intermediate E: Synthesis of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



[0330] (6-fluoropyridin-3-yl)boronic acid (1.90g, 13.48mmol) was mixed with DME (50mL) in a sealable tube. A 2M solution of sodium carbonate in water (11.24mL, 22.48mmol) was added followed by a solution of di-tert-butyl [3-(3-(chloromethyl)-1,2-oxazol-5-yl)pyridin-2-yl]imidodicarbonate (Intermediate A, 3.68g, 8.99mmol) in DME (6mL). Palladium tetrakis triphenylphosphine (0.935g, 0.809mmol) was added and the sealable tube was flushed with argon and sealed. The mixture was stirred for 4h at 90°C. The cooled reaction mixture was poured into ethyl acetate (500mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to give the di-Boc protected coupling intermediate (2.10g, 4.46mmol), to which was added formic acid (10mL). The resulting mixture was stirred for 13h at 21-25°C to complete the di-Boc de-protection. Ice-water (100mL) and ethyl acetate (300mL) were added and the pH was adjusted to 8-9 by the addition of 5N aqueous NaOH. The layers were separated and the aqueous phase was extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and the product was precipitated through the addition of hexane. The product was filtered and dried under vacuum to yield 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

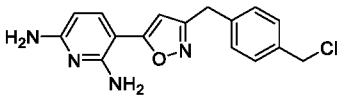
(1.06g, 3.92mmol, 44%) as a white solid. 500 MHz ^{1}H NMR (DMSO-d6) δ 8.27 – 8.22 (m, 1H), 8.09 (dd, *J* = 4.8, 1.9 Hz, 1H), 7.95 (td, *J* = 8.2, 2.6 Hz, 1H), 7.87 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.16 (dd, *J* = 8.4, 2.9 Hz, 1H), 6.85 (s, 1H), 6.70 (dd, *J* = 7.7, 4.8 Hz, 1H), 6.27 (s, 2H), 4.11 (s, 2H). MS: 271.4 $[M+H]^+$.

Intermediate F: Synthesis of 4-((5-(2,6-diaminopyridin-3-yl)isoxazol-3-yl)methyl)phenol



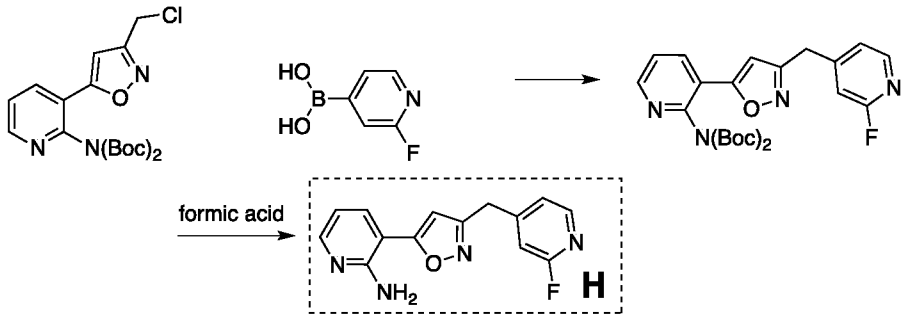
[0331] 3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridine-2,6-diamine (0.300 g, 0.806 mmol) and TFA (4.96 ml, 64.4 mmol) was added thioanisole (0.381 ml, 3.22 mmol) at room temperature and stirred for 2 hours. To the mixture was added a saturated sodium hydrogen carbon solution and was extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 4-((5-(2,6-diaminopyridin-3-yl)isoxazol-3-yl)methyl)phenol (0.170 g, 0.602 mmol, 74.8 % yield). MS: 283.3 $[M+H]^+$.

Intermediate G: Synthesis of 3-(3-(4-(chloromethyl)benzyl)isoxazol-5-yl)pyridine-2,6-diamine



[0332] 3-(3-(4-((pyridin-2-yloxy)methyl)benzyl)isoxazol-5-yl)pyridine-2,6-diamine (0.100 g, 0.268 mmol) was dissolved in dioxane (1mL) and added HCl (0.098 ml, 3.21 mmol). The mixture was heated at reflux for 2 hours. The cooled mixture was poured into ice cold buffer with pH7 and neutralized with NaOH and then extracted with EtOAc. Organic solvents were removed under reduced pressure and the residue was purified using flash chromatography to give 3-(3-(4-(chloromethyl)benzyl)isoxazol-5-yl)pyridine-2,6-diamine (0.075 g, 0.238 mmol, 89 % yield). MS: 315.7 $[M+H]^+$.

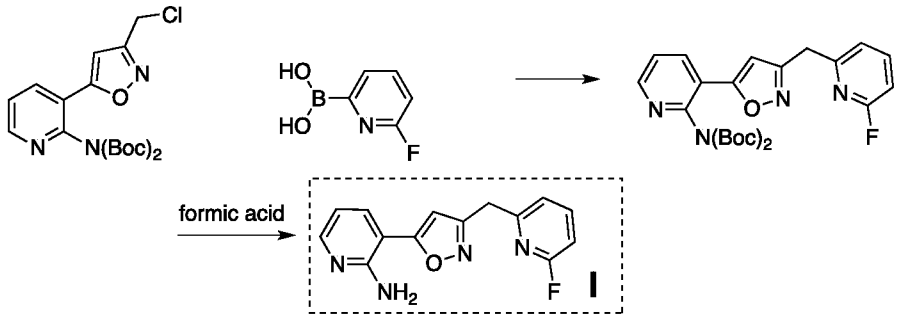
Intermediate H: Synthesis of 3-(3-((2-fluoropyridin-4-yl)methyl)isoxazol-5-yl)pyridin-2-amine



[0333] (2-fluoropyridin-4-yl)boronic acid (0.894g, 6.34mmol) was mixed with DME (25mL) in a sealable tube. A 2M solution of sodium carbonate in water (7.32mL, 14.64mmol) was added followed by a solution of di-tert-butyl [3-(3-(chloromethyl)-1,2-oxazol-5-yl)pyridin-2-yl]imidodicarbonate (Intermediate A, 2.00g, 4.88mmol) in DME (4mL). Palladium tetrakis triphenylphosphine (0.395g, 0.342mmol) was added and the sealable tube was flushed with argon and sealed. The mixture was stirred for 2h at 90°C. The cooled reaction mixture was poured into ethyl acetate (200mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to give the di-Boc protected coupling intermediate (1.050g, 2.232mmol), to which was added formic acid (6.1mL). The resulting mixture was stirred for 18h at 21-25°C to complete

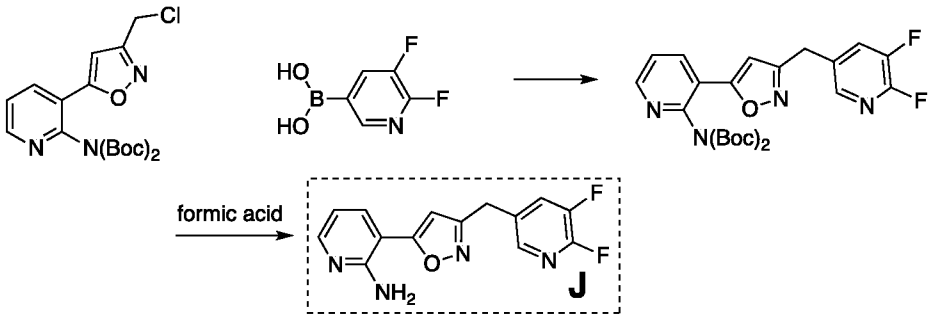
the di-Boc de-protection. Ice-water (50mL) and ethyl acetate (150mL) were added and the pH was adjusted to 8-9 by the addition of 5N aqueous NaOH. The layers were separated and the aqueous phase was extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and the product was precipitated through the addition of hexane. The product was filtered and dried under vacuum to yield 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (0.515g, 1.91mmol, 41%) as a white solid. 500 MHz ^{1}H NMR (DMSO-d6) δ 8.19 (d, J = 5.1 Hz, 1H), 8.10 (dd, J = 4.8, 1.8 Hz, 1H), 7.87 (dd, J = 7.7, 1.8 Hz, 1H), 7.32 (dt, J = 5.1, 1.7 Hz, 1H), 7.17 (s, 1H), 6.87 (s, 1H), 6.71 (dd, J = 7.7, 4.8 Hz, 1H), 6.27 (s, 1H), 4.17 (s, 2H). MS: 271.2 $[M+H]^+$.

Intermediate I: Synthesis of 3-(3-((6-fluoropyridin-2-yl)methyl)isoxazol-5-yl)pyridin-2-amine



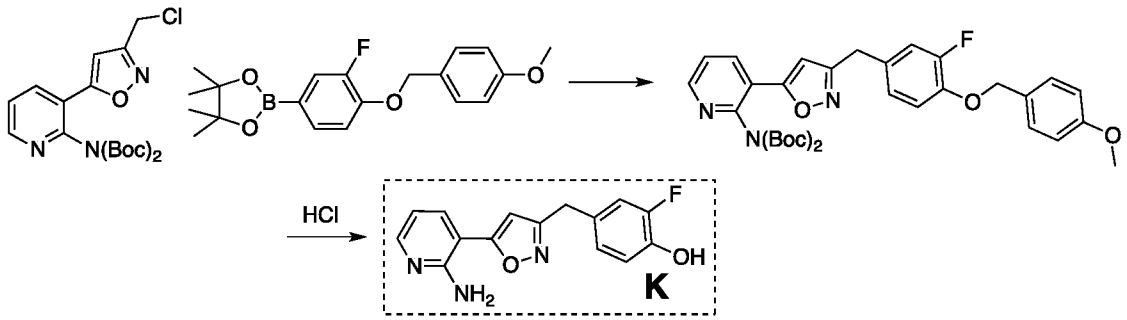
[0334] (6-fluoropyridin-2-yl)boronic acid (0.670g, 4.76mmol) was mixed with DME (20mL) in a sealable tube. A 2M solution of sodium carbonate in water (5.49mL, 10.98mmol) was added followed by a solution of di-tert-butyl [3-(3-(chloromethyl)-1,2-oxazol-5-yl)pyridin-2-yl]imidodicarbonate (Intermediate A, 1.500 g, 3.66mmol) in DME (2mL). Palladium tetrakis triphenylphosphine (0.296 g, 0.256 mmol) was added and the sealable tube was flushed with argon and sealed. The mixture was stirred for 4h at 90 °C. The cooled reaction mixture was poured into ethyl acetate (200mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to give the di-Boc protected coupling intermediate (0.900g, 1.91mmol), to which was added formic acid (5.5mL). The resulting mixture was stirred for 18h at 21-25 °C to complete the di-Boc de-protection. Ice-water (50mL) and ethyl acetate (150mL) were added and the pH was adjusted to 8-9 by the addition of 5N aqueous NaOH. The layers were separated and the aqueous phase was extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and the product was precipitated through the addition of hexane. The product was filtered and dried under vacuum to yield 3-(3-((6-fluoropyridin-2-yl)methyl)isoxazol-5-yl)pyridin-2-amine (0.440g, 1.63mmol, 44%) as a white solid. MS: 271.2 $[M+H]^+$.

Intermediate J: Synthesis of 3-(3-((5,6-difluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



[0335] (5,6-difluoropyridin-3-yl)boronic acid (1.06g, 6.65mmol) and di-tert-butyl [3-(3-(chloromethyl)-1,2-oxazol-5-yl)pyridin-2-yl]imidodicarbonate (Intermediate A, 3.00g, 7.32mmol) were mixed with DME (25mL) in a sealable tube. A 2M solution of sodium carbonate in water (8.32mL, 16.64mmol) was added followed by palladium tetrakis triphenylphosphine (0.54g, 0.47mmol). The sealable tube was flushed with argon and sealed. The mixture was stirred for 3h at 90 °C. The cooled reaction mixture was poured into ethyl acetate (500mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to give the di-Boc protected coupling intermediate to which was added formic acid (8mL). The resulting mixture was stirred for 13h at 21-25°C to complete the di-Boc de-protection. Toluene (100mL) and acetonitrile (50mL) were added and all volatiles were removed under reduced pressure. This addition/evaporation procedure was repeated three times to complete the removal of formic acid. Ethyl acetate was added and the precipitation of the product was completed by the addition of some hexane. The product was filtered off and dried under vacuum to yield 3-(3-((5,6-difluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (0.894g, 3.10mmol, 47% overall yield) as a white solid. 500 MHz ^{1}H NMR (DMSO-d6) δ 8.12 – 8.01 (m, 3H), 7.86 (dd, J = 7.6, 1.9 Hz, 1H), 6.87 (s, 1H), 6.70 (dd, J = 7.7, 4.7 Hz, 1H), 6.28 (s, 2H), 4.15 (s, 2H). MS: 289.4 $[M+H]^+$.

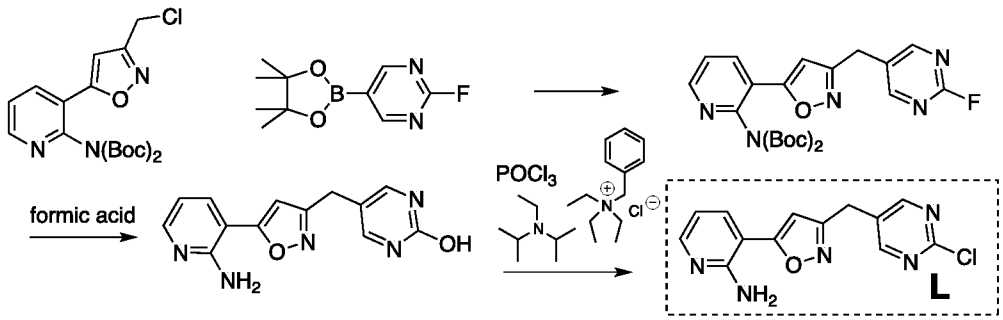
Intermediate K: Synthesis of 4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-2-fluorophenol



[0336] 2-(3-fluoro-4-((4-methoxybenzyl)oxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.29g, 17.57mmol) and di-tert-butyl [3-(3-(chloromethyl)-1,2-oxazol-5-yl)pyridin-2-yl]imidodicarbonate (Intermediate A, 6.00g, 14.64mmol) were mixed with DME (60mL) in a sealable tube. A 2M solution of sodium carbonate in water (18.30mL, 36.60mmol) and palladium tetrakis triphenylphosphine (1.18g, 1.03mmol) were added and the sealable tube was flushed with argon and sealed. The mixture was stirred for 2h at 90°C. The cooled reaction mixture was poured into a stirring mixture of water (300mL) and warm ethyl acetate (500mL). The layers were separated the aqueous phase was further extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with brine (50 mL), dried over

Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to give the di-Boc protected coupling intermediate, which was dissolved in dioxane (90mL). To the resulting solution was added conc. HCl (12M; 6.27mL, 75mmol). The mixture was stirred at 55 °C for 2.5h and then poured into a stirred mixture of a solution of sodium hydroxide (2.82g, 70.6mmol) in water (200mL) and EtOAc (300mL). Layers were separated and the aqueous phase was extracted with EtOAc (2x 50mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Before reachig complete dryness, the product started to precipitate out. At this point, ether (100mL) was added and the product was collected by filtration to obtain 4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-2-fluorophenol (2.18g, 7.64 mmol, 52% overall yield) as a white powder. 500 MHz ^{1}H NMR (DMSO-d6) δ 9.72 (s, 1H), 8.09 (dd, J = 4.8, 1.8 Hz, 1H), 7.87 (dd, J = 7.7, 1.8 Hz, 1H), 7.11 (dd, J = 12.2, 2.0 Hz, 1H), 6.96 – 6.85 (m, 2H), 6.79 (s, 1H), 6.69 (dd, J = 7.7, 4.8 Hz, 1H), 6.26 (s, 2H), 3.92 (s, 2H). MS: 286.4 $[M+H]^+$.

Intermediate L: Synthesis of 3-(3-((2-chloropyrimidin-5-yl)methyl)isoxazol-5-yl)pyridin-2-amine



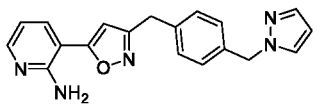
[0337] 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (1.00g, 4.44mmol) and di-tert-butyl [3-(3-(chloromethyl)-1,2-oxazol-5-yl)pyridin-2-yl]imidodicarbonate (Intermediate A, 2.00g, 4.88mmol) were mixed with DME (15mL) in a sealable tube. A 2M solution of sodium carbonate in water (5.55mL, 11.09mmol) and palladium tetrakis triphenylphosphine (0.36g, 0.31mmol) were added and the sealable tube was flushed with argon and sealed. The mixture was stirred for 2h at 95°C. The cooled reaction mixture was poured into ethyl acetate (500mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to give the di-Boc protected coupling intermediate, to which was added formic acid (8mL). The resulting mixture was stirred for 13h at 21-25°C to complete the di-Boc de-protection. During this step the fluoropyridine also completely hydrolyzed. Toluene (100mL) and acetonitrile (50mL) were added and all volatiles were removed under reduced pressure. This addition/evaporation procedure was repeated three times to complete the removal of formic acid and to obtain a solid residue of (5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)pyrimidin-2-ol (570mg, 2.12mmol). The residue was suspended in acetonitrile (2mL). N-benzyl-N,N-diethylethanaminium chloride (237mg, 1.04mmol) and phosphoryl trichloride (0.58mL, 6.24mmol) were added, followed by the addition of N-ethyl-N-isopropylpropan-2-amine (0.71mL, 4.16mmol). The mixture was heated in a sealed tube at 90°C for 20h and then slowly added to a stirred solution of $NaHCO_3$ in water. Some ice was added to maintain a temperature around 30°C. After quenching was complete, the mixture was extracted with EtOAc. The

combined organic layers were dried and concentrated under reduced pressure to obtain the crude product (3-(3-((2-chloropyrimidin-5-yl)methyl)isoxazol-5-yl)pyridin-2-amine (180mg, 0.63mmol, 13% overall yield)) as a solid, which was directly used in the following experiments without further purification. 500 MHz ^{1}H NMR (DMSO-d6) δ 8.80 (s, 2H), 8.10 (dd, J = 4.8, 1.9 Hz, 1H), 7.86 (dd, J = 7.7, 1.9 Hz, 1H), 6.89 (s, 1H), 6.71 (dd, J = 7.7, 4.8 Hz, 1H), 6.28 (s, 2H), 4.15 (s, 2H). MS: 287.9 $[M+H]^+$.

EXAMPLES

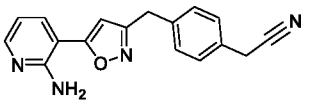
[0338] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes

[0339] **Example 1**: Synthesis of 3-(3-(4-((1H-pyrazol-1-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



[0340] A solution of 1H-pyrazole (91mg, 1.33mmol) in NMP (0.5mL) was added to a suspension of sodium hydride (60% w/mineral oil, 40mg, 1.00mmol) in NMP (1mL). After stirring for 20min at 21-25°C, a solution of 3-(3-(4-(chloromethyl)benzyl)isoxazol-5-yl)pyridin-2-amine (Intermediate B, 100mg, 0.33mmol) in NMP (1ml) was added and the mixture was stirred for 4min at 60°C. The cooled reaction mixture was directly purified by column chromatography (SiO_2, hexane/ethyl acetate). Fractions containing the product were concentrated under reduced pressure and further purified by HPLC to yield 3-(3-(4-((1H-pyrazol-1-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine (75mg, 0.23mmol, 68%) as a white solid. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.12 (dd, J = 4.9, 1.8 Hz, 1H), 7.68 (dd, J = 7.7, 1.8 Hz, 1H), 7.54 (d, J = 1.8 Hz, 1H), 7.39 (dd, J = 2.3, 0.7 Hz, 1H), 7.29 – 7.21 (m, 2H), 7.21 – 7.13 (m, 2H), 6.69 (dd, J = 7.7, 4.9 Hz, 1H), 6.31 – 6.20 (m, 2H), 5.42 (s, 2H), 5.30 (s, 2H), 4.03 (s, 2H). MS: 332.2 $[M+H]^+$.

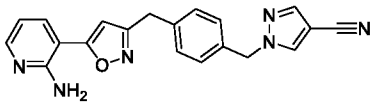
[0341] **Example 2**: Synthesis of 2-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenyl)acetonitrile



[0342] Potassium cyanide (209mg, 3.20mmol) was added to PEG400 (1.5ml) and carefully ground to a fine suspension using a glass rod. 3-(3-(4-(chloromethyl)benzyl)isoxazol-5-yl)pyridin-2-amine (Intermediate B, 120mg, 0.40mmol) was added and the mixture was stirred for 30min at 80°C. To the cooled reaction mixture was added to water (50 mL), and then extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to yield 2-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenyl)acetonitrile (102mg, 0.35mmol, 88%) as a white solid. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.09 (dd, J = 4.9, 1.8 Hz, 1H),

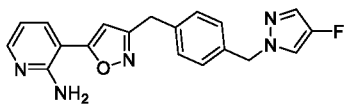
7.65 (dd, J = 7.7, 1.8 Hz, 1H), 7.26 (m, 4H), 6.66 (dd, J = 7.7, 4.9 Hz, 1H), 6.20 (s, 1H), 5.38 (s, 2H), 4.01 (s, 2H), 3.69 (s, 2H). MS: 291.2 $[M+H]^+$.

[0343] Example 3: Synthesis of 1-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)-1H-pyrazole-4-carbonitrile



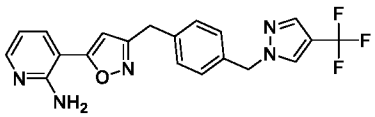
[0344] 3-(3-(4-(chloromethyl)benzyl)isoxazol-5-yl)pyridin-2-amine (Intermediate B, 80mg, 0.27mmol) and 1H-pyrazole-4-carbonitrile (99mg, 1.07mmol) were dissolved in NMP (1ml). Potassium 2-methylpropane-2-olate (1M in THF, 0.80mL, 0.80mmol) was added and the mixture was stirred for 5min at 60°C. The cooled reaction mixture was directly purified by column chromatography (SiO_2, hexane/ethyl acetate). Fraction containing the product were concentrated under reduced pressure and further purified by HPLC to yield 1-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)-1H-pyrazole-4-carbonitrile (66mg, 0.19mmol, 69%) as a white solid. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.13 (dd, J = 5.0, 1.8 Hz, 1H), 7.79 (dd, J = 18.1, 0.7 Hz, 2H), 7.69 (dd, J = 7.7, 1.8 Hz, 1H), 7.35 – 7.25 (m, 2H), 7.27 – 7.17 (m, 2H), 6.70 (dd, J = 7.7, 4.8 Hz, 1H), 6.25 (s, 1H), 5.43 (s, 2H), 5.30 (s, 2H), 4.05 (s, 2H). MS: 357.3 $[M+H]^+$.

[0345] Example 4: Synthesis of 3-(3-(4-((4-fluoro-1H-pyrazol-1-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



[0346] 3-(3-(4-(chloromethyl)benzyl)isoxazol-5-yl)pyridin-2-amine (Intermediate B, 80mg, 0.27mmol) and 4-fluoro-1H-pyrazole (92mg, 1.07mmol) were dissolved in NMP (1ml). Potassium 2-methylpropane-2-olate (1M in THF, 0.80mL, 0.80mmol) was added and the mixture was stirred for 5min at 60°C. The cooled reaction mixture was directly purified by column chromatography (SiO_2, hexane/ethyl acetate). Fraction containing the product were concentrated under reduced pressure and further purified by HPLC to yield 3-(3-(4-((4-fluoro-1H-pyrazol-1-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine (75mg, 0.22mmol, 80%) as a white solid. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.14 (s, 1H), 7.69 (dd, J = 7.7, 1.7 Hz, 1H), 7.35 (dd, J = 4.3, 0.8 Hz, 1H), 7.31 – 7.13 (m, 5H), 6.70 (dd, J = 7.7, 4.7 Hz, 1H), 6.24 (s, 1H), 5.43 (s, 2H), 5.18 (s, 2H), 4.04 (s, 2H). MS: 350.3 $[M+H]^+$.

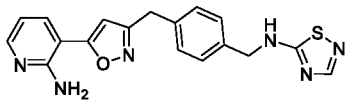
[0347] Example 5: Synthesis of 3-(3-(4-((4-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



[0348] 3-(3-(4-(chloromethyl)benzyl)isoxazol-5-yl)pyridin-2-amine (Intermediate B, 80mg, 0.27mmol) and 4-(trifluoromethyl)-1H-pyrazole (145mg, 1.07mmol) were dissolved in NMP (1ml). Potassium 2-methylpropane-2-olate (1M in THF, 0.80mL, 0.80mmol) was added and the mixture was stirred for 5min at 60°C. The cooled reaction mixture was directly purified by column chromatography (SiO_2,

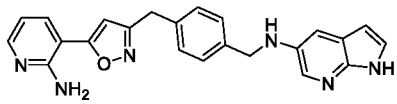
hexane/ethyl acetate). Fraction containing the product were concentrated under reduced pressure and further purified by HPLC to yield 3-(3-(4-((4-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine (75mg, 0.19mmol, 70%) as a white solid. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.14 (d, J = 3.7 Hz, 1H), 7.73 (s, 1H), 7.69 (dd, J = 7.7, 1.8 Hz, 1H), 7.64 (s, 1H), 7.30 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 8.2 Hz, 2H), 6.70 (dd, J = 7.7, 4.9 Hz, 1H), 6.25 (s, 1H), 5.43 (s, 2H), 5.29 (s, 2H), 4.05 (s, 2H). MS: 400.3 $[M+H]^+$.

[0349] Example 6: Synthesis of N-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)-1,2,4-thiadiazol-5-amine



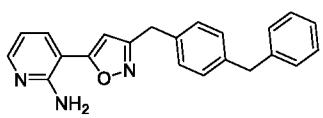
[0350] 3-(3-(4-(Chloromethyl)benzyl)isoxazol-5-yl)pyridin-2-amine (Intermediate B, 0.10 g, 0.33 mmol) and 1,2,4-thiadiazol-5-amine (0.17 g, 1.7 mmol) were dissolved in tetrahydrofuran. Diisopropylethylamine (0.14 mL, 0.80 mmol) was added and the homogeneous amber-colored solution was stirred at room temperature. After 3 hours an additional 2 equivalents of 1,2,4-thiadiazol-5-amine (0.070 g, 0.66 mmol) and another 1.2 equivalents of diisopropylethylamine (0.070 mL, 0.40 mmol) were added. The mixture was heated at 60 °C for 72 hours. The mixture was cooled to room temperature and extracted three times with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The obtained residue was purified using Biotage reverse phase flash chromatography (12g C18 SNAP, 5-95% acetonitrile in water with 0.1% formic acid). The desired fraction was lyophilized to give the title compound as a white solid (2.0 mg, 0.0051 mmol, 2%). MS: 365.2 $[M+H]^+$.

[0351] Example 7: Synthesis of N-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)-1H-pyrrolo[2,3-b]pyridin-5-amine



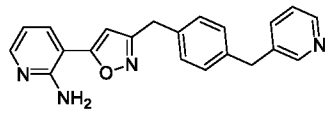
[0352] 3-(3-(4-(Chloromethyl)benzyl)isoxazol-5-yl)pyridin-2-amine (Intermediate B, 0.10 g, 0.33 mmol) and 1H-pyrrolo[2,3-b]pyridin-5-amine (0.22 g, 1.7 mmol), were dissolved in tetrahydrofuran. Diisopropylethylamine (0.14 mL, 0.80 mmol) was added and the heterogenous mixture was stirred at room temperature for 3 hours, and then heated at 60 °C for 72 hours. The mixture was cooled to room temperature and extracted three times with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The obtained residue was purified using Biotage reverse phase flash chromatography (12g C18 SNAP, 5-95% acetonitrile in water with 0.1% formic acid). The desired fraction was lyophilized to give the title compound as a white solid (20 mg, 0.051 mmol, 15%). MS: 397.3 $[M+H]^+$.

[0353] Example 8: Synthesis of 3-(3-(4-benzylbenzyl)isoxazol-5-yl)pyridin-2-amine



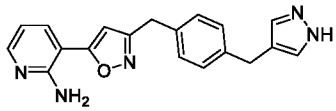
[0354] Phenylboronic acid (61mg, 0.50mmol) and 3-(3-(4-(chloromethyl)benzyl)isoxazol-5-yl)pyridin-2-amine (Intermediate B, 100mg, 0.33mmol) were mixed in DME (4mL) in a sealable tube. A 2M solution of sodium carbonate in water (0.45mL, 0.90mmol) and palladium tetrakis triphenylphosphine (27mg, 0.023mmol) were added and the sealable tube was flushed with argon and sealed. The mixture was stirred for 2h at 90°C. The cooled reaction mixture was poured into ethyl acetate and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to yield 3-(3-(4-benzylbenzyl)isoxazol-5-yl)pyridin-2-amine (84mg, 0.25mmol, 74%) as a white solid. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.16 – 8.10 (m, 1H), 7.69 (dd, J = 7.7, 1.7 Hz, 1H), 7.33 – 7.12 (m, 9H), 6.69 (dd, J = 7.7, 4.8 Hz, 1H), 6.24 (s, 1H), 5.40 (s, 2H), 4.01 (s, 2H), 3.96 (s, 2H). MS: 342.2 $[M+H]^+$.

[0355] **Example 9**: Synthesis of 3-(3-(4-(pyridin-3-ylmethyl)benzyl)isoxazol-5-yl)pyridin-2-amine



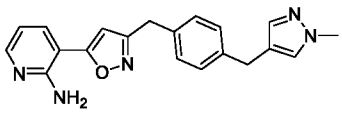
[0356] The title compound was prepared according to the procedure described in Example 8 using pyridin-3-ylboronic acid (61.5mg, 0.50mmol) to yield 3-(3-(4-(pyridin-3-ylmethyl)benzyl)isoxazol-5-yl)pyridin-2-amine (64mg, 0.19mmol, 56%) as a white solid. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.52 (s, 2H), 8.06 (d, J = 4.1 Hz, 1H), 7.73 (dd, J = 7.7, 1.7 Hz, 1H), 7.52 (d, J = 7.7 Hz, 1H), 7.30 – 7.24 (m, 1H), 7.22 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 6.70 (dd, J = 7.7, 4.9 Hz, 1H), 6.26 (s, 1H), 5.94 (s, 2H), 4.03 (s, 2H), 3.97 (s, 2H). MS: 343.2 $[M+H]^+$.

[0357] **Example 10**: Synthesis of 3-(3-(4-((1H-pyrazol-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



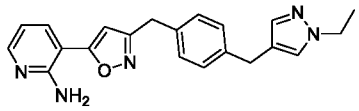
[0358] The title compound was prepared according to the procedure described in Example 8 using (1H-pyrazol-4-yl)boronic acid (56.0mg, 0.50mmol) and heating for 14h at 90°C to yield 3-(3-(4-((1H-pyrazol-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine (40mg, 0.12mmol, 36%) as a white solid. MS: 332.3 $[M+H]^+$.

[0359] **Example 11**: Synthesis of 3-(3-(4-((1-methyl-1H-pyrazol-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



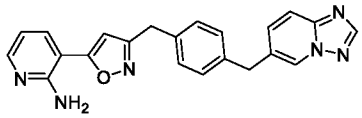
[0360] The title compound was prepared according to the procedure described in Example 8 using (1-methyl-1H-pyrazol-4-yl)boronic acid (63.0mg, 0.50mmol) to yield 3-(3-(4-((1-methyl-1H-pyrazol-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine (60mg, 0.17mmol, 52%) as a white solid. MS: 346.2 $[M+H]^+$.

[0361] **Example 12**: Synthesis of 3-(3-(4-((1-ethyl-1H-pyrazol-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



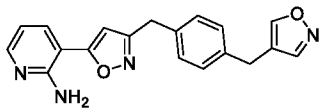
[0362] The title compound was prepared according to the procedure described in Example 8 using (1-ethyl-1H-pyrazol-4-yl)boronic acid (70.0mg, 0.50mmol) to yield 3-(3-(4-((1-ethyl-1H-pyrazol-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine (76mg, 0.21mmol, 63%) as a white solid. MS: 360.3 $[M+H]^+$.

[0363] **Example 13**: Synthesis of 3-(3-(4-([1,2,4]triazolo[1,5-a]pyridin-6-ylmethyl)benzyl)isoxazol-5-yl)pyridin-2-amine



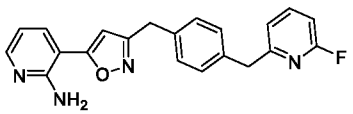
[0364] The title compound was prepared according to the procedure described in Example 8 using 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (180mg, 0.73mmol) to yield 3-(3-(4-([1,2,4]triazolo[1,5-a]pyridin-6-ylmethyl)benzyl)isoxazol-5-yl)pyridin-2-amine (85mg, 0.22mmol, 61%) as a white solid. MS: 383.3 $[M+H]^+$.

[0365] **Example 14**: Synthesis of 3-(3-(4-(isoxazol-4-ylmethyl)benzyl)isoxazol-5-yl)pyridin-2-amine



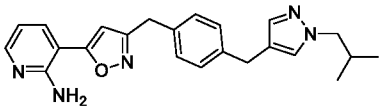
[0366] The title compound was prepared according to the procedure described in Example 8 using isoxazol-4-ylboronic acid (56.5mg, 0.50mmol) to yield 3-(3-(4-(isoxazol-4-ylmethyl)benzyl)isoxazol-5-yl)pyridin-2-amine (76mg, 0.23mmol, 69%) as a white solid. MS: 333.2 $[M+H]^+$.

[0367] **Example 15**: Synthesis of 3-(3-(4-((6-fluoropyridin-2-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



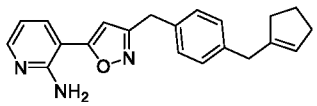
[0368] The title compound was prepared according to the procedure described in Example 8 using (6-fluoropyridin-2-yl)boronic acid (70.5mg, 0.50mmol) to yield 3-(3-(4-((6-fluoropyridin-2-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine (82mg, 0.23mmol, 68%) as a white solid. 500 MHz ^{1}H NMR (DMSO-d6) δ 8.08 (dd, J = 4.8, 1.8 Hz, 1H), 7.93 – 7.83 (m, 2H), 7.29 – 7.20 (m, 5H), 6.97 (dd, J = 8.1, 2.6 Hz, 1H), 6.80 (s, 1H), 6.69 (dd, J = 7.7, 4.8 Hz, 1H), 6.24 (s, 2H), 4.01 (s, 2H), 3.99 (s, 2H). MS: 361.4 $[M+H]^+$.

[0369] **Example 16**: Synthesis if 3-(3-(4-((1-isobutyl-1H-pyrazol-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



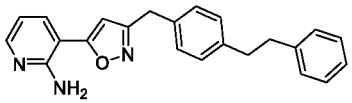
[0370] The title compound was prepared according to the procedure for described in Example 8 using (1-isobutyl-1H-pyrazol-4-yl)boronic acid (95.0mg, 0.57mmol) to yield 3-(3-(4-((1-isobutyl-1H-pyrazol-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine (72mg, 0.19mmol, 56%) as a white solid. MS: 388.3 $[M+H]^+$.

[0371] **Example 17**: Synthesis of 3-(3-(4-(cyclopent-1-en-1-ylmethyl)benzyl)isoxazol-5-yl)pyridin-2-amine



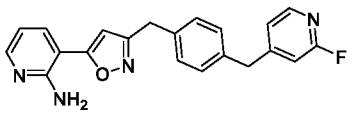
[0372] The title compound was prepared according to the procedure described in Example 8 using cyclopent-1-en-1-ylboronic acid (63.5mg, 0.57mmol) to yield 3-(3-(4-(cyclopent-1-en-1-ylmethyl)benzyl)isoxazol-5-yl)pyridin-2-amine (72mg, 0.22mmol, 65%) as a white solid. MS: 332.2 $[M+H]^+$.

[0373] **Example 18**: Synthesis of 3-(3-(4-phenethylbenzyl)isoxazol-5-yl)pyridin-2-amine



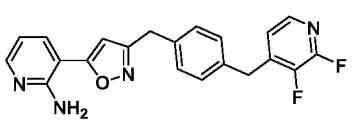
[0374] The title compound was prepared according to the procedure described in Example 8 using 2-benzyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (124mg, 0.57mmol) to yield 3-(3-(4-phenethylbenzyl)isoxazol-5-yl)pyridin-2-amine (41mg, 0.12mmol, 35%) as a white solid. MS: 356.2 $[M+H]^+$.

[0375] **Example 19**: Synthesis of 3-(3-(4-((2-fluoropyridin-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



[0376] The title compound was prepared according to the procedure described in Example 8 using (2-fluoropyridin-4-yl)boronic acid (70.5mg, 0.50mmol) to yield 3-(3-(4-((2-fluoropyridin-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine (86mg, 0.24mmol, 72%) as a white solid. MS: 346.2 $[M+H]^+$.

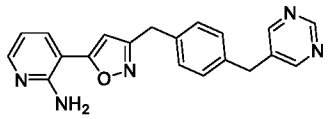
[0377] **Example 20**: Synthesis of 3-(3-(4-((2,3-difluoropyridin-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



[0378] The title compound was prepared according to the procedure described in Example 8 using (2,3-difluoropyridin-4-yl)boronic acid (106mg, 0.67mmol) to yield 3-(3-(4-((2,3-difluoropyridin-4-

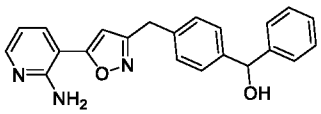
yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine (85mg, 0.23mmol, 67%) as a white solid. MS: 379.2 $[M+H]^+$.

[0379] **Example 21**: Synthesis of 3-(3-(4-(pyrimidin-5-ylmethyl)benzyl)isoxazol-5-yl)pyridin-2-amine



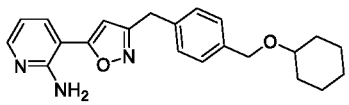
[0380] The title compound was prepared according to the procedure described in Example 8 using pyrimidin-5-ylboronic acid (83.0mg, 0.67mmol) to yield 3-(3-(4-(pyrimidin-5-ylmethyl)benzyl)isoxazol-5-yl)pyridin-2-amine (78mg, 0.23mmol, 68%) as a white solid. MS: 344.3 $[M+H]^+$.

[0381] **Example 22**: Synthesis of (4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenyl)(phenyl)methanol



[0382] Di-tert-butyl [3-(3-(chloromethyl)-1,2-oxazol-5-yl)pyridin-2-yl]imidodicarbonate (Intermediate A, 200mg, 0.49mmol) and (4-(hydroxy(phenyl)methyl)phenyl)boronic acid (122mg, 0.54mmol) were mixed in DME (4mL) in a sealable tube. A 2M solution of sodium carbonate in water (0.56mL, 1.12mmol) and palladium tetrakis triphenylphosphine (45mg, 0.039mmol) were added and the sealable tube was flushed with argon and sealed. The mixture was stirred for 2h at 100°C. The cooled reaction mixture was poured into ethyl acetate and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to give the di-Boc protected coupling product as a yellow oil to which was added formic acid (4mL). This mixture was stirred for 3h at 21-25°C to complete the di-Boc de-protection. To this mixture was added dioxane (10mL), ice and a 5M solution of NaOH in water until the pH of the resulting mixture was about 10-12. The mixture was stirred for 30min at 21-25°C to complete the hydrolysis of the formate ester on the hydroxyl group, which was formed during the di-Boc de-protection. The mixture was diluted with water (50mL) and extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to yield (4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenyl)(phenyl)methanol (75mg, 0.21mmol, 43%) as a white solid. MS: 358.2 $[M+H]^+$.

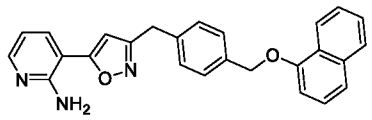
[0383] **Example 23**: Synthesis of 3-(3-(4-((cyclohexyloxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



[0384] In a microwave vial was combined di-*tert*-butyl [3-(3-(chloromethyl)-1,2-oxazol-5-yl)pyridin-2-yl]imidodicarbonate (Intermediate A, 0.20 g, 0.48 mmol), (4-((cyclohexyloxy)methyl)phenyl)boronic acid (0.17 g, 0.73 mmol), cesium carbonate (0.48 g, 1.5 mmol), copper(I) iodide (0.0047 g, 0.024 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)dichloromethane complex (0.020 g, 0.024 mmol), and 1,2-dimethoxyethane (3 mL). The vial was sealed and heated at 90 °C for 40 min under

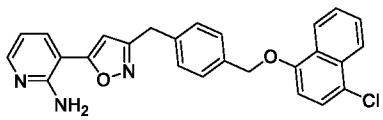
microwave irradiation. The mixture was filtered through Celite with ethyl acetate. The solvents were evaporated under reduced pressure and the residue was purified using Biotage flash chromatography (50g SNAP, 2-75% acetone/hexane). Like fractions were combined and evaporated to give the desired di-BOC-protected intermediate. This material was dissolved in dichloromethane (10 mL) and treated with 4M hydrogen chloride in dioxane (3 mL). After stirring for 16 hours at room temperature, the mixture was diluted with water and basified with 5M aqueous sodium hydroxide solution to pH 13. The layers were separated, and the aqueous phase was extracted twice more with dichloromethane. The combined organic phase was washed with brine, dried over sodium sulfate, and evaporated under reduced pressure. The residue was purified using Biotage reverse phase flash chromatography (12g C18 SNAP, 5-95% acetonitrile/water containing 0.1% Formic Acid). The desired fractions were combined and lyophilized to give the title compound as a white solid (0.055 g, 0.15 mmol, 31%). MS: 364.5 $[M+H]^+$.

[0385] **Example 24**: Synthesis of 3-(3-(4-((naphthalen-1-yloxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



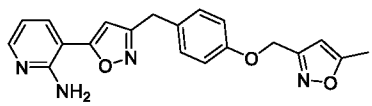
[0386] The title compound was prepared according to the procedure described in Example 23 using (4-((naphthalen-1-yloxy)methyl)phenyl)boronic acid (0.20 g, 0.73 mmol) to yield the title compound as a white solid (0.056 g, 0.14 mmol, 29%). MS: 408.5 $[M+H]^+$.

[0387] **Example 25**: Synthesis of 3-(3-(4-(((4-chloronaphthalen-1-yl)oxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



[0388] The title compound was prepared according to the procedure described in Example 23 using (4-(((4-chloronaphthalen-1-yl)oxy)methyl)phenyl)boronic acid (0.23 g, 0.73 mmol) to yield the title compound as a white solid (0.063 g, 0.14 mmol, 29%). MS: 442.4 $[M+H]^+$.

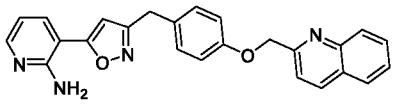
[0389] **Example 26**: Synthesis of 3-(3-(4-((5-methylisoxazol-3-yl)methoxy)benzyl)isoxazol-5-yl)pyridin-2-amine



[0390] 4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenol (Intermediate C, 80mg, 0.30mmol) was dissolved in DMF (1mL) and potassium 2-methylpropane-2-olate (1M in THF, 0.33mL, 0.33mmol) was added dropwise. The mixture was stirred for 5min and a solution of 3-(bromomethyl)-5-methylisoxazole (63.2mg, 0.36mmol) in DMF (0.5mL) was added. The resulting mixture was stirred for 30min and directly purified by column chromatography (SiO_2, hexane/ethyl acetate). Fraction containing the product were concentrated under reduced pressure and further purified by reversed phase flash chromatography (C18, acetonitrile/water) to yield 3-(3-(4-((1H-pyrazol-1-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine

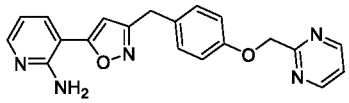
(71mg, 0.20mmol, 66%) as a white solid. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.13 (s, 1H), 7.70 (dd, J = 7.7, 1.8 Hz, 1H), 7.24 – 7.16 (m, 2H), 6.98 – 6.89 (m, 2H), 6.70 (dd, J = 7.7, 4.8 Hz, 1H), 6.23 (s, 1H), 6.10 (d, J = 1.1 Hz, 1H), 5.44 (s, 2H), 5.09 (s, 2H), 3.99 (s, 2H), 2.42 (d, J = 0.9 Hz, 3H). MS: 363.3 $[M+H]^+$.

[0391] **Example 27**: Synthesis of 3-(3-(4-(quinolin-2-ylmethoxy)benzyl)isoxazol-5-yl)pyridin-2-amine



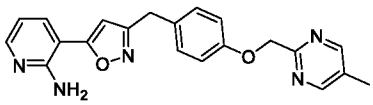
[0392] The title compound was prepared according to the procedure described in Example 26 using 2-(chloromethyl)quinoline hydrochloride (83mg, 0.39mmol) and potassium 2-methylpropane-2-olate (1M in THF, 0.72mL, 0.72mmol) to yield 3-(3-(4-(quinolin-2-ylmethoxy)benzyl)isoxazol-5-yl)pyridin-2-amine (80mg, 0.20mmol, 66%) as a white solid. MS: 409.3 $[M+H]^+$.

[0393] **Example 28**: Synthesis of 3-(3-(4-(pyrimidin-2-ylmethoxy)benzyl)isoxazol-5-yl)pyridin-2-amine



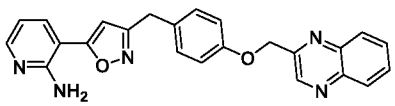
The title compound was prepared according to the procedure described in Example 26 using 2-(chloromethyl)pyrimidine hydrochloride (69mg, 0.42mmol) and potassium 2-methylpropane-2-olate (1M in THF, 0.75mL, 0.75mmol) to yield 3-(3-(4-(pyrimidin-2-ylmethoxy)benzyl)isoxazol-5-yl)pyridin-2-amine (56mg, 0.16mmol, 52%) as a white solid. MS: 360.3 $[M+H]^+$.

[0394] **Example 29:** Synthesis of 3-(3-(4-((5-methylpyrimidin-2-yl)methoxy)benzyl)isoxazol-5-yl)pyridin-2-amine



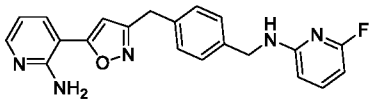
The title compound was prepared according to the procedure described in Example 26 using 2-(chloromethyl)-5-methylpyrimidine hydrochloride (75mg, 0.42mmol) and potassium 2-methylpropane-2-olate (1M in THF, 0.75mL, 0.75mmol) to yield 3-(3-(4-((5-methylpyrimidin-2-yl)methoxy)benzyl)isoxazol-5-yl)pyridin-2-amine (79mg, 0.21mmol, 71%) as a white solid. MS: 374.3 $[M+H]^+$.

[0395] **Example 30:** Synthesis of 3-(3-(4-(quinoxalin-2-ylmethoxy)benzyl)isoxazol-5-yl)pyridin-2-amine



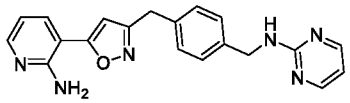
[0396] The title compound was prepared according to the procedure described in Example 26 using 4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenol (Intermediate C, 90mg, 0.34mmol), 2-(bromomethyl)quinoxaline (90mg, 0.40mmol) and potassium 2-methylpropane-2-olate (1M in THF, 0.34mL, 0.34mmol) to yield 3-(3-(4-(quinoxalin-2-ylmethoxy)benzyl)isoxazol-5-yl)pyridin-2-amine (73mg, 0.18mmol, 53%) as a white solid. MS: 410.3 $[M+H]^+$.

[0397] **Example 31**: Synthesis of N-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)-6-fluoropyridin-2-amine



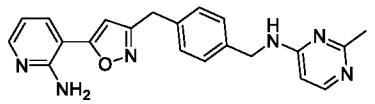
[0398] 3-(3-(4-(aminomethyl)benzyl)isoxazol-5-yl)pyridin-2-amine diformate (Intermediate D, 80mg, 0.22mmol) was dissolved in DMSO (0.5mL). N-ethyl-N-isopropylpropan-2-amine (83mg, 0.65mmol) and 2,6-difluoropyridine (148mg, 1.29mmol) were added and the mixture was stirred for 2h at 120°C. The mixture was diluted with water (15mL) and extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to yield N-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)-6-fluoropyridin-2-amine (47mg, 0.13mmol, 58%) as a white solid. 500 MHz ^{1}H NMR (DMSO-d6) δ 8.08 (dd, J = 4.8, 1.8 Hz, 1H), 7.86 (dd, J = 7.7, 1.8 Hz, 1H), 7.52 – 7.40 (m, 2H), 7.28 (s, 4H), 6.79 (s, 1H), 6.69 (dd, J = 7.7, 4.8 Hz, 1H), 6.35 (dd, J = 8.0, 2.5 Hz, 1H), 6.25 (s, 2H), 6.08 (dd, J = 7.6, 2.2 Hz, 1H), 4.38 (d, J = 6.0 Hz, 2H), 4.00 (s, 2H). MS: 376.3 $[M+H]^+$.

[0399] **Example 32**: Synthesis of N-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)pyrimidin-2-amine



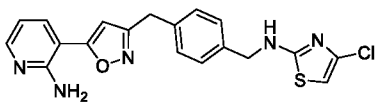
[0400] The title compound was prepared according to the procedure described in Example 31 using 2-chloropyrimidine (148mg, 1.29mmol) to yield N-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)pyrimidin-2-amine (45mg, 0.17mmol, 58%) as a white solid. MS: 359.2 $[M+H]^+$.

[0401] **Example 33**: Synthesis of N-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)-2-methylpyrimidin-4-amine



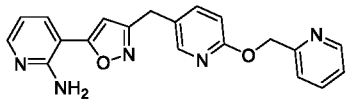
[0402] The title compound was prepared according to the procedure described in Example 31 using 4-chloro-2-methylpyrimidine (166mg, 1.29mmol) to yield N-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)-2-methylpyrimidin-4-amine (41mg, 0.11mmol, 51%) as a slight yellow oil. MS: 373.2 $[M+H]^+$.

[0403] **Example 34**: Synthesis of N-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)-4-chlorothiazol-2-amine



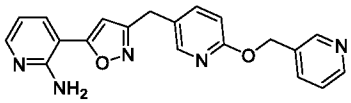
[0404] The title compound was prepared according to the procedure described in Example 31 using 2,4-dichlorothiazole (265mg, 1.72mmol) to yield N-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)-4-chlorothiazol-2-amine (15mg, 0.04mmol, 18%) as a white solid. MS: 398.1 $[M+H]^+$.

[0405] **Example 35**: Synthesis of 3-(3-((6-(pyridin-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



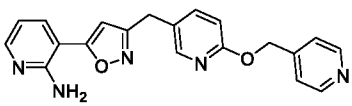
[0406] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50mg, 0.19mmol) and pyridin-2-ylmethanol (121mg, 1.11mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was diluted with ice-water (15mL) and the pH was adjusted to 8 using diluted HCl. The mixture was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to yield 3-(3-((6-(pyridin-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (38mg, 0.11mmol, 57%) as a white solid. MS: 360.3 $[M+H]^+$.

[0407] **Example 36**: Synthesis of 3-(3-((6-(pyridin-3-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



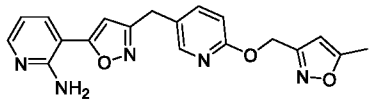
[0408] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 60 mg, 0.22mmol) and pyridin-3-ylmethanol (242mg, 2.22mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 2.22mL, 2.22mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(pyridin-3-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (19mg, 0.052mmol, 23%) as a white solid. MS: 360.2 $[M+H]^+$.

[0409] **Example 37**: Synthesis of 3-(3-((6-(pyridin-4-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



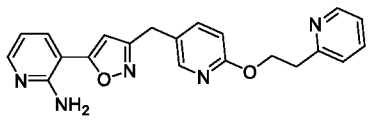
[0410] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 60 mg, 0.22mmol) and pyridin-3-ylmethanol (242mg, 2.22mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 2.22mL, 2.22mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(pyridin-4-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (31mg, 0.086mmol, 39%) as a white solid. MS: 360.2 $[M+H]^+$.

[0411] **Example 38**: Synthesis of 3-(3-((6-((5-methylisoxazol-3-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



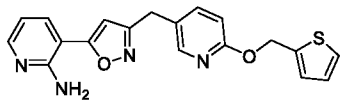
[0412] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 60 mg, 0.22mmol) and 5-methylisoxazol-3-yl)methanol (251mg, 2.22mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 2.22mL, 2.22mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-((5-methylisoxazol-3-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (62mg, 0.171mmol, 77%) as a white solid. MS: 364.1 $[M+H]^+$.

[0413] **Example 39**: Synthesis of 3-(3-((6-(2-(pyridin-2-yl)ethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



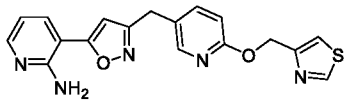
[0414] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 60 mg, 0.22mmol) and 2-(pyridin-2-yl)ethan-1-ol (273mg, 2.22mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 2.22mL, 2.22mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(2-(pyridin-2-yl)ethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (6.4mg, 0.017mmol, 7.7%) as a white solid. MS: 374.1 $[M+H]^+$.

[0415] **Example 40**: Synthesis of 3-(3-((6-(thiophen-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



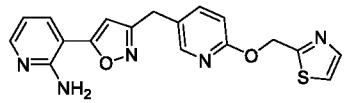
[0416] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) and thiophen-2-ylmethanol (211mg, 1.85mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(thiophen-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (25mg, 0.069mmol, 37%) as a light yellow solid. MS: 365.1 $[M+H]^+$.

[0417] **Example 41**: Synthesis of 3-(3-((6-(thiazol-4-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



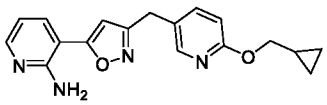
[0418] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) and thiazol-4-ylmethanol (213mg, 1.85mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(thiazol-4-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (35mg, 0.097mmol, 52%) as a white solid. MS: 366.1 $[M+H]^+$.

[0419] **Example 42**: Synthesis of 3-(3-((6-(thiazol-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



[0420] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) and thiazol-2-ylmethanol (213mg, 1.85mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(thiazol-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (36mg, 0.097mmol, 53%) as a white solid. MS: 366.1 $[M+H]^+$.

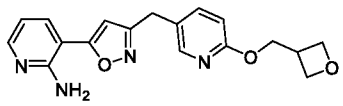
[0421] **Example 43**: Synthesis of 3-(3-((6-(cyclopropylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



[0422] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) and cyclopropylmethanol (133mg, 1.85mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(cyclopropylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (38mg, 0.097mmol, 64%) as a white solid. 500 MHz ^{1}H NMR (DMSO-d6) δ 8.12 (dd, J = 2.5, 0.8 Hz, 1H), 8.09 (dd, J = 4.8, 1.8 Hz, 1H), 7.86 (dd, J = 7.7, 1.8 Hz,

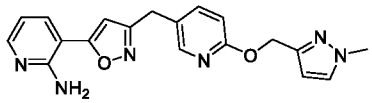
1H), 7.64 (dd, J = 8.5, 2.5 Hz, 1H), 6.82 (s, 1H), 6.78 (dd, J = 8.5, 0.7 Hz, 1H), 6.69 (dd, J = 7.7, 4.8 Hz, 1H), 6.26 (s, 2H), 4.06 (d, J = 7.1 Hz, 2H), 3.98 (s, 2H), 1.27 – 1.18 (m, 1H), 0.58 – 0.48 (m, 2H), 0.35 – 0.24 (m, 2H). MS: 323.2 $[M+H]^+$.

[0423] **Example 44**: Synthesis of 3-(3-((6-(oxetan-3-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



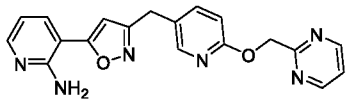
[0424] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) and oxetan-3-ylmethanol (196mg, 1.85mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(oxetan-3-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (11mg, 0.031mmol, 14%) as a white solid. MS: 339.3 $[M+H]^+$.

[0425] **Example 45**: Synthesis of 3-(3-((6-((1-methyl-1H-pyrazol-3-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



[0426] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) and 1-methyl-1H-pyrazol-3-yl-methanol (207mg, 1.85mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-((1-methyl-1H-pyrazol-3-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (10mg, 0.028mmol, 15%) as a white solid. MS: 363.2 $[M+H]^+$.

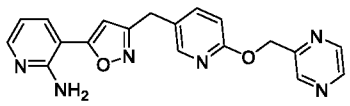
[0427] **Example 46**: Synthesis of 3-(3-((6-(pyrimidin-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



[0428] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) and pyrimidin-2-ylmethanol (204mg, 1.85mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate).

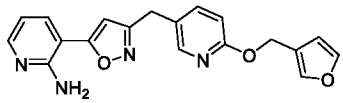
Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(pyrimidin-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (21mg, 0.058mmol, 31%) as a white solid. MS: 361.2 $[M+H]^+$.

[0429] **Example 47**: Synthesis of 3-(3-((6-(pyrazin-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



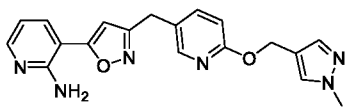
[0430] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) and pyrazin-2-ylmethanol (204mg, 1.85mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(pyrazin-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (20mg, 0.055mmol, 30%) as a white solid. MS: 361.2 $[M+H]^+$.

[0431] **Example 48**: Synthesis of 3-(3-((6-(furan-3-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



[0432] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) and furan-3-ylmethanol (181mg, 1.85mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(furan-3-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (8.0mg, 0.023mmol, 12%) as a white solid. MS: 349.1 $[M+H]^+$.

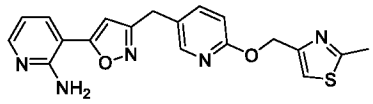
[0433] **Example 49**: Synthesis of 3-(3-((6-((1-methyl-1H-pyrazol-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



[0434] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) and 1-methyl-1H-pyrazol-4-yl-methanol (207mg, 1.85mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile

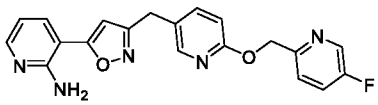
(5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-((1-methyl-1H-pyrazol-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (8.5mg, 0.023mmol, 13%) as a white solid. MS: 363.2 $[M+H]^+$.

[0435] **Example 50**: Synthesis of 3-(3-((6-((2-methylthiazol-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



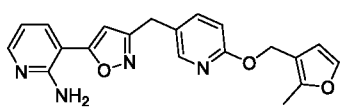
[0436] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) and 2-methylthiazol-4-ylmethanol (213mg, 1.85mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(2-methylthiazol-4-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (25mg, 0.067mmol, 36%) as a white solid. MS: 380.1 $[M+H]^+$.

[0437] **Example 51**: Synthesis of 3-(3-((6-((5-fluoropyridin-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



[0438] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) and 5-fluoropyridin-2-yl)methanol (212mg, 1.67mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-((5-fluoropyridin-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (21mg, 0.056mmol, 30%) as a white solid. MS: 378.0 $[M+H]^+$.

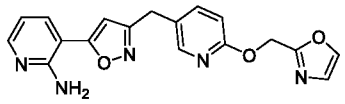
[0439] **Example 52**: Synthesis of 3-(3-((6-((2-methylfuran-3-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



[0440] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) and 2-methylfuran-3-ylmethanol (124mg, 1.11mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a

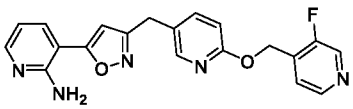
Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(2-methylfuran-3-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (15mg, 0.040mmol, 22%) as a white solid. MS: 362.8 $[M+H]^+$.

[0441] **Example 53**: Synthesis of 3-(3-((6-(oxazol-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



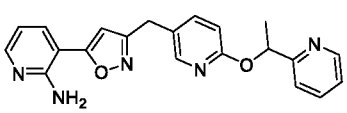
[0442] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) and oxazol-2-ylmethanol (128mg, 1.30mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(oxazol-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (25mg, 0.072mmol, 39%) as a white solid. MS: 350.0 $[M+H]^+$.

[0443] **Example 54**: Synthesis of 3-(3-((6-((3-fluoropyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



[0444] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) and 3-fluoropyridin-2-yl)methanol (235mg, 1.85mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-((3-fluoropyridin-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (40mg, 0.11mmol, 57%) as a white solid. MS: 378.2 $[M+H]^+$.

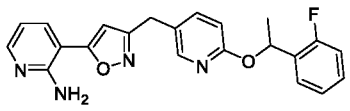
[0445] **Example 55**: Synthesis of 3-(3-((6-(1-(pyridin-2-yl)ethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



[0446] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 60 mg, 0.22mmol) and 1-(pyridin-2-yl)ethan-1-ol (164mg, 1.33mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 2.22mL, 2.22mmol) and the mixture was stirred for

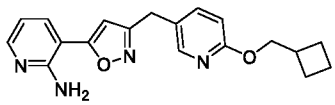
30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(1-(pyridin-2-yl)ethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (32mg, 0.086mmol, 39%) as a white solid. MS: 374.1 $[M+H]^+$.

[0447] **Example 56**: Synthesis of 3-(3-((6-(1-(2-fluorophenyl)ethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



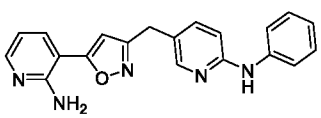
[0448] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) and 1-(2-fluorophenyl)ethan-1-ol (207mg, 1.48mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 2.22mL, 2.22mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(1-(2-fluorophenyl)ethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (30mg, 0.078mmol, 42%) as a white solid. MS: 391.3 $[M+H]^+$.

[0449] **Example 57**: Synthesis of 3-(3-((6-(cyclobutylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



[0450] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) and cyclobutylmethanol (159mg, 1.85mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(cyclobutylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (30mg, 0.089mmol, 48%) as a white solid. MS: 337.4 $[M+H]^+$.

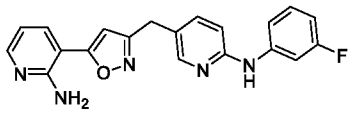
[0451] **Example 58**: Synthesis of 5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-phenylpyridin-2-amine



[0452] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) and aniline (172mg, 1.85mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 2 hours. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap

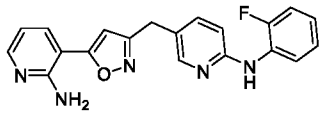
column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-phenylpyridin-2-amine (4.8mg, 0.014mmol, 7.6%) as an orange solid. MS: 344.1 $[M+H]^+$.

[0453] Example 59: Synthesis of 5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(3-fluorophenyl)pyridin-2-amine



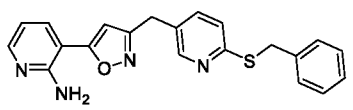
[0454] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) and 3-fluoroaniline (206mg, 1.85mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 2 hours. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(3-fluorophenyl)pyridin-2-amine (8.0mg, 0.022mmol, 12%) as a light orange solid. MS: 362.3 $[M+H]^+$.

[0455] Example 60: Synthesis of 5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(2-fluorophenyl)pyridin-2-amine



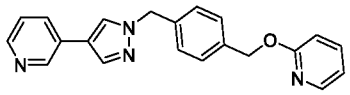
[0456] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) and 2-fluoroaniline (206mg, 1.85mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 2 hours. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(3-fluorophenyl)pyridin-2-amine (18mg, 0.048mmol, 26%) as a pink solid. 500 MHz ^{1}H NMR (formic acid-salt, DMSO-d6) δ 9.07 (s, 1H), 8.20 (dd, J = 7.7, 1.7 Hz, 1H), 8.13 (dd, J = 5.6, 1.7 Hz, 1H), 8.11 (d, J = 2.4 Hz, 1H), 8.03 (td, J = 8.3, 1.7 Hz, 1H), 7.64 (dd, J = 8.7, 2.4 Hz, 1H), 7.25 (ddd, J = 11.6, 8.1, 1.4 Hz, 1H), 7.16 (td, J = 7.8, 1.4 Hz, 1H), 7.10 – 7.03 (m, 1H), 7.00 (d, J = 8.7 Hz, 1H), 6.96 (s, 1H), 6.93 (dd, J = 7.6, 5.7 Hz, 1H), 4.00 (s, 2H) signal for -NH_2 not observed. MS: 362.3 $[M+H]^+$.

[0457] Example 61: Synthesis of 3-(3-((6-(benzylthio)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

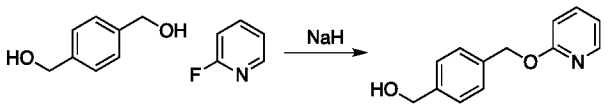


[0458] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 60 mg, 0.22mmol) and phenylmethanethiol (165mg, 1.33mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(benzylthio)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (5.8mg, 0.015mmol, 7%) as a white solid. MS: 375.2 $[M+H]^+$.

[0459] **Example 62**: Synthesis of 2-((4-((4-(pyridin-3-yl)-1H-pyrazol-1-yl)methyl)benzyl)oxy)pyridine

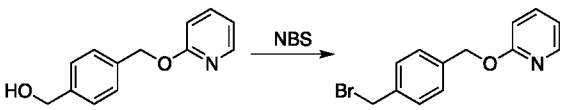


Step 1: (4-((pyridin-2-yloxy)methyl)phenyl)methanol



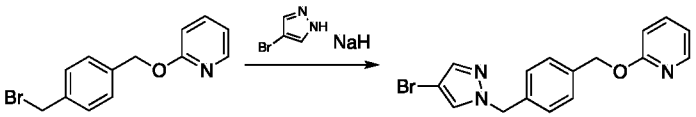
[0460] 1,4-phenylenedimethanol (7.50g, 54.3mmol) and 2-fluoropyridine (1.76g, 18.09mmol) were dissolved in DMF (40mL) and sodium hydride (60% w/mineral oil, 2.171g, 54.3mmol) was added at 0°C in 10 portions over the course of 20min. The resulting mixture was allowed to warm to 21-25°C within 30min and then warmed to 70°C and stirred for 30min at this temperature. The cooled reaction mixture was poured into a stirring mixture of ice-water (300mL) and ethyl acetate (500mL). The layers were separated and the aqueous phase was further extracted with ethyl acetate (3×100mL). The combined organic layers were washed with brine (50mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to give (4-((pyridin-2-yloxy)methyl)phenyl)methanol (2.6g, 12.08mmol, 67%).

Step 2: 2-((4- (bromomethyl)benzyl)oxy)pyridine



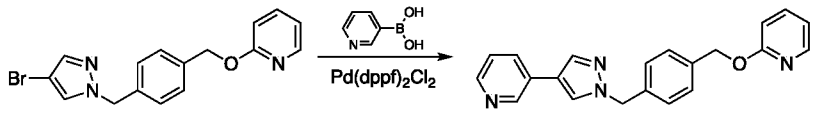
[0461] (4-((pyridin-2-yloxy)methyl)phenyl)methanol (500 mg, 2.32mmol) and triphenylphosphane (914mg, 3.48mmol) were dissolved in THF (15mL) and 2g of celite were added. To the stirred mixture was added a partial solution/suspension of 1-bromopyrrolidine-2,5-dione (NBS, 558mg, 3.14mmol) in THF at 0°C. The mixture was allowed to warm to 21-25°C and stirred for 30min. All volatiles were removed under reduced pressure and the residue was purified by flash chromatography to obtain 2-((4-(bromomethyl)benzyl)oxy)pyridine (250mg, 0.90mmol, 39%) as a colorless oil.

Step 3: 2-((4-((4-bromo-1H-pyrazol-1-yl)methyl)benzyl)oxy)pyridine



[0462] Sodium hydride (60% w/mineral oil, 48.3mg, 1.21mmol) was suspended in DMF (2mL) and a solution of 4-bromo-1H-pyrazole (165 mg, 1.12mmol) in DMF (1.5mL) was added at 0°C. The mixture was allowed to warm to 23°C and stirred for 15min. A solution of 2-((4-(bromomethyl)benzyl)oxy)pyridine (240 mg, 0.86 mmol) in DMF (1.5mL) was added at 0°C and the mixture was stirred at 21-25°C for 10min. The mixture was warmed to 40°C for 2min. The cooled reaction mixture was then directly purified by flash chromatography to obtain 2-((4-((4-bromo-1H-pyrazol-1-yl)methyl)benzyl)oxy)pyridine (220mg, 0.64mmol, 74%) as a white solid.

Step 4: 2-((4-((4-(pyridin-3-yl)-1H-pyrazol-1-yl)methyl)benzyl)oxy)pyridine

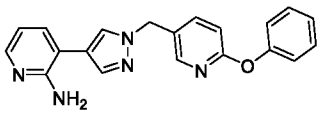


[0463] 2-((4-((4-bromo-1H-pyrazol-1-yl)methyl)benzyl)oxy)pyridine (110mg, 0.32mmol) and pyridin-3-ylboronic acid (62.8mg, 0.51mmol) were mixed in a sealable tube with dioxane (3.5mL). A 2M solution of sodium carbonate in water (511µL, 1.02mmol) was added followed by $Pd(dppf)_2Cl_2$ (CH_2Cl_2 adduct, 26mg, 0.03mmol) and the tube was flushed with argon and sealed. The mixture was heated in the MW at 100°C for 10 min. The cooled reaction mixture was poured into a stirring mixture of water (30mL) and ethyl acetate (50mL). The layers were separated the aqueous phase was further extracted with ethyl acetate (3×20mL). The combined organic layers were washed with brine (10mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate).

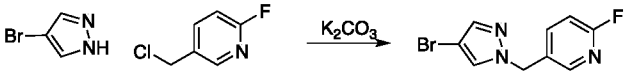
[0464] Fractions containing the product also contained a small amount of inseparable impurities and were re-purified using RP flash chromatography (Biotage). Fractions containing the product were lyophilized to obtain 2-((4-((4-(pyridin-3-yl)-1H-pyrazol-1-yl)methyl)benzyl)oxy)pyridine (53mg, 0.16mmol, 49%) as a white solid. 400 MHz ^{1}H NMR (TFA-salt, $CDCl_3$) δ 9.00 (s, 1H), 8.57 (dd, J = 5.6, 1.4 Hz, 1H), 8.29 (dt, J = 8.2, 1.6 Hz, 1H), 8.23 – 8.16 (m, 1H), 7.93 (s, 1H), 7.87 (s, 1H), 7.77 (dd, J = 8.2, 5.4 Hz, 1H), 7.63 (ddd, J = 8.4, 7.1, 2.0 Hz, 1H), 7.48 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 6.93 (ddd, J = 7.2, 5.2, 1.0 Hz, 1H), 6.83 (dt, J = 8.3, 0.9 Hz, 1H), 5.38 (s, 2H), 5.37 (s, 2H). MS: 343.4 $[M+H]^+$.

[0465] The free base (RP chromatography solvent contained 0.05% TFA as modifier) was obtained as followed: The product was dissolved in DCM (2mL) and MP-Carbonate resin from Biotage (600mg) was added. The mixture was stirred for 30min and filtered. The resin was washed multiple times with DCM and all solvents were removed under reduced pressure. The residue was dissolved in a small amount of acetonitrile, water was added and the final product obtained by lyophilization.

[0466] **Example 63**: Synthesis of 3-(1-((6-phenoxypyridin-3-yl)methyl)-1H-pyrazol-4-yl)pyridin-2-amine

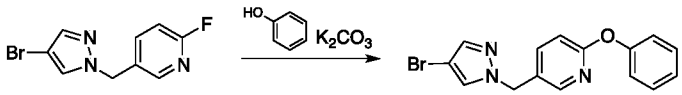


Step 1: 5-((4-bromo-1H-pyrazol-1-yl)methyl)-2-fluoropyridine



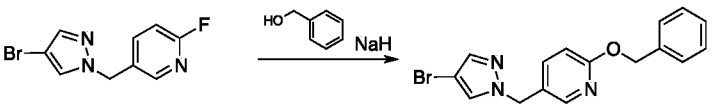
[0467] 4-bromo-1H-pyrazole (2.02g, 13.74mmol) was dissolved in DMF (9mL) and potassium carbonate (1.90g, 13.74mmol) was added. 5-(chloromethyl)-2-fluoropyridine (1g, 6.87mmol) was dissolved in DMF (1mL) and added to the reaction mixture. The mixture was stirred for 4h at 21-25°C and directly purified by flash chromatography to give 5-((4-bromo-1H-pyrazol-1-yl)methyl)-2-fluoropyridine (1.66g, 6.48mmol, 94%).

Step 2: 5-((4-bromo-1H-pyrazol-1-yl)methyl)-2-phenoxypyridine



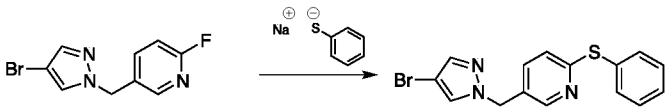
[0468] 5-((4-bromo-1H-pyrazol-1-yl)methyl)-2-fluoropyridine (550mg, 2.15mmol) was dissolved in NMP (2.8mL). Phenol (1.01g, 10.75mmol) and potassium carbonate (1.48g, 10.75mmol) were added and the mixture was heated in the MW at 120°C for 20min. The crude mixture was purified using flash chromatography to obtain 5-((4-bromo-1H-pyrazol-1-yl)methyl)-2-phenoxypyridine (260mg, 0.79mmol, 37%).

Step 3: 2-(benzyloxy)-5-((4-bromo-1H-pyrazol-1-yl)methyl)pyridine



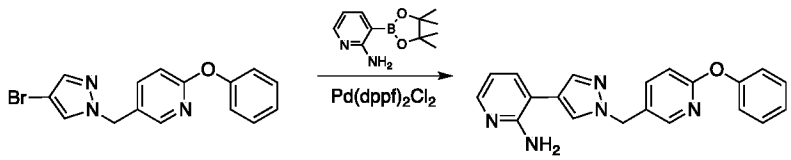
[0469] Phenylmethanol (845mg, 7.81mmol) was added to a suspension of sodium hydride (60% w/mineral oil, 312mg, 7.81mmol) in DMF (4mL). After no more gases evolved, a solution of 5-((4-bromo-1H-pyrazol-1-yl)methyl)-2-fluoropyridine (500mg, 1.95mmol) in DMF (2mL) was added and the mixture was stirred at 21-25°C for 1h. The reaction mixture was poured into a stirring mixture of ice-water (50mL) and ethyl acetate (150mL). The layers were separated and the aqueous phase was further extracted with ethyl acetate (3×50mL). The combined organic layers were washed with brine (30mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to give 2-(benzyloxy)-5-((4-bromo-1H-pyrazol-1-yl)methyl)pyridine (440mg, 1.28mmol, 66%).

Step 4: 5-((4-bromo-1H-pyrazol-1-yl)methyl)-2-(phenylthio)pyridine



[0470] 5-((4-bromo-1H-pyrazol-1-yl)methyl)-2-fluoropyridine (500mg, 1.95mmol) was dissolved in NMP (2.8mL) and sodium benzenethiolate (516mg, 3.91mmol) was added. The mixture was heated in the MW at 100°C for 15min. The crude mixture was purified using flash chromatography to obtain 5-((4-bromo-1H-pyrazol-1-yl)methyl)-2-(phenylthio)pyridine (270mg, 0.78mmol, 40%).

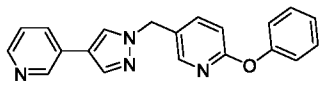
Step 5: 3-(1-((6-phenoxypyridin-3-yl)methyl)-1H-pyrazol-4-yl)pyridin-2-amine



[0471] 5-((4-bromo-1H-pyrazol-1-yl)methyl)-2-phenoxypyridine (130mg, 0.39mmol) and 3-(4,4,5,5-tetramethyl- 1,3,2-dioxaborolan-2-yl)pyridin-2-amine (139mg, 0.63mmol) were mixed in a sealable tube with dioxane (3.5mL). A 2M solution of sodium carbonate in water (492µL, 0.98mmol) was added followed by $Pd(dppf)_2Cl_2$ (CH_2Cl_2 adduct, 32mg, 0.04mmol) and the tube was flushed with argon and sealed. The mixture was heated in the MW at 100 °C for 20min. The cooled reaction mixture was poured into a stirring mixture of water (30mL) and ethyl acetate (50mL). The layers were separated the aqueous phase was further extracted with ethyl acetate (3×20mL). The combined organic layers were washed with brine (10mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate).

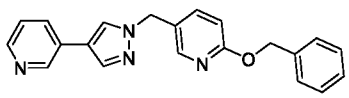
[0472] Fractions containing the product also contained a small amount of inseparable impurities and were re-purified using RP flash chromatography (Biotage). Fractions containing the product were lyophilized to obtain 3-(1-((6-phenoxypyridin-3-yl)methyl)-1H-pyrazol-4-yl)pyridin-2-amine (80mg, 0.23mmol, 59%). 400 MHz ^{1}H NMR (TFA-salt, DMSO-d6) δ 8.34 (s, 1H), 8.18 (d, J = 2.3 Hz, 1H), 8.03 – 7.81 (m, 6H), 7.46 – 7.36 (m, 2H), 7.20 (t, J = 7.4 Hz, 1H), 7.14 – 7.06 (m, 2H), 7.02 (d, J = 8.4 Hz, 1H), 6.95 (t, J = 6.8 Hz, 1H), 5.38 (s, 2H). MS: 344.4 $[M+H]^+$.

[0473] **Example 64**: Synthesis of 2-phenoxy-5-((4-(pyridin-3-yl)-1H-pyrazol-1-yl)methyl)pyridine



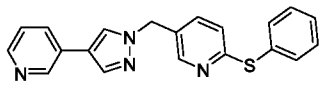
[0474] The title compound was prepared according to the procedure described for Example 63 using pyridin-3-ylboronic acid (121mg, 0.98mmol) to yield 2-phenoxy-5-((4-(pyridin-3-yl)-1H-pyrazol-1-yl)methyl)pyridine (78mg, 0.24mmol, 60%). 400 MHz ^{1}H NMR (DMSO-d6) δ 9.21 (d, J = 2.0 Hz, 1H), 8.81 – 8.65 (m, 3H), 8.26 (d, J = 0.8 Hz, 1H), 8.18 (d, J = 2.0 Hz, 1H), 8.04 (dd, J = 8.2, 5.7 Hz, 1H), 7.83 (dd, J = 8.5, 2.5 Hz, 1H), 7.47 – 7.36 (m, 2H), 7.28 – 7.16 (m, 1H), 7.15 – 7.07 (m, 2H), 7.03 (d, J = 8.5 Hz, 1H), 5.40 (s, 2H). MS: 329.3 $[M+H]^+$.

[0475] **Example 65**: Synthesis of 2-(benzyloxy)-5-((4-(pyridin-3-yl)-1H-pyrazol-1-yl)methyl)pyridine



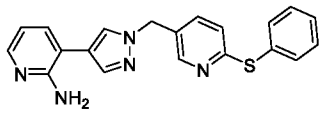
[0476] The title compound was prepared according to the procedure described for Example 63 using 2-(benzyloxy)-5-((4-bromo-1H-pyrazol-1-yl)methyl)pyridine (130mg, 0.38mmol) and pyridin-3-ylboronic acid (84mg, 0.68mmol) to yield 2-(benzyloxy)-5-((4-(pyridin-3-yl)-1H-pyrazol-1-yl)methyl)pyridine (75mg, 0.22mmol, 58%). MS: 343.3 $[M+H]^+$.

[0477] **Example 66**: Synthesis of 2-(phenylthio)-5-((4-(pyridin-3-yl)-1H-pyrazol-1-yl)methyl)pyridine



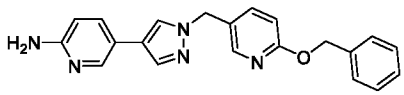
[0478] The title compound was prepared according to the procedure described for Example 63 using 5-((4-bromo-1H-pyrazol-1-yl)methyl)-2-(phenylthio)pyridine (130mg, 0.38mmol) and pyridin-3-ylboronic acid (83mg, 0.68mmol) to yield 2-(phenylthio)-5-((4-(pyridin-3-yl)-1H-pyrazol-1-yl)methyl)pyridine (25mg, 0.07mmol, 19%). MS: 345.3 $[M+H]^+$.

[0479] **Example 67**: Synthesis of 3-(1-((6-(phenylthio)pyridin-3-yl)methyl)-1H-pyrazol-4-yl)pyridin-2-amine



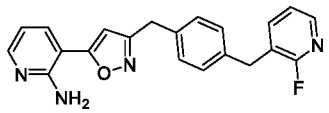
[0480] The title compound was prepared according to the procedure described for Example 63 using 5-((4-bromo-1H-pyrazol-1-yl)methyl)-2-(phenylthio)pyridine (130mg, 0.38mmol) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (149mg, 0.68mmol) to yield 3-(1-((6-(phenylthio)pyridin-3-yl)methyl)-1H-pyrazol-4-yl)pyridin-2-amine (40mg, 0.11mmol, 30%). MS: 360.4 $[M+H]^+$.

[0481] **Example 68**: Synthesis of 5-(1-((6-(benzyloxy)pyridin-3-yl)methyl)-1H-pyrazol-4-yl)pyridin-2-amine



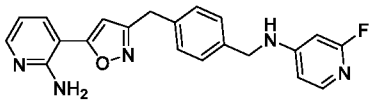
[0482] The title compound was prepared according to the procedure described for Example 63 using 2-(benzyloxy)-5-((4-bromo-1H-pyrazol-1-yl)methyl)pyridine (170mg, 0.49mmol) and (6-aminopyridin-3-yl)boronic acid (123mg, 0.89mmol) to yield 5-(1-((6-(benzyloxy)pyridin- 3-yl)methyl)-1H-pyrazol-4-yl)pyridin-2-amine (82mg, 0.23mmol, 47%). 400 MHz ^{1}H NMR (DMSO-d6) δ 8.16 (m, 2H), 8.10 (s, 1H), 7.75 (s, 1H), 7.66 (dd, J = 8.5, 2.5 Hz, 1H), 7.54 (d, J = 8.7 Hz, 1H), 7.46 – 7.25 (m, 5H), 6.86 (d, J = 8.6, 1H), 6.46 (d, J = 7.5 Hz, 1H), 5.87 (s, 2H), 5.33 (s, 2H), 5.26 (s, 2H). MS: 358.4 $[M+H]^+$.

[0483] **Example 69**: Synthesis of 3-(3-(4-((2-fluoropyridin-3-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



[0484] The title compound was prepared according to the procedure described for Example 8 using (6-fluoropyridin-2-yl)boronic acid (94.0mg, 0.67mmol) to yield 3-(3-(4-((2-fluoropyridin-3-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine (62mg, 0.17mmol, 52%) as a white solid. MS: 361.4 $[M+H]^+$.

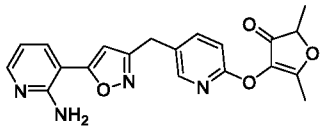
[0485] **Example 70**: Synthesis of 3-(3-(4-(((2-fluoropyridin-4-yl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



[0486] The title compound was prepared according to the procedure described for Example 31 using 2,4-difluoropyridine (185mg, 1.61mmol) to yield 3-(3-(4-(((2-fluoropyridin-4-

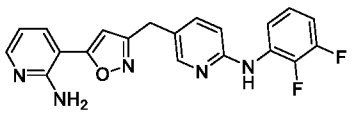
yl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine (36mg, 0.10mmol, 36%) as a white solid. MS: 376.4 $[M+H]^+$.

[0487] **Example 71**: Synthesis of 4-((5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)pyridin-2-yl)oxy)-2,5-dimethylfuran-3(2H)-one



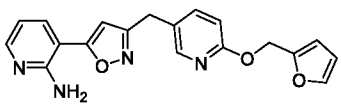
[0488] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) and 4-hydroxy-2,5-dimethylfuran-3(2H)-one (190mg, 1.48mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 4-((5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)pyridin-2-yl)oxy)-2,5-dimethylfuran-3(2H)-one (3.3mg, 0.0087mmol, 4.7%) as a white solid. MS: 379.3 $[M+H]^+$.

[0489] **Example 72**: Synthesis of 5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(2,3-difluorophenyl)pyridin-2-amine



[0490] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) and 2,3-difluoroaniline (191mg, 1.48mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the stirred mixture was heated to 90°C for 2 hours. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(2,3-difluorophenyl)pyridin-2-amine (21mg, 0.055mmol, 30.%) as a white solid. MS: 380.3 $[M+H]^+$.

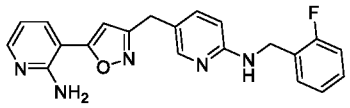
[0491] **Example 73**: Synthesis of 3-(3-((6-(furan-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



[0492] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) furan-2-ylmethanol (181mg, 1.85mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap

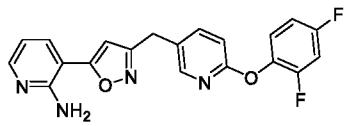
column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(furan-2-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (32mg, 0.092mmol, 50.%) as a white solid. MS: 349.3 $[M+H]^+$.

[0493] Example 74: Synthesis of 5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(2-fluorobenzyl)pyridin-2-amine



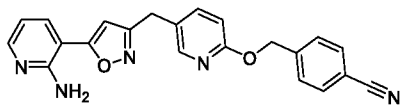
[0494] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) 2-fluorobenzylamine (139mg, 1.10mmol) was added diisopropylethylamine (0.323mL, 1.85mmol), DMSO (1.0mL), THF (1.0mL) and the mixture was stirred for 16 hours. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(2-fluorobenzyl)pyridin-2-amine as a white solid. MS: 376.2 $[M+H]^+$.

[0495] Example 75: Synthesis of 3-(3-((6-(2,4-difluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



[0496] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol) 2,4-difluorophenol (144mg, 1.10mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred at 90 °C for 2 hours. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(2,4-difluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (29mg, 0.075mmol, 41%) as a white solid. MS: 381.3 $[M+H]^+$.

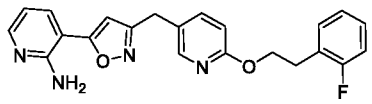
[0497] Example 76: Synthesis of 4-(((5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)pyridin-2-yl)oxy)methyl)benzonitrile



[0498] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50 mg, 0.19mmol), 4-(hydroxymethyl)benzonitrile (197mg, 1.48mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a

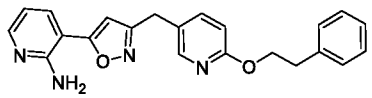
Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 4-(((5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)pyridin-2-yl)oxy)methyl)benzonitrile (4.3mg, 0.011mmol, 6.0%) as a white solid. MS: 384.2 $[M+H]^+$.

[0499] **Example 77**: Synthesis of 3-(3-((6-(2-fluorophenethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



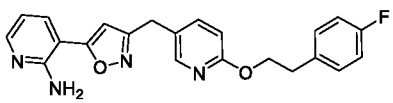
[0500] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50mg, 0.19mmol) 2-(2-fluorophenyl)ethan-1-ol (156mg, 1.10mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(2-fluorophenethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (24mg, 0.062mmol, 33%) as a white solid. MS: 391.1 $[M+H]^+$.

[0501] **Example 78**: Synthesis of 3-(3-((6-phenethoxypyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



[0502] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50mg, 0.19mmol) 2-(2-fluorophenyl)ethan-1-ol (156mg, 1.10mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-phenethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (28mg, 0.074mmol, 40.%) as a white solid. MS: 373.0 $[M+H]^+$.

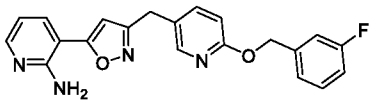
[0503] **Example 79**: Synthesis of 3-(3-((6-(4-fluorophenethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



[0504] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50mg, 0.19mmol) 2-(4-fluorophenyl)ethan-1-ol (207mg, 1.48mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a

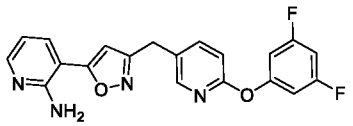
Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-phenethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (25mg, 0.046mmol, 25%) as a white solid. MS: 391.4 $[M+H]^+$.

[0505] **Example 80**: Synthesis of 3-(3-((6-((3-fluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



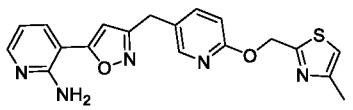
[0506] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50mg, 0.19mmol), (3-fluorophenyl)methanol (187mg, 1.48mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-((3-fluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (45mg, 0.12mmol, 65%) as a white solid. MS: 377.3 $[M+H]^+$.

[0507] **Example 81**: Synthesis of 3-(3-((6-(3,5-difluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



[0508] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50mg, 0.19mmol) 3,5-difluorophenol (193mg, 1.48mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred at 90°C for 2 hours. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(3,5-difluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (7.4mg, 0.019mmol, 11%) as a white solid. 500 MHz ^{1}H NMR (DMSO-d6) δ 8.21 (dt, J = 2.4, 0.7 Hz, 1H), 8.09 (dd, J = 4.9, 1.9 Hz, 1H), 7.90 – 7.83 (m, 2H), 7.13 – 7.05 (m, 2H), 7.00 – 6.91 (m, 2H), 6.86 (s, 1H), 6.70 (ddd, J = 7.7, 4.7, 0.5 Hz, 1H), 6.27 (s, 2H), 4.06 (s, 2H). MS: 381.1 $[M+H]^+$.

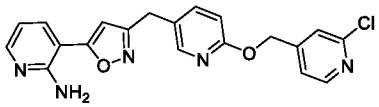
[0509] **Example 82**: Synthesis of 3-(3-((6-((4-methylthiazol-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



[0510] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50mg, 0.19mmol), 4-methylthiazol-2-yl)methanol (191mg, 1.48mmol) was added

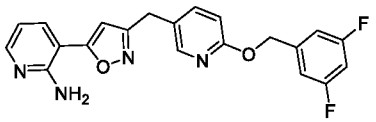
potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-((4-methylthiazol-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (46mg, 0.12mmol, 66%) as a white solid. MS: 380.2 $[M+H]^+$.

[0511] Example 83: Synthesis of 3-(3-((6-((2-chloropyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



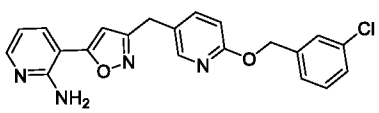
[0512] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50mg, 0.19mmol), 2-chloropyridin-4-yl)methanol (32mg, 0.22mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-((2-chloropyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (2.7mg, 0.0068mmol, 3.7%) as a white solid. MS: 394.2 $[M+H]^+$.

[0513] Example 84: Synthesis of 3-(3-((6-((3,5-difluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



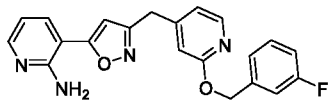
[0514] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50mg, 0.19mmol), (3,5-difluorophenyl)methanol (213mg, 1.48mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-((3,5-difluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (49mg, 0.12mmol, 67%) as a white solid. MS: 395.2 $[M+H]^+$.

[0515] Example 85: Synthesis of 3-(3-((6-((3-chlorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



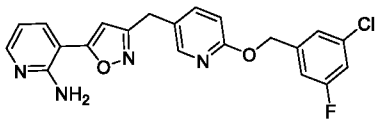
[0516] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50mg, 0.19mmol), (3-chlorophenyl)methanol (211mg, 1.48mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-((3-chlorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (40mg, 0.10mmol, 55%) as a white solid. MS: 393.2 $[M+H]^+$.

[0517] **Example 86**: Synthesis of 3-(3-((2-((3-fluorobenzyl)oxy)pyridin-4-yl)methyl)isoxazol-5-yl)pyridin-2-amine



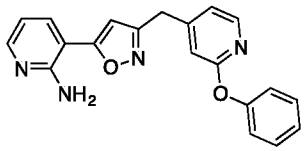
[0518] To a neat mixture of 3-(3-((2-fluoropyridin-4-yl)methyl)isoxazol-5-yl)pyridin-2-amine (40 mg, 0.15mmol), (3-fluorophenyl)methanol (187mg, 1.48mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.48mL, 1.48mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((2-((3-fluorobenzyl)oxy)pyridin-4-yl)methyl)isoxazol-5-yl)pyridin-2-amine (23mg, 0.061mmol, 41%) as a white solid. 500 MHz ^{1}H NMR (DMSO-d6) δ 8.11 (dd, J = 5.2, 0.7 Hz, 1H), 8.09 (dd, J = 4.8, 1.8 Hz, 1H), 7.87 (dd, J = 7.7, 1.9 Hz, 1H), 7.43 – 7.38 (m, 1H), 7.29 – 7.24 (m, 2H), 7.16 – 7.11 (m, 1H), 6.98 (dd, J = 5.2, 1.4 Hz, 1H), 6.88 – 6.85 (m, 2H), 6.70 (dd, J = 7.7, 4.8 Hz, 1H), 6.26 (s, 2H), 5.35 (s, 2H), 4.05 (s, 2H). MS: 377.0 $[M+H]^+$.

[0519] **Example 87**: Synthesis of 3-(3-((6-((3-chloro-5-fluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



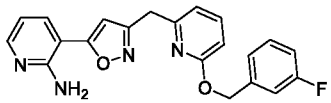
[0520] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50mg, 0.19mmol), (3-chloro-5-fluorophenyl)methanol (178mg, 1.11mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-((3-chloro-5-fluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (52mg, 0.13mmol, 69%) as a white solid. MS: 411.3 $[M+H]^+$.

[0521] **Example 88**: Synthesis of 3-(3-((2-((phenoxypyridin-4-yl)methyl)isoxazol-5-yl)pyridin-2-amine



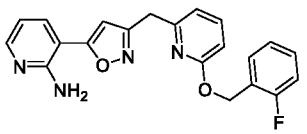
[0522] To a neat mixture of 3-(3-((2-fluoropyridin-4-yl)methyl)isoxazol-5-yl)pyridin-2-amine (40 mg, 0.148mmol), phenol (139mg, 1.48mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.48mL, 1.48mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((2-((phenoxypyridin-4-yl)methyl)isoxazol-5-yl)pyridin-2-amine (7.4mg, 0.021mmol, 15%) as a white solid. MS: 345.1 $[M+H]^+$.

[0523] **Example 89**: Synthesis of 3-(3-((6-((3-fluorobenzyl)oxy)pyridin-2-yl)methyl)isoxazol-5-yl)pyridin-2-amine



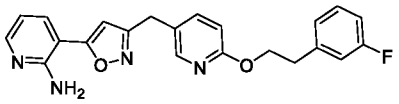
[0524] To a neat mixture of 3-(3-((6-fluoropyridin-2-yl)methyl)isoxazol-5-yl)pyridin-2-amine (40mg, 0.15mmol), (3-fluorophenyl)methanol (187mg, 1.48mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.48mL, 1.48mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-((3-fluorobenzyl)oxy)pyridin-2-yl)methyl)isoxazol-5-yl)pyridin-2-amine (10mg, 0.027mmol, 18%) as a white solid. MS: 377.3 $[M+H]^+$.

[0525] **Example 90**: Synthesis of 3-(3-((6-((2-fluorobenzyl)oxy)pyridin-2-yl)methyl)isoxazol-5-yl)pyridin-2-amine



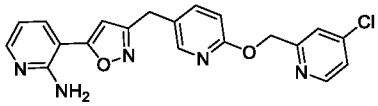
[0526] To a neat mixture of 3-(3-((6-fluoropyridin-2-yl)methyl)isoxazol-5-yl)pyridin-2-amine (40mg, 0.15mmol), (2-fluorophenyl)methanol (187mg, 1.48mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.48mL, 1.48mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-((2-fluorobenzyl)oxy)pyridin-2-yl)methyl)isoxazol-5-yl)pyridin-2-amine (25mg, 0.065mmol, 44%) as a white solid. MS: 377.2 $[M+H]^+$.

[0527] **Example 91**: Synthesis of 3-(3-((6-(3-fluorophenethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



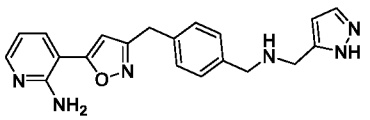
[0528] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50mg, 0.19mmol), 2-(3-fluorophenyl)ethan-1-ol (207mg, 1.48mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(3-fluorophenethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (10mg, 0.026mmol, 14%) as a white solid. MS: 391.4 $[M+H]^+$.

[0529] **Example 92**: Synthesis of 3-(3-((6-((4-chloropyridin-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



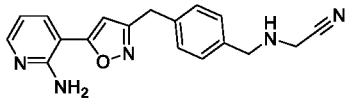
[0530] To a neat mixture of 3-(3-((6-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate E, 50mg, 0.19mmol), (4-chloropyridin-2-yl)methanol (159mg, 1.11mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(3-fluorophenethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (10mg, 0.025mmol, 14%) as a white solid. MS: 394.2 $[M+H]^+$.

[0531] **Example 93**: Synthesis of 3-(3-(4-((((1H-pyrazol-5-yl)methyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



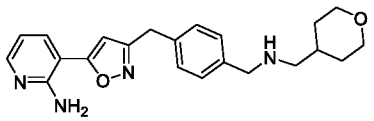
[0532] 3-(3-(4-(chloromethyl)benzyl)isoxazol-5-yl)pyridin-2-amine (Intermediate B, 0.10 g, 0.33 mmol) and (1H-pyrazol-5-yl)methanamine (0.16 g, 1.7 mmol) were suspended in tetrahydrofuran (2 mL). Diisopropylethylamine (0.14 mL, 0.80 mmol) was added and the mixture was stirred at 60 °C for 18h. The mixture was diluted with water and ethyl acetate, and the layers were partitioned. The aqueous phase was extracted twice more with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The residue was purified using Biotage reverse-phase flash chromatography (12g C18 SNAP, 5-95% acetonitrile/water with 0.1% formic acid). The desired fractions were combined and lyophilized to give the title compound as a formate salt (0.0040 g, 0.010 mmol, 3%). MS: 361.2 $[M+H]^+$.

[0533] **Example 94**: Synthesis of 2-((4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)amino)acetonitrile



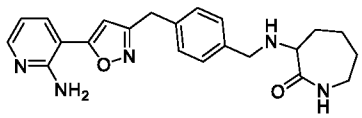
[0534] Prepared according to the procedure described in Example 93 using 2-aminoacetonitrile hydrochloride (0.15 g, 1.7 mmol). The title compound was obtained as a formate salt (0.0087 g, 0.024 mmol, 7%). MS: 320.2 $[M+H]^+$.

[0535] **Example 95**: Synthesis of 3-(3-(4-((((tetrahydro-2H-pyran-4-yl)methyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



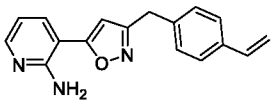
[0536] 3-(3-(4-(chloromethyl)benzyl)isoxazol-5-yl)pyridin-2-amine (Intermediate B, 0.10 g, 0.33 mmol) and (tetrahydro-2H-pyran-4-yl)methanamine (0.19 g, 1.7 mmol) were suspended in tetrahydrofuran (2 mL). Diisopropylethylamine (0.14 mL, 0.80 mmol) was added the heterogeneous mixture was stirred at room temperature for 3 hours. LCMS indicated a small peak with m/z corresponding to the desired product. The milky yellow mixture was heated at 60 °C for 72h. Significant progress was noted, but the mixture was still mostly starting material. The mixture was diluted with water and ethyl acetate, and the layers were partitioned. The aqueous phase was extracted twice more with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The residue was purified using Biotage reverse phase flash chromatography (12g C18 SNAP, 5-95% acetonitrile/water with 0.1% formic acid). The desired fractions were combined and lyophilized to give the titled compound as a formate salt (0.0055 g, 0.013 mmol, 4%). MS: 379.3 $[M+H]^+$.

[0537] **Example 96**: Synthesis of 3-((4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)amino)azepan-2-one



[0538] Prepared according to the procedure described in Example 93 using 3-aminoazepan-2-one (0.21 g, 1.7 mmol) and a 2-day reaction time. The title compound was obtained as a formate salt (0.056 g, 0.13 mmol, 39%). MS: 392.3 $[M+H]^+$.

[0539] Example 97: Synthesis of 3-(3-(4-Vinylbenzyl)isoxazol-5-yl)pyridin-2-amine



Step 1: synthesis of Di-tert-butyl [3-(3-(4-vinylbenzyl)isoxazol-5-yl)pyridin-2-yl]imidodicarbonate

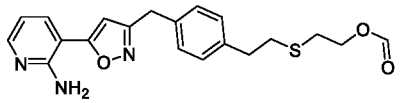
[0540] Di-tert-butyl [3-(3-(chloromethyl)-1,2-oxazol-5-yl)pyridin-2-yl]imidodicarbonate (Intermediate A, 1.7 g, 4.5 mmol), (4-vinylphenyl)boronic acid (0.82 g, 5.5 mmol), **bis[(2-diphenylphosphino)phenyl] ether** (0.11 g, 0.21 mmol), palladium(II) acetate (0.048 g, 0.21 mmol), potassium carbonate (0.76 g, 5.5 mmol), dimethylformamide (17 mL) and water (1.2 mL) were combined in a 50 mL sealed tube and heated at 60 °C for 18 hours. The mixture was cooled to ambient temperature, and then diluted with water

and toluene. The layers were partitioned, and the aqueous phase was extracted twice more with toluene. The combined organic phase was washed with water, and then brine. The organic phase was dried over sodium sulfate and then the solvents were evaporated. The residue was purified in two portions, each using Biotage normal-phase flash chromatography (50 g SNAP Ultra, 5-65% ethyl acetate / hexane). The desired fractions from each purification were combined to give the title compound as a pale-yellow oil (1.3 g, 2.7 mmol, 65%). This material was taken forward without further purification.

Step 2: synthesis of 3-(3-(4-Vinylbenzyl)isoxazol-5-yl)pyridin-2-amine

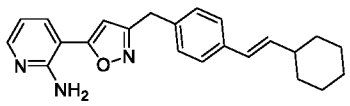
[0541] Di-tert-butyl [3-(3-(4-vinylbenzyl)isoxazol-5-yl)pyridin-2-yl]imidodicarbonate (0.017 g, 0.036 mmol) was dissolved in formic acid (3 mL). The mixture was stirred at room temperature for 4 days. The solution was treated with pH7 buffer (3 mL), and then basified with 5N aqueous sodium hydroxide to pH 9-10. Ethyl acetate was added, and the layers were partitioned. The aqueous phase was extracted twice more with ethyl acetate. The combined organic phase was washed with water, and then brine. The organic phase was dried over sodium sulfate, and then the solvents were evaporated. The residue was purified using Biotage reverse-phase flash chromatography (12 g C18 SNAP, 5-95% acetonitrile/water with 0.1% formic acid). The desired fractions were combined and lyophilized to give the title compound as a white solid (0.0020g, 0.0072 mmol, 20%). MS: 378.3 $[M+H]^+$.

[0542] **Example 98**: Synthesis of 2-((4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenethyl)thio)ethyl formate



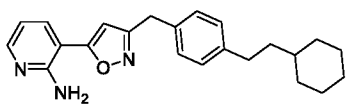
[0543] Di-tert-butyl [3-(3-(4-vinylbenzyl)isoxazol-5-yl)pyridin-2-yl]imidodicarbonate (0.20 g, 0.42 mmol), 2,2-dimethoxy-2-phenylacetophenone (0.0054 g, 0.021 mmol), 2-mercaptoethanol (0.030 mL, 0.42 mmol), dichloromethane (0.7 mL) were combined in a 2 mL sealed tube and stirred under UV light (365 nm, 4W) at ambient temperature for 4h. The mixture was concentrated somewhat and then purified using Biotage normal-phase flash chromatography (25 g SNAP Ultra, 5-65% acetone/hexane). The desired fractions were combined and evaporated to give the di-BOC protected product. This material was dissolved in formic acid (6 mL) and stirred at room temperature for 13 hours. The mixture was treated with pH7 buffer (20 mL), and then basified to pH 10 with 45% aqueous potassium hydroxide. The mixture was stirred for 15 minutes, then ethyl acetate was added and the mixture stirred for another 5 hours. The layers were partitioned. The aqueous phase was extracted twice more with ethyl acetate. The combined organic phase was washed with water, and then brine. The organic phase was dried over sodium sulfate, and then the solvents were evaporated. The residue was partially dissolved in methanol. The insoluble material was further (but not completely) dissolved in dimethyl sulfoxide. Both crude solutions were purified separately using Biotage reverse phase flash chromatography (12 g C18 SNAP, 5-95% acetonitrile/water with 0.1% formic acid). The like fractions from each purification were combined to give the title compound as a white solid (40 mg, 0.10 mmol, 25%). MS: 384.1 $[M+H]^+$.

[0544] **Example 99**: Synthesis of (E)-3-(3-(4-(2-cyclohexylvinyl)benzyl)isoxazol-5-yl)pyridin-2-amine



[0545] Di-tert-butyl [3-(3-(4-vinylbenzyl)isoxazol-5-yl)pyridin-2-yl]imidodicarbonate (0.50 g, 1.1 mmol), vinylcyclohexane (0.29 mL, 4.2 mmol), Grubbs catalyst 2nd generation (0.053 g, 0.0.064 mmol), and dichloromethane (7 mL) were combined in a sealed tube. The mixture was sparged with argon for 2 minutes, and then heated to 40 °C. After 16 hours, another 2 equivalents of vinylcyclohexane (0.29 mL, 4.2 mmol) and another 0.03 equivalents of catalyst (0.026 g, 0.032) were added. The vial was sealed and sparged with argon for 2 min. The mixture was again heated to 40 °C and stirred for another 24 hours. After cooling to room temperature the reaction was quenched by addition of Isolute Si-Thiol resin (10 equivalents relative to Ru, 0.74 g, 0.96 mmol). The mixture was stirred for 3 hours before filtering through a plug of Celite. The filtrate was evaporated and the residue was purified using Biotage normal-phase flash chromatography (100 g SNAP Ultra, 5-60% ethyl acetate / hexane. The desired fractions were combined and evaporated to give di-tert-butyl [(E)-3-(3-(4-(2-cyclohexylvinyl)benzyl)isoxazol-5-yl)pyridin-2-yl]imidodicarbonate (0.17 g, 0.30 mmol, 28%). A portion of this material (0.10 g, 0.18 mmol) was dissolved in formic acid (5 mL) and stirred at room temperature for 4 hours. The solution was cooled to 0 °C and then basified to pH 10 with 50% aqueous sodium hydroxide solution. The mixture was further diluted with water and extracted three times with ethyl acetate. The combined organic phase was washed with water, and then brine. The organic phase was dried over sodium sulfate, and then the solvents were evaporated to give a solid residue. The solid was dissolved in 1,2-dimethoxyethane (5 mL), transferred through a 0.45µ syringe filter into a 50 mL conical tube, and then treated with 4M hydrogen chloride in dioxane (1.5 mL). No precipitate formed. The solvent was evaporated to give an off-white solid. The material was washed into a 50 mL conical tube using 1,2-dimethoxyethane (5 mL). The tube was centrifuged at 3200 rpm for 7 minutes. The supernatant was decanted, more 1,2-dimethoxyethane was added to the pellet. The suspension was vortexed, and then centrifuged at 3200 rpm for 7 min. The supernatant was decanted and the white pellet was dissolved with acetonitrile, transferred to a round bottom flask, and extensively dried under vacuum to give the title compound as a white solid hydrochloride salt (0.066 g, 0.17 mmol, 93%). MS: 360.2 $[M+H]^+$.

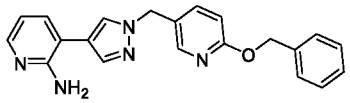
[0546] **Example 100**: Synthesis of 3-(3-(4-(2-cyclohexylethyl)benzyl)isoxazol-5-yl)pyridin-2-amine



[0547] Palladium on carbon (10 wt%, 3 mg) was placed into a round bottom flask and covered with ethanol (0.5 mL). Di-tert-butyl [(E)-3-(3-(4-(2-cyclohexylvinyl)benzyl)isoxazol-5-yl)pyridin-2-yl]imidodicarbonate (0.070 g, 0.13 mmol) was transferred into the flask with more ethanol (0.5 mL). The head-space was purged with argon, and then with hydrogen. A balloon filled with hydrogen was affixed to the flask with a needle through a rubber septum. The mixture was stirred briskly for 3 hours, before carefully filtering through a pad of Celite with methanol. The solvent was evaporated to give an oil which was purified using Biotage normal-phase flash chromatography (10 g SNAP Ultra, 5-60% ethyl

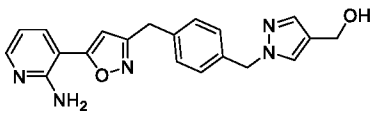
acetate/hexane). The desired fractions were combined and evaporated to give di-tert-butyl [3-(3-(4-(2-cyclohexylethyl)benzyl)isoxazol-5-yl)pyridin-2-yl]imidodicarbonate (0.050 g, 0.089 mmol, 69%). This material was dissolved in formic acid (1 mL) and stirred at room temperature for 18 hours. The solution was cooled to 0 °C and then basified to pH 10 with 50% aqueous sodium hydroxide solution. The mixture was further diluted with water and extracted three times with ethyl acetate. The combined organic phase was washed with water, and then brine. The organic phase was dried over sodium sulfate, and then the solvents were evaporated. The residue was dissolved in 1,2-dimethoxyethane (5 mL), transferred through a 0.45µ syringe filter into a 50 mL conical tube, and then treated with 4M hydrogen chloride in dioxane (1.5 mL). A white precipitate formed. The tube was centrifuged at 3200 rpm for 7 minutes. The supernatant was decanted, more 1,2-dimethoxyethane was added to the pellet. The suspension was vortexed, and then centrifuged at 3200 rpm for 7 min. The centrifuge procedure was repeated for a third time. The supernatant was decanted and the white pellet was dissolved with acetonitrile, transferred to a round bottom flask, and extensively dried under vacuum to give the title compound as a white solid hydrochloride salt (0.030 g, 0.076 mmol, 85%). MS: 362.1 $[M+H]^+$.

[0548] **Example 101**: Synthesis of 3-(1-((6-(benzyloxy)pyridin-3-yl)methyl)-1H-pyrazol-4-yl)pyridin-2-amine



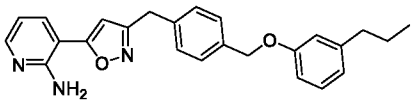
[0549] The title compound was prepared according to the procedure described for Example 63 using 2-(benzyloxy)-5-((4-bromo-1H-pyrazol-1-yl)methyl)pyridine (130mg, 0.38mmol) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (150mg, 0.68mmol) to yield 3-(1-((6-(benzyloxy)pyridin-3-yl)methyl)-1H-pyrazol-4-yl)pyridin-2-amine (50mg, 0.14mmol, 37%). MS: 358.3 $[M+H]^+$.

[0550] **Example 102**: Synthesis of (1-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)-1H-pyrazol-4-yl)methanol



[0551] The title compound was prepared according to the procedure described for Example 4 using (1H-pyrazol-4-yl)methanol (105mg, 1.07mmol) to yield (1-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)-1H-pyrazol-4-yl)methanol (59mg, 0.16mmol, 61%) as a white solid. MS: 362.4 $[M+H]^+$.

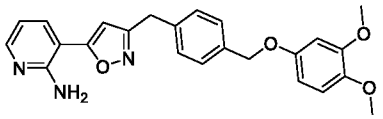
[0552] Example 103: Synthesis of 3-(3-(4-((3-propylphenoxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



[0553] A solution of 3-propylphenol (182mg, 1.33mmol) in NMP (0.5mL) was added to a suspension of sodium hydride (60% w/mineral oil, 40mg, 1.00mmol) in NMP (1.5mL). After stirring for 20min at 21-

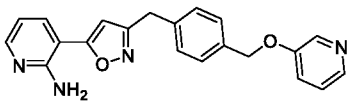
25°C, a solution of 3-(3-(4-(chloromethyl)benzyl)isoxazol-5-yl)pyridin-2-amine (Intermediate B, 100mg, 0.33mmol) in NMP (1ml) was added and the mixture was stirred for 4min at 60°C. The cooled reaction mixture was directly purified by column chromatography (SiO_2, hexane/ethyl acetate). Fraction containing the product were concentrated under reduced pressure and further purified by HPLC to yield 3-(3-(4-((3-propylphenoxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine (35mg, 0.09mmol, 26%). MS: 400.4 $[M+H]^+$.

[0554] **Example 104**: Synthesis of 3-(3-(4-((3,4-dimethoxyphenoxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



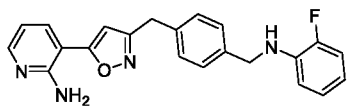
[0555] The title compound was prepared according to the procedure described for Example 103 using 3,4-dimethoxyphenol (206mg, 1.33mmol) to yield 3-(3-(4-((3,4-dimethoxyphenoxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine (64mg, 0.15mmol, 46%) as a white solid. MS: 418.4 $[M+H]^+$.

[0556] **Example 105**: Synthesis of 3-(3-(4-((pyridin-3-yloxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



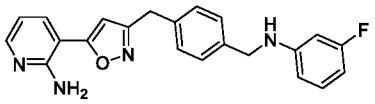
[0557] 3-(3-(4-(chloromethyl)benzyl)isoxazol-5-yl)pyridin-2-amine (Intermediate B, 120mg, 0.40mmol), pyridine-3-ol (305mg, 3.20mmol) and potassium carbonate (443mg, 3.20mmol) were mixed in DMF (2mL). The mixture was stirred for 1h at 80°C. The cooled reaction mixture was directly purified by column chromatography (SiO_2, hexane/ethyl acetate). Fraction containing the product were concentrated under reduced pressure and further purified by HPLC to yield 3-(3-(4-((pyridin-3-yloxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine (12mg, 0.03mmol, 8%). 400 MHz ^1H NMR ($CDCl_3$) δ 8.38 (dd, J = 2.8, 0.9 Hz, 1H), 8.23 (dd, J = 4.4, 1.6 Hz, 1H), 8.14 (dd, J = 4.9, 1.8 Hz, 1H), 7.70 (dd, J = 7.7, 1.8 Hz, 1H), 7.41 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.28 – 7.19 (m, 2H), 6.71 (dd, J = 7.7, 4.9 Hz, 1H), 6.26 (s, 1H), 5.41 (s, 2H), 5.10 (s, 2H), 4.08 (s, 2H). MS: 359.4 $[M+H]^+$.

[0558] **Example 106**: Synthesis of 3-(3-(4-(((2-fluorophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



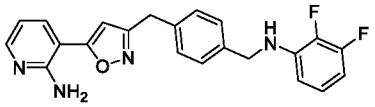
[0559] 3-(3-(4-(chloromethyl)benzyl)isoxazol-5-yl)pyridin-2-amine (Intermediate B, 80mg, 0.27mmol) was dissolved in DMF (1.5mL) and 2-fluoroaniline (297mg, 2.67mmol) was added. The mixture was stirred for 40min at 90°C. The cooled reaction mixture was directly purified by column chromatography (SiO_2, hexane/ethyl acetate) to yield 3-(3-(4-(((2-fluorophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine (54mg, 0.14mmol, 54%). MS: 375.3 $[M+H]^+$.

[0560] **Example 107**: Synthesis of 3-(3-(4-(((3-fluorophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



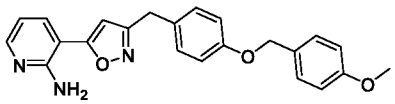
[0561] 3-(3-(4-(chloromethyl)benzyl)isoxazol-5-yl)pyridin-2-amine (Intermediate B, 80mg, 0.27mmol) was dissolved in DMF (1.5mL) and 3-fluoroaniline (297mg, 2.67mmol) was added. The mixture was stirred for 40min at 90°C. The cooled reaction mixture was directly purified by column chromatography (SiO_2, hexane/ethyl acetate) to yield 3-(3-(4-(((3-fluorophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine (67mg, 0.18mmol, 67%). MS: 375.3 $[M+H]^+$.

[0562] **Example 108**: Synthesis of 3-(3-(4-(((2,3-difluorophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



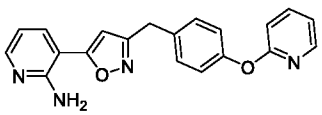
[0563] 3-(3-(4-(chloromethyl)benzyl)isoxazol-5-yl)pyridin-2-amine (Intermediate B, 80mg, 0.27mmol) was dissolved in DMF (1.5mL) and 2,3-difluoroaniline (345mg, 2.67mmol) was added. The mixture was stirred for 2h at 110°C. The cooled reaction mixture was directly purified by column chromatography (SiO_2, hexane/ethyl acetate) to yield 3-(3-(4-(((2,3-difluorophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine (46mg, 0.12mmol, 44%). MS: 393.4 $[M+H]^+$.

[0564] **Example 109**: Synthesis of 3-(3-(4-((4-methoxybenzyl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine



[0565] The title compound was prepared according to the procedure described for Example 26 using 1-(chloromethyl)-4-methoxybenzene (56mg, 0.36mmol) to yield 3-(3-(4-((4-methoxybenzyl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine (64mg, 0.16mmol, 55%) as a white solid. MS: 388.3 $[M+H]^+$.

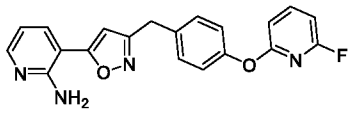
[0566] **Example 110**: Synthesis of 3-(3-(4-(pyridin-2-yloxy)benzyl)isoxazol-5-yl)pyridin-2-amine



[0567] 4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenol (100mg, 0.37mmol) was dissolved in DMF (1mL) and potassium 2-methylpropane-2-olate (1M in THF, 0.33mL, 0.33mmol) was added dropwise. The mixture was stirred for 5min and a solution of 2,6-difluoropyridine (51mg, 0.52mmol) in DMF (0.5mL) was added. The resulting mixture was stirred for 6h at 90°C and directly purified by column chromatography (SiO_2, hexane/ethyl acetate). Fraction containing the product were concentrated under reduced pressure and further purified by reversed phase flash chromatography (C18,

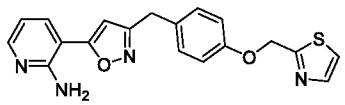
acetonitrile/water) to yield 3-(3-(4-(pyridin-2-yloxy)benzyl)isoxazol-5-yl)pyridin-2-amine (35mg, 0.10mmol, 27%) as a white solid. MS: 345.3 $[M+H]^+$.

[0568] **Example 111**: Synthesis of 3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine



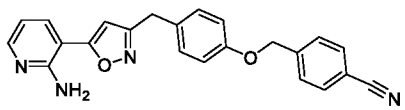
[0569] 4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenol (80mg, 0.30mmol) was dissolved in DMF (1mL) and potassium 2-methylpropane-2-olate (1M in THF, 0.33mL, 0.33mmol) was added dropwise. The mixture was stirred for 5min and a solution of 2,6-difluoropyridine (48.2mg, 0.42mmol) in DMF (0.5mL) was added. The resulting mixture was stirred for 3min at 90°C and directly purified by column chromatography (SiO_2, hexane/ethyl acetate). Fraction containing the product were concentrated under reduced pressure and further purified by reversed phase flash chromatography (C18, acetonitrile/water) to yield 3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine (65mg, 0.18mmol, 60%) as a white solid. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.14 (s, 1H), 7.80 – 7.69 (m, 2H), 7.31 (d, J = 8.5 Hz, 2H), 7.11 (d, J = 8.5 Hz, 2H), 6.77 – 6.68 (m, 2H), 6.60 (dd, J = 7.8, 2.6 Hz, 1H), 6.30 (s, 1H), 5.43 (s, 2H), 4.07 (s, 2H). MS: 363.3 $[M+H]^+$.

[0570] **Example 112**: Synthesis of 3-(3-(4-(thiazol-2-ylmethoxy)benzyl)isoxazol-5-yl)pyridin-2-amine



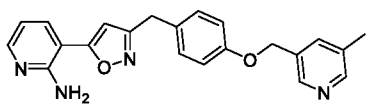
The title compound was prepared according to the procedure described for Example 26 using 2-(chloromethyl)thiazole (48mg, 0.36mmol) to yield 3-(3-(4-(thiazol-2-ylmethoxy)benzyl)isoxazol-5-yl)pyridin-2-amine (62mg, 0.17mmol, 57%) as a white solid. MS: 365.3 $[M+H]^+$.

[0571] **Example 113:** Synthesis of 4-((4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenoxy)methyl)benzonitrile



[0572] The title compound was prepared according to the procedure described for Example 26 using 4-(chloromethyl)benzonitrile (54mg, 0.36mmol) to yield 4-((4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenoxy)methyl)benzonitrile (69mg, 0.18mmol, 60%) as a white solid. MS: 383.3 $[M+H]^+$.

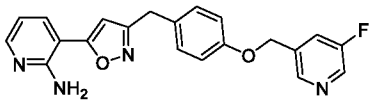
[0573] Example 114: Synthesis of 3-(3-(4-((5-methylpyridin-3-yl)methoxy)benzyl)isoxazol-5-yl)pyridin-2-amine



[0574] The title compound was prepared according to the procedure described for Example 26 using 3-(chloromethyl)-5-methylpyridine hydrochloride (75mg, 0.42mmol) and potassium 2-methylpropane-2-

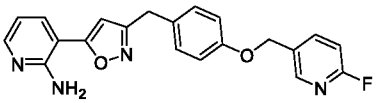
olate (1M in THF, 0.75mL, 0.75mmol) to yield 3-(3-(4-((5-methylpyridin-3-yl)methoxy)benzyl)isoxazol-5-yl)pyridin-2-amine (87mg, 0.23mmol, 78%) as a white solid. MS: 373.3 $[M+H]^+$.

[0575] **Example 115**: Synthesis of 3-(3-(4-((5-fluoropyridin-3-yl)methoxy)benzyl)isoxazol-5-yl)pyridin-2-amine



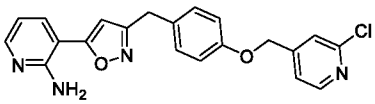
[0576] The title compound was prepared according to the procedure described for Example 26 using 3-(chloromethyl)-5-fluoropyridine hydrochloride (76mg, 0.42mmol) and potassium 2-methylpropane-2-olate (1M in THF, 0.75mL, 0.75mmol) to yield 3-(3-(4-((5-fluoropyridin-3-yl)methoxy)benzyl)isoxazol-5-yl)pyridin-2-amine (50mg, 0.13mmol, 44%) as a white solid. MS: 377.3 $[M+H]^+$.

[0577] **Example 116**: Synthesis of 3-(3-(4-((6-fluoropyridin-3-yl)methoxy)benzyl)isoxazol-5-yl)pyridin-2-amine



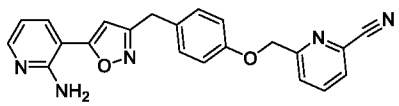
[0578] The title compound was prepared according to the procedure described for Example 26 using 5-(chloromethyl)-2-fluoropyridine (59mg, 0.40mmol) to yield 3-(3-(4-((6-fluoropyridin-3-yl)methoxy)benzyl)isoxazol-5-yl)pyridin-2-amine (56mg, 0.15mmol, 44%) as a white solid. MS: 377.4 $[M+H]^+$.

[0579] **Example 117**: Synthesis of 3-(3-(4-((2-chloropyridin-4-yl)methoxy)benzyl)isoxazol-5-yl)pyridin-2-amine



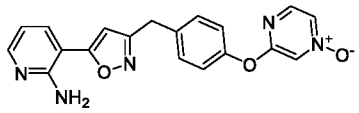
[0580] The title compound was prepared according to the procedure described for Example 26 using 2-chloro-4-(chloromethyl)pyridine (66mg, 0.40mmol) to yield 3-(3-(4-((2-chloropyridin-4-yl)methoxy)benzyl)isoxazol-5-yl)pyridin-2-amine (54mg, 0.14mmol, 41%) as a white solid. MS: 393.5 $[M+H]^+$.

[0581] **Example 118**: Synthesis of 6-((4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenoxy)methyl)picolinonitrile



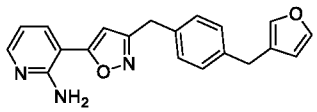
[0582] The title compound was prepared according to the procedure described for Example 26 using 6-(chloromethyl)picolinonitrile (62mg, 0.40mmol) to yield 6-((4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenoxy)methyl)picolinonitrile (65mg, 0.17mmol, 50%) as a white solid. MS: 384.4 $[M+H]^+$.

[0583] **Example 119**: Synthesis of 3-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenoxy)pyrazine 1-oxide



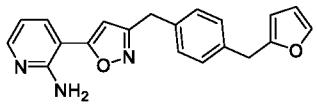
[0584] The title compound was prepared according to the procedure described for Example 111 using 3-chloropyrazine 1-oxide (55mg, 0.42mmol) to yield 3-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenoxy)pyrazine 1-oxide (64mg, 0.18mmol, 60%) as a white solid. MS: 362.4 $[M+H]^+$.

[0585] **Example 120**: Synthesis of 3-(3-(4-(furan-3-ylmethyl)benzyl)isoxazol-5-yl)pyridin-2-amine



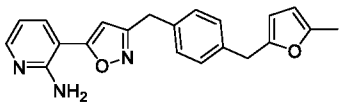
[0586] The title compound was prepared according to the procedure described for Example 8 using furan-3-ylboronic acid (56mg, 0.50mmol) to yield 3-(3-(4-(furan-3-ylmethyl)benzyl)isoxazol-5-yl)pyridin-2-amine (69mg, 0.21mmol, 62%) as a white solid. MS: 332.2 $[M+H]^+$.

[0587] **Example 121**: Synthesis of 3-(3-(4-(furan-2-ylmethyl)benzyl)isoxazol-5-yl)pyridin-2-amine



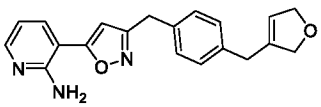
[0588] The title compound was prepared according to the procedure described for Example 8 using furan-2-ylboronic acid (56mg, 0.50mmol) to yield 3-(3-(4-(furan-2-ylmethyl)benzyl)isoxazol-5-yl)pyridin-2-amine (62mg, 0.19mmol, 56%) as a white solid. MS: 332.3 $[M+H]^+$.

[0589] **Example 122**: Synthesis of 3-(3-(4-((5-methylfuran-2-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



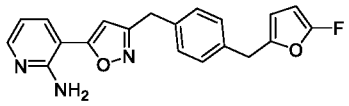
[0590] The title compound was prepared according to the procedure described for Example 8 using 4,4,5,5-tetramethyl-2-(5-methylfuran-2-yl)-1,3,2-dioxaborolane (104mg, 0.50mmol) to yield 3-(3-(4-((5-methylfuran-2-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine (73mg, 0.21mmol, 63%) as a white solid. MS: 346.3 $[M+H]^+$.

[0591] **Example 123**: Synthesis of 3-(3-(4-((2,5-dihydrofuran-3-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



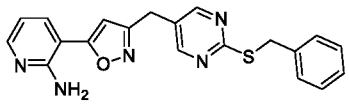
[0592] The title compound was prepared according to the procedure described for Example 8 using 2-(2,5-dihydrofuran-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (98mg, 0.50mmol) to yield 3-(3-(4-((2,5-dihydrofuran-3-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine (68mg, 0.20mmol, 61%) as a white solid. MS: 334.3 $[M+H]^+$.

[0593] **Example 124**: Synthesis of 3-(3-(4-((5-fluorofuran-2-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



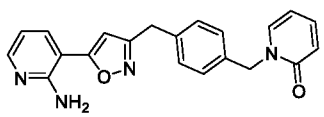
[0594] The title compound was prepared according to the procedure described for Example 8 using 2-(5-fluorofuran-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (106mg, 0.50mmol) to yield 3-(3-(4-((5-fluorofuran-2-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine (84mg, 0.24mmol, 72%) as a white solid. MS: 350.3 $[M+H]^+$.

[0595] **Example 125**: Synthesis of 3-(3-((2-(benzylthio)pyrimidin-5-yl)methyl)isoxazol-5-yl)pyridin-2-amine



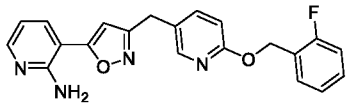
[0596] Di-tert-butyl [3-(3-(chloromethyl)-1,2-oxazol-5-yl)pyridin-2-yl]imidodicarbonate (1.67g, 4.06mmol) and (2-(benzylthio)pyrimidin-5-yl)boronic acid (1.00g, 4.06mmol) were mixed in DME (20mL) in a sealable tube. A 2M solution of sodium carbonate in water (4.67mL, 9.34mmol) and palladium tetrakis triphenylphosphine (470mg, 0.41mmol) were added and the sealable tube was flushed with argon and sealed. The mixture was stirred for 5h at 95°C. The cooled reaction mixture was poured into ethyl acetate (400mL) and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to give the di-Boc protected coupling product as a yellow oil to which was added formic acid (8mL). This mixture was stirred for 13h at 21-25°C to complete the di-Boc de-protection. To this mixture was added ice-water (80mL) and ethyl acetate (160mL). A 5M solution of NaOH in water was added until the pH of the aqueous layer was adjusted to 8-9. The layers were separated and the aqueous phase was extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to yield 3-(3-((2-(benzylthio)pyrimidin-5-yl)methyl)isoxazol-5-yl)pyridin-2-amine (620mg, 1.65mmol, 41%) as a white solid. MS: 376.4 $[M+H]^+$.

[0597] **Example 126**: Synthesis of 1-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)pyridin-2(1H)-one



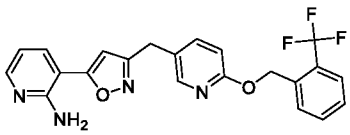
[0598] 3-(3-(4-((pyridin-2-yloxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine (200mg, 0.56mmol) was dissolved in acetonitrile (2.5mL) and lithium iodide (224mg, 1.68mmol) was added. The mixture was heated in the MW at 180 °C for 10min. The cooled reaction mixture was poured into ethyl acetate (50mL) and water (30mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to yield 1-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)pyridin-2(1H)-one (46mg, 0.13mmol, 23%) as a white solid. MS: 359.4 $[M+H]^+$.

[0599] **Example 127**: Synthesis of 3-(3-((6-((2-fluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



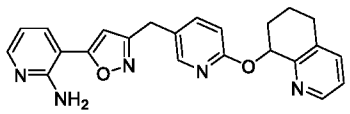
[0600] To a neat mixture of 3-(3-((6-fluoropyridin-4-yl)methyl)isoxazol-5-yl)pyridin-2-amine (60.mg, 0.22mmol), (2-fluorophenyl)methanol (168mg, 1.33mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 2.22mL, 2.22mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-((2-fluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (27mg, 0.073mmol, 33%) as a white solid. MS: 377.0 $[M+H]^+$.

[0601] **Example 128**: Synthesis of 3-(3-((6-((2-(trifluoromethyl)benzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



[0602] To a neat mixture of 3-(3-((6-fluoropyridin-4-yl)methyl)isoxazol-5-yl)pyridin-2-amine (50.mg, 0.19mmol), (2-trifluoromethylphenyl)methanol (196mg, 1.33mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 2.22mL, 2.22mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-((2-(trifluoromethyl)benzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (38mg, 0.089mmol, 48%) as a light pink solid. MS: 427.0 $[M+H]^+$.

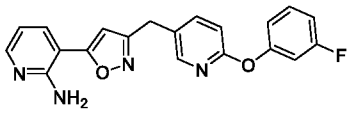
[0603] **Example 129**: Synthesis of 3-(3-((6-((5,6,7,8-tetrahydroquinolin-8-yl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



[0604] To a neat mixture of 3-(3-((6-fluoropyridin-4-yl)methyl)isoxazol-5-yl)pyridin-2-amine (50.mg, 0.19mmol), 5,6,7,8-tetrahydroquinolin-8-ol (221mg, 1.48mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 30min. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-((5,6,7,8-tetrahydroquinolin-8-yl)oxy)pyridin-3-

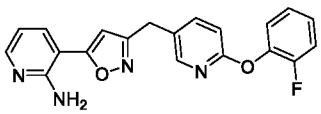
yl)methyl)isoxazol-5-yl)pyridin-2-amine (30mg, 0.076mmol, 41%) as an orange glassy solid. MS: 400.3 $[M+H]^+$.

[0605] Example 130: Synthesis of 3-(3-((6-(3-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine



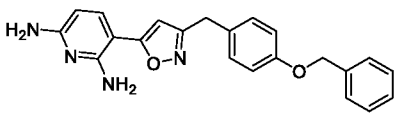
[0606] To a neat mixture of 3-(3-((6-fluoropyridin-4-yl)methyl)isoxazol-5-yl)pyridin-2-amine (50.mg, 0.19mmol), 3-fluorophenol (124mg, 1.11mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 45min at 140°C in a sealed high pressure reaction vessel. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(3-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (32mg, 0.088mmol, 48%) as a white solid. MS: 363.1 $[M+H]^+$.

[0607] Example 131: Synthesis of 3-(3-((6-(2-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

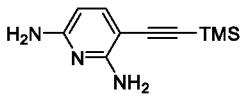


[0608] To a neat mixture of 3-(3-((6-fluoropyridin-4-yl)methyl)isoxazol-5-yl)pyridin-2-amine (50.mg, 0.19mmol), 2-fluorophenol (207mg, 1.85mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 1.85mL, 1.85mmol) and the mixture was stirred for 45min at 140°C in a sealed high pressure reaction vessel. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-((6-(2-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (19mg, 0.052mmol, 28%) as a white solid. MS: 363.2 $[M+H]^+$.

[0609] Example 132: Synthesis of 3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridine-2,6-diamine



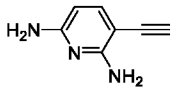
Step 1: Synthesis of 3-((trimethylsilyl)ethynyl)pyridine-2,6-diamine



[0610] 3-iodopyridine-2,6-diamine (2.640 g, 11.23 mmol), ethynyltrimethylsilane (2.207 g, 22.47 mmol), DIEA (4.90 ml, 28.1 mmol), and copper (I) iodide (0.214 g, 1.123 mmol) were combined in N-

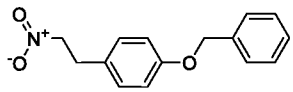
Methyl-2-pyrrolidinone (10 ml) under argon and was stirred for 2.5 hours at 45 °C. The reaction mixture was poured into water and extracted with ethyl acetate three times. The organic phase was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography. Combined fractions were concentrated under reduced pressure to give 3-((trimethylsilyl)ethynyl)pyridine-2,6-diamine (1.20 g, 5.84 mmol, 52.0 % yield). MS: 206.3 $[M+H]^+$.

Step 2: Synthesis of 3-ethynylpyridine-2,6-diamine



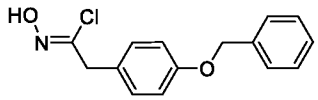
[0611] To a solution of 3-((trimethylsilyl)ethynyl)pyridine-2,6-diamine (1.200 g, 5.84 mmol) in THF (10 ml) was added TBAF (1.169 ml, 1.169 mmol) at 0 °C. Reaction mixture was slowly brought up to room temperature and stirred at room temperature for 10 minutes. Water was added to the reaction mixture and then extracted with ethyl acetate three times. Combined organic phase was dried over sodium sulfate and the solvent was removed at reduced pressure. The residue was purified by silica gel chromatography to give 3-ethynylpyridine-2,6-diamine (0.724 g, 5.44 mmol, 93 % yield). MS: 134.1 $[M+H]^+$.

Step 3: Synthesis of 1-(benzyloxy)-4-(2-nitroethyl)benzene



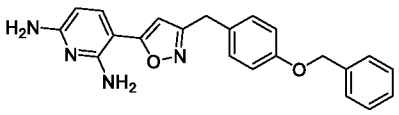
[0612] To a mixture of (E)-1-(benzyloxy)-4-(2-nitrovinyl)benzene (5.000 g, 19.59 mmol), acetic acid (5.000 ml, 87 mmol), and DMSO (60 ml) was added sodium borohydride (1.250 g, 33.0 mmol) at room temperature and stirred for 40 minutes. Water was added to the reaction mixture and organics were extacted with ethyl acetate. Solvents removed at reduced pressure. Residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:3). Combined fractions were concentrated under reduced pressure to give 1-(benzyloxy)-4-(2-nitroethyl)benzene (1.500 g, 5.83 mmol, 29.8 % yield). MS: 258.3 $[M+H]^+$.

Step 4: Synthesis of (Z)-2-(4-(benzyloxy)phenyl)-N-hydroxyacetimidoyl chloride



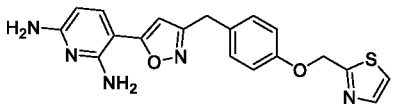
[0613] To a mixture of 1-(benzyloxy)-4-(2-nitroethyl)benzene (1.500 g, 5.83 mmol) in Methanol (15 ml) was added lithium methanolate (11.66 ml, 11.66 mmol) and was stirred for 15 minutes at room temperature. The reaction mixture was concentrated at reduced pressure. Dichloromethane (12 ml) and tetrahydrofuran (6 ml) were added to the residue. Reaction mixture was cooled to -78 °C and titanium tetrachloride (18.66 ml, 18.66 mmol) was added and stirred at 0 °C for 1 hour. The reaction mixture was cooled to -78 °C and water was added. Reaction mixture was gradually warmed to room temperature. Organics were dissolved in DCM and washed with brine. Residue was purified by normal phase chromatography to give (Z)-2-(4-(benzyloxy)phenyl)-N-hydroxyacetimidoyl chloride (1.500 g, 5.44 mmol, 93 % yield) MS: 276.7 $[M+H]^+$.

Step 5: Synthesis of 3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridine-2,6-diamine



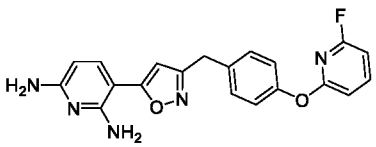
[0614] To a mixture of (Z)-2-(4-(benzyloxy)phenyl)-N-hydroxyacetimidoyl chloride (1.500 g, 5.44 mmol) and 3-ethynylpyridine-2,6-diamine (0.724 g, 5.44 mmol) in THF was added triethylamine (1.517 ml, 10.88 mmol) and let stir overnight at room temperature. Reaction mixture was concentrated under reduced pressure. Residue was purified by silica gel chromatography. Combined fractions were concentrated under reduced pressure to give 3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridine-2,6-diamine (0.425 g, 1.141 mmol, 20.98 % yield). MS: 373.3 $[M+H]^+$.

[0615] **Example 133**: Synthesis of 3-(3-(4-(thiazol-2-ylmethoxy)benzyl)isoxazol-5-yl)pyridine-2,6-diamine



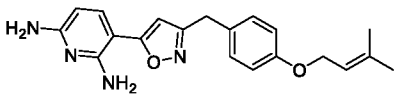
[0616] To a neat mixture of 4-((5-(2,6-diaminopyridin-3-yl)isoxazol-3-yl)methl)phenol (Intermediate F, 55mg, 0.20mmol), 2-(chloromethyl)thiazole (31mg, 0.23mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 0.21mL, 0.21mmol) and the mixture was stirred for 2 hours at room temperature. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-(4-(thiazol-2-ylmethoxy)benzyl)isoxazol-5-yl)pyridine-2,6-diamine (22mg, 0.057mmol, 30%) as a white solid. MS: 380.4 $[M+H]^+$.

[0617] **Example 134**: Synthesis of 3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridine-2,6-diamine



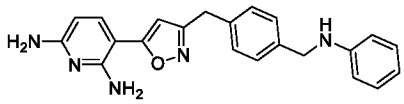
[0618] To a neat mixture of 4-((5-(2,6-diaminopyridin-3-yl)isoxazol-3-yl)methl)phenol (Intermediate F, 55mg, 0.20mmol), 2,6-difluoropyridine (31mg, 0.27mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 0.21mL, 0.21mmol) and the mixture was stirred for 2 hours at room temperature. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridine-2,6-diamine (2.7mg, 0.0072mmol, 3.7%) as a white solid. MS: 378.4 $[M+H]^+$.

[0619] **Example 135**: Synthesis of 3-(3-(4-((3-methylbut-2-en-1-yl)oxy)benzyl)isoxazol-5-yl)pyridine-2,6-diamine



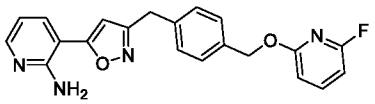
[0620] To a neat mixture of 4-((5-(2,6-diaminopyridin-3-yl)isoxazol-3-yl)methl)phenol (Intermediate F, 45mg, 0.16mmol), 1-bromo-3-methylbut-2-ene (29mg, 0.19mmol) was added potassium 2-methylpropane-2-olate (1M in THF, 0.35mL, 0.35mmol) and the mixture was stirred for 2 hours at room temperature. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-(4-((3-methylbut-2-en-1-yl)oxy)benzyl)isoxazol-5-yl)pyridine-2,6-diamine (17mg, 0.049mmol, 30%) as a white solid. MS: 351.4 $[M+H]^+$.

[0621] **Example 136**: Synthesis of 3-(3-(4-((phenylamino)methyl)benzyl)isoxazol-5-yl)pyridine-2,6-diamine

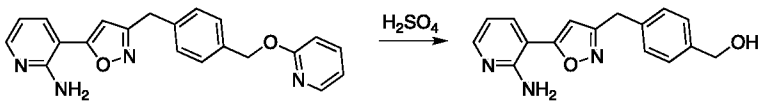


[0622] 3-(3-(4-(chloromethyl)benzyl)isoxazol-5-yl)pyridine-2,6-diamine (Intermediate G, 75mg, 0.24mmol) and aniline (31mg, 0.27mmol) were dissolved in THF and the mixture was stirred for 18 hours at room temperature. The mixture was transferred to a silica gel samplet which was subsequently loaded on to a Biotage Snap column. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate). Combined fractions were concentrated under reduced pressure. Residue was dissolved in acetonitrile (5mL) and water (10mL), frozen and lyophilized to yield 3-(3-(4-((phenylamino)methyl)benzyl)isoxazol-5-yl)pyridine-2,6-diamine (36mg, 0.098mmol, 41%) as a white solid. MS: 372.5 $[M+H]^+$.

[0623] **Example 137**: Synthesis of 3-(3-(4-(((6-fluoropyridin-2-yl)oxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine

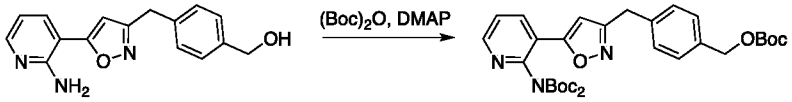


Step 1: Synthesis of (4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenyl)methanol



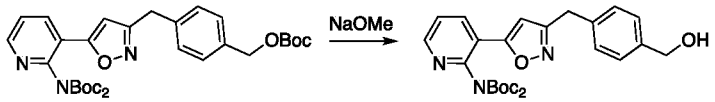
[0624] 3-(3-(4-((pyridin-2-yloxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine (1.5g, 4.19mmol) was dissolved in dioxane (20mL) and water (20mL) was added. Concentrated sulfuric acid (0.82g, 8.37mmol) was added and the mixture was heated to reflux for 6h. The cooled mixture was poured into ice-cold pH7 phosphate buffer (150mL) containing 330mg of NaOH (to neutralize excess of H_2SO_4) and was extracted with EtOAc (3x50mL). The combined organic layers were washed with brine (50mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified using flash chromatography to give (4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenyl)methanol (1.09g, 3.87mmol, 93%) as a white solid. MS: 282.4 $[M+H]^+$.

Step 2: Synthesis of (4-((5-(2-(di-tert-butoxycarbonyl)-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenyl)methanol tert-butyl carbonate



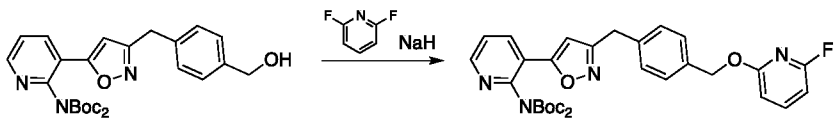
[0625] (4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenyl)methanol (1g, 3.55mmol) was dissolved in THF (8mL) and N,N-dimethylpyridin-4-amine (DMAP, 0.043g, 0.355mmol) and di-tert-butyl dicarbonate ($(Boc)_2O$, 2.72g, 12.44mmol) were added. The mixture was stirred for 15min at 21-25°C and then for another 15min at 50°C. The mixture was loaded directly onto celite and purified by flash chromatography to give (4-((5-(2-(di-tert-butoxycarbonyl)-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenyl)methanol tert-butyl carbonate (1.21g, 2.08mmol, 58%). MS: 604.4 $[M+Na]^+$.

Step 3: Synthesis of (4-((5-(2-(di-tert-butoxycarbonyl)-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenyl)methanol



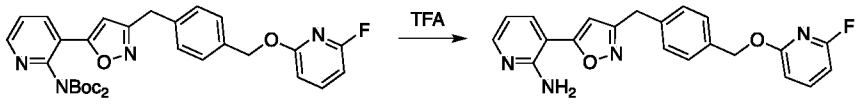
[0626] (4-((5-(2-(di-tert-butoxycarbonyl)-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenyl)methanol tert-butyl carbonate (1g, 1.72mmol) was dissolved in MeOH (20mL) and sodium methanolate (25%Wt in MeOH, 1.86g, 8.60mmol) was added. The mixture was stirred at 21-25°C for 2h. The reaction mixture was poured into a stirring mixture of water (100mL) and ethyl acetate (100mL). The layers were separated and the aqueous phase was further extracted with ethyl acetate (3×40mL). The combined organic layers were washed with brine (40mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to give (4-((5-(2-(di-tert-butoxycarbonyl)-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenyl)methanol (320mg, 0.66mmol, 38%). MS: 482.5 $[M+H]^+$.

Step 4: Synthesis of di-tert-butyl [3-(3-(4-(((6-fluoropyridin-2-yl)oxy)methyl)benzyl)-1,2-oxazol-5-yl)pyridin-2-yl]imidodicarbonate



[0627] Sodium hydride (60% w/mineral oil, 13mg, 0.32mmol) was added at 0°C to a solution of (4-((5-(2-(di-tert-butoxycarbonyl)-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenyl)methanol (130mg, 0.27mmol) and 2,6-difluoropyridine (155mg, 1.35mmol) in DMF (5mL) and the mixture was stirred at 50°C for 30min. The cooled reaction mixture was poured into a stirring mixture of water (50mL) and ethyl acetate (50mL). The layers were separated and the aqueous phase was further extracted with ethyl acetate (3×20mL). The combined organic layers were washed with brine (10mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to obtain di-tert-butyl [3-(3-(4-(((6-fluoropyridin-2-yl)oxy)methyl)benzyl)-1,2-oxazol-5-yl)pyridin-2-yl]imidodicarbonate (116mg, 0.20mmol, 75%). MS: 577.5 $[M+H]^+$.

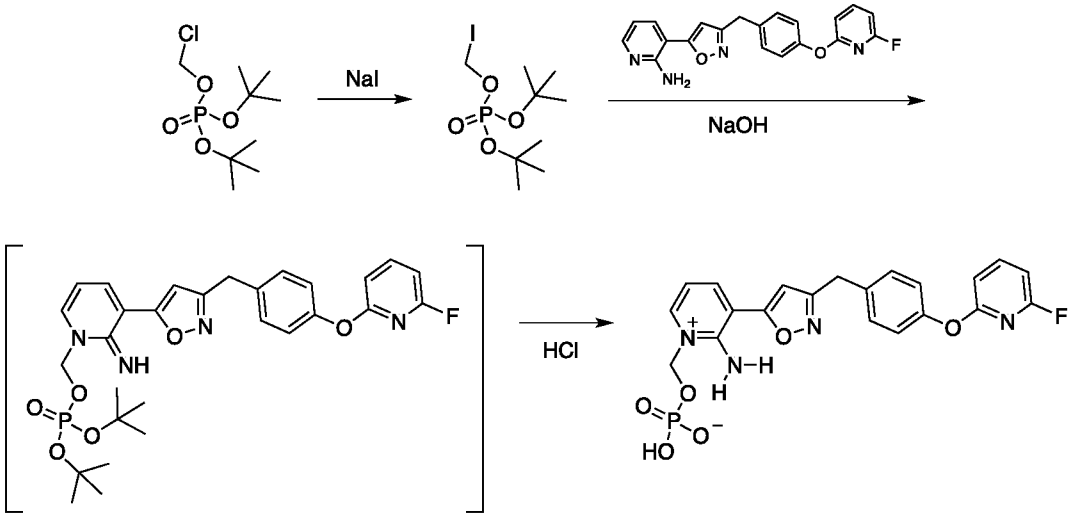
Step 5: Synthesis of 3-(3-(4-(((6-fluoropyridin-2-yl)oxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine



[0628] Di-tert-butyl [3-(3-(4-(((6-fluoropyridin-2-yl)oxy)methyl)benzyl)-1,2-oxazol-5-yl)pyridin-2-yl]imidodicarbonate (116mg, 0.20mmol) was dissolved in DCM (3mL) and dioxane (3mL). TFA (77µL, 1.01mmol) and HCl (4M in dioxane, 0.3mL, 1.20mmol) were added and the mixture was stirred for 3days at 21-25°C. The mixture was poured into an ice-cold mixture of pH7 phosphate buffer solution (0.5M, 50mL) containing an additional amount of NaOH (89mg, 2.22mmol), to neutralize the excess of acids, and ethyl acetate (50mL). The layers were separated and the aqueous phase was further extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to yield 3-(3-(4-(((6-fluoropyridin-2-yl)oxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine (48mg, 0.13mmol, 63%). MS: 377.2 $[M+H]^+$.

[0629] **Examples 138-171** can be synthesized as described in any of the examples above.

[0630] **Example 172**: Synthesis of (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate



[0631] Sodium iodide (2.379g, 15.87mmol) and N-ethyl-N-isopropylpropan-2-amine (0.205g, 1.587mmol) were added to THF (7mL). Di-tert-butyl (chloromethyl) phosphate (2.463g, 9.52mmol) was added and the mixture was stirred at 45°C for 1.5h. 3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine (2.3g, 6.35mmol) and toluene (7mL) were added followed by the addition of sodium hydroxide (5N, 7mL, 35mmol). The mixture was stirred at 45°C for 30min and then for 1h at 23°C. Another batch of freshly prepared iodomethyl phosphate (following the same procedure as described above, but using 1.2g sodium iodide, 0.1g N-ethyl-N-isopropylpropan-2-amine and 1.25g di-tert-butyl (chloromethyl) phosphate in 4mL of THF) was added and the mixture was stirred at 23°C for 12h. The organic layer was separated and the aq. phase extracted 3x with 5mL of mixture of THF/toluene (1:1).

The combined organic layers were cooled to 0°C and 5N HCl (7mL) was added. The mixture was stirred at 23°C for 2h. Water, ice and EtOAc were added and the pH of the aqueous phase was adjusted to 8-10. The aq. layer was extracted 3x with EtOAc and then its pH was adjusted to about 7 to 7.5. The mixture became slightly cloudy during this process, but no significant precipitation occurred. The mixture was now filtered through a plug of reversed phase C18 silica gel (or alternatively a 0.45micrometer PTFE filter). The pH of the clear filtrate was adjusted slowly to 4-5, while precipitation of the product occurred. The mixture was stirred for about 1.5h and the product collected by filtration. The filter cake was thoroughly washed with water and 1x with a small amount of MeOH and finally dried under vacuum to give (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate (1.45g, 3.07mmol, 48 % yield). MS: 473.4 $[M+H]^+$. ^{31}P NMR (200MHz, DMSO-d_6/D_2O) δ 3.61. ^1H NMR (400MHz, DMSO-d_6/D_2O) δ 7.83 (q, J = 8.1 Hz, 1H), 7.73 (d, J = 7.0 Hz, 2H), 7.30 (m, 2H), 7.00 (m, 2H), 6.76 (s, 1H), 6.72 (m, 2H), 6.33 (t, J = 7.0 Hz, 1H), 5.39 (d, J = 7.4 Hz, 2H), 3.99 (s, 2H), signals for -NH_2 and -OH not observed.

[0632] Example 173: Synthesis of (2-amino-3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

[0633] The title compound was prepared according to the procedure of **Example 146** using sodium iodide (944mg, 6.3mmol), N-ethyl-N-isopropylpropan-2-amine (81mg, 0.63mmol), di-tert-butyl (chloromethyl) phosphate (977mg, 3.78mmol), 3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-2-amine (900mg, 2.52mmol) and sodium hydroxide (5N, 2.77mL, 13.85mmol) to give (2-amino-3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate (390mg, 0.83mmol, 33 % yield). ^{31}P NMR (200MHz, DMSO-d_6/D_2O) δ 3.21. ^1H NMR (500MHz, DMSO-d_6/D_2O) δ 7.64 – 7.55 (m, 2H), 7.37 – 7.21 (m, 5H), 7.20 – 7.13 (m, 2H), 6.92 – 6.85 (m, 2H), 6.75 – 6.71 (m, 1H), 6.07 (t, J = 7.0 Hz, 1H), 5.28 (d, J = 6.9 Hz, 2H), 5.00 (s, 2H), 3.88 (s, 2H), signals for -NH_2 and -OH not observed. MS: 468.4 $[M+H]^+$.

[0634] Example 174: Synthesis (2-amino-3-(3-((6-(benzyloxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

[0635] The title compound was prepared similarly to the procedure **Example 146** using sodium iodide (1.5g, 9.8mmol), N-ethyl-N-isopropylpropan-2-amine (0.17 mL, 0.98mmol), di-tert-butyl (chloromethyl) phosphate (1.4mL, 5.9mmol), 3-(3-((6-(benzyloxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (1.4g, 3.9mmol) and sodium hydroxide (5N, 4.4mL, 22mmol) to give (2-amino-3-(3-((6-(benzyloxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate (0.58g, 1.2mmol, 32 % yield). MS: 469.4 $[M+H]^+$.

[0636] Example 175: Synthesis of (2-amino-3-(3-((6-(2-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

[0637] The title compound was prepared according to the procedure of **Example 146** using sodium iodide (2.64g, 17.59mmol), N-ethyl-N-isopropylpropan-2-amine (0.227g, 1.76mmol), di-tert-butyl (chloromethyl) phosphate (2.73g, 10.56mmol), 3-(3-((6-(2-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (2.55g, 7.04mmol) and sodium hydroxide (5N, 7.74mL, 38.7mmol) to give (2-

amino-3-(3-((6-(2-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate (340mg, 0.72mmol, 10 % yield). MS: 473.4 $[M+H]^+$.

[0638] Example 176: (2-amino-3-(3-((6-(3,5-difluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

[0639] The compound was synthesized from Example 81 according to methods described above. MS: 491.1 $[M+H]^+$.

[0640] **Examples 177-184** can be synthesized as described in any of the above examples.

[0641] **Example 185**: 3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-2-amine

[0642] The compound was synthesized from Intermediate A and (4-(benzyloxy)phenyl)boronic acid according to methods described above. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.12 (dd, J = 4.9, 1.8 Hz, 1H), 7.70 (dd, J = 7.7, 1.8 Hz, 1H), 7.47 – 7.27 (m, 5H), 7.26 – 7.16 (m, 2H), 7.02 – 6.90 (m, 2H), 6.70 (dd, J = 7.7, 4.9 Hz, 1H), 6.24 (s, 1H), 5.50 (s, 2H), 5.05 (s, 2H), 4.00 (s, 2H). MS: 358.3 $[M+H]^+$.

[0643] **Example 186**: 3-(3-((6-(phenylthio)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0644] The compound was synthesized from Intermediate E and benzenethiol according to methods described above. MS: 361.3 $[M+H]^+$.

[0645] **Example 187**: 3-(3-((6-((4-fluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0646] The compound was synthesized from Intermediate E and (4-fluorophenyl)methanol according to methods described above. MS: 377.2 $[M+H]^+$.

[0647] **Example 188**: 3-(3-((6-(2-phenylazetidin-1-yl)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0648] The compound was synthesized from Intermediate E and 2-phenylazetidine according to methods described above. MS: 384.2 $[M+H]^+$.

[0649] **Example 189**: 3-(3-(4-((2,5-difluorophenoxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine

[0650] The compound was synthesized from Intermediate B and 2,5-difluorophenol according to methods described above. MS: 393.8 $[M+H]^+$.

[0651] **Example 190**: 3-(3-(4-((2,3,5-trifluorophenoxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine

[0652] The compound was synthesized from Intermediate B and 2,3,5-trifluorophenol according to methods described above. MS: 411.9 $[M+H]^+$.

[0653] **Example 191**: (4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)phenyl)(phenyl)methanone

[0654] The compound was synthesized from Intermediate A and (4-benzoylphenyl)boronic acid according to methods described above. 500 MHz ^{1}H NMR (DMSO-d6) δ 8.10 (dd, J = 4.8, 1.8 Hz, 1H), 7.88 (dd, J = 7.7, 1.8 Hz, 1H), 7.76 – 7.62 (m, 5H), 7.59 – 7.50 (m, 4H), 6.87 (s, 1H), 6.70 (dd, J = 7.7, 4.7 Hz, 1H), 6.28 (s, 2H), 4.17 (s, 2H). MS: 356.1 $[M+H]^+$.

[0655] **Example 192**: 3-(3-(4-((5-fluoro-2-methoxyphenoxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine

[0656] The compound was synthesized from Intermediate B and 5-fluoro-2-methoxyphenol according to methods described above. MS: 406.0 $[M+H]^+$.

[0657] **Example 193**: 3-(3-(4-(((2,3,4-trifluorophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine

[0658] The compound was synthesized from Intermediate B and 2,3,4-trifluoroaniline according to methods described above. MS: 411.1 $[M+H]^+$.

[0659] **Example 194**: (E)-3-(3-(4-(3-phenylprop-1-en-1-yl)benzyl)isoxazol-5-yl)pyridin-2-amine

[0660] The compound was synthesized from Example 97 according to methods described for Example 99, but using allylbenzene. 500 MHz ^{1}H NMR (DMSO-d6) δ 8.08 (dd, J = 4.8, 1.8 Hz, 1H), 7.86 (dd, J = 7.7, 1.8 Hz, 1H), 7.40 – 7.16 (m, 9H), 6.79 (s, 1H), 6.69 (dd, J = 7.7, 4.7 Hz, 1H), 6.50 – 6.36 (m, 2H), 6.25 (s, 2H), 4.00 (s, 2H), 3.51 (d, J = 6.4 Hz, 2H). MS: 368.2 $[M+H]^+$.

[0661] **Example 195**: 3-(3-((6-((2-bromopyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0662] The compound was synthesized from Intermediate E and (2-bromopyridin-4-yl)methanol according to methods described above. MS: 440.2 $[M+H]^+$.

[0663] **Example 196**: 3-(3-(4-(((2,5-difluorophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine

[0664] The compound was synthesized from Intermediate B and 2,5-difluoroaniline according to methods described above. MS: 293.2 $[M+H]^+$.

[0665] **Example 197**: (2-amino-3-(3-((6-(3-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate

[0666] The compound was synthesized from Example 130 according to methods described above. ^{31}P NMR (200MHz, DMSO-d_6/D_2O) δ 5.16. ^{1}H NMR (500MHz, DMSO-d_6/D_2O) δ 8.15 (dd, J = 7.5, 1.5 Hz, 1H), 8.10 – 8.04 (m, 2H), 7.79 (dd, J = 8.5, 2.5 Hz, 1H), 7.38 (td, J = 8.5, 6.9 Hz, 1H), 7.01 – 6.83 (m, 6H), 5.59 (d, J = 8.0 Hz, 2H), 4.04 (s, 2H), signals for -NH_2 and -OH not observed. MS: 473.3 $[M+H]^+$.

[0667] **Example 198**: 3-(3-(4-(((3,5-difluoro-2-methoxyphenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine

[0668] The compound was synthesized from Intermediate B and 3,5-difluoro-2-methoxyaniline according to methods described above. MS: 423.1 $[M+H]^+$.

[0669] **Example 199**: 3-(3-(4-((1H-1,2,4-triazol-1-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine

[0670] The compound was synthesized from Intermediate B and 1H-1,2,4-triazole according to methods described above. 500 MHz ^{1}H NMR (DMSO-d6) δ 8.64 (s, 1H), 8.08 (dd, J = 4.8, 1.8 Hz, 1H), 7.96 (s, 1H), 7.85 (dd, J = 7.7, 1.9 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.28 – 7.22 (m, 2H), 6.79 (s, 1H), 6.69 (dd, J = 7.7, 4.8 Hz, 1H), 6.24 (s, 2H), 5.39 (s, 2H), 4.01 (s, 2H). MS: 333.1 $[M+H]^+$.

[0671] **Example 200**: 3-(3-(4-((4H-1,2,4-triazol-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine

[0672] The compound was synthesized from Intermediate B and 1H-1,2,4-triazole according to methods described above. 500 MHz ^{1}H NMR (DMSO-d6) δ 8.59 (s, 2H), 8.08 (dd, J = 4.8, 1.9 Hz, 1H), 7.85 (dd, J = 7.7, 1.8 Hz, 1H), 7.37 – 7.24 (m, 4H), 6.79 (s, 1H), 6.69 (dd, J = 7.7, 4.7 Hz, 1H), 6.24 (s, 2H), 5.25 (s, 2H), 4.02 (s, 2H). MS: 333.2 $[M+H]^+$.

[0673] **Example 201**: 3-(3-(4-(((3-fluoro-5-methoxyphenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine

[0674] The compound was synthesized from Intermediate B and 3-fluoro-5-methoxyaniline according to methods described above. MS: 405.2 $[M+H]^+$.

[0675] **Example 202**: 3-(3-((6-(2-(1H-1,2,4-triazol-1-yl)ethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0676] The compound was synthesized from Intermediate E and 2-(1H-1,2,4-triazol-1-yl)ethan-1-ol according to methods described above. MS: 364.2 $[M+H]^+$.

[0677] **Example 203**: 3-(3-(4-(pyridin-2-yl)benzyl)isoxazol-5-yl)pyridin-2-amine

[0678] The compound was synthesized from Intermediate A and 4-(2-Pyridinyl)phenylboronic acid pinacol ester according to methods described above. 500 MHz ^{1}H NMR (DMSO-d6) δ 8.79 (ddd, J = 5.5, 1.8, 0.8 Hz, 1H), 8.44 – 8.33 (m, 2H), 8.31 – 8.19 (m, 4H), 8.15 – 8.09 (m, 2H), 7.81 – 7.74 (m, 1H), 7.60 – 7.54 (m, 2H), 7.12 (s, 1H), 7.05 (dd, J = 7.6, 6.2 Hz, 1H), 4.21 (s, 2H). MS: 329.1 $[M+H]^+$.

[0679] **Example 204**: 3-(3-(4-(pyridin-4-yl)benzyl)isoxazol-5-yl)pyridin-2-amine

[0680] The compound was synthesized from Intermediate A and 4-(Pyridin-4-yl)phenylboronic acid pinacol ester according to methods described above. MS: 329.2 $[M+H]^+$.

[0681] **Example 205**: 3-(3-((6-(4-fluorophenyl)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0682] The compound was synthesized from Intermediate A and 6-(4-Fluorophenyl)pyridine-3-boronic acid according to methods described above. 500 MHz ^{1}H NMR (DMSO-d6) δ 8.75 (dd, J = 2.3, 1.0 Hz, 1H), 8.39 (dd, J = 7.7, 1.6 Hz, 1H), 8.28 – 8.02 (m, 7H), 7.42 – 7.33 (m, 2H), 7.12 (s, 1H), 7.05 (dd, J = 7.6, 6.1 Hz, 1H), 4.26 (s, 2H). MS: 347.1 $[M+H]^+$.

[0683] **Example 206**:3-(3-((6-(imidazo[1,2-a]pyridine-7-ylmethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0684] The compound was synthesized from Intermediate E and imidazo[1,2-a]pyridin-7-ylmethanol according to methods described above. MS: 399.2 $[M+H]^+$.

[0685] **Example 207**: 3-(3-((6-((5-fluoro-2-methoxypyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0686] The compound was synthesized from Intermediate E and (5-fluoro-2-methoxypyridin-4-yl)methanol according to methods described above. MS: 408.0 $[M+H]^+$.

[0687] **Example 208**: 3-(3-(4-(3-fluorobenzyl)benzyl)isoxazol-5-yl)pyridin-2-amine

[0688] The compound was synthesized from Intermediate B and (3-fluorophenyl)boronic acid according to methods described above. 500 MHz ^{1}H NMR (DMSO-d6) δ 8.08 (dd, J = 4.8, 1.8 Hz, 1H), 7.86 (dd, J = 7.7, 1.9 Hz, 1H), 7.34 – 7.28 (m, 1H), 7.25 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 7.09 – 7.03 (m, 2H), 7.02 – 6.96 (m, 1H), 6.79 (s, 1H), 6.69 (dd, J = 7.7, 4.8 Hz, 1H), 6.24 (s, 2H), 3.98 (s, 2H), 3.93 (s, 2H). MS: 360.0 $[M+H]^+$.

[0689] **Example 209**: 2-(3-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)phenyl)propan-2-ol

[0690] The compound was synthesized from Intermediate B and (3-(2-hydroxypropan-2-yl)phenyl)boronic acid according to methods described above. MS: 400.3 $[M+H]^+$.

[0691] **Example 210**: 3-(3-((6-((2-chloro-3-fluoropyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine.

[0692] The compound was synthesized from Intermediate E and (2-chloro-3-fluoropyridin-4-yl)methanol according to methods described above. MS: 412.2 $[M+H]^+$.

[0693] **Example 211**: N-(3-(4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)phenyl)methanesulfonamide

[0694] The compound was synthesized from Intermediate B and (3-(methylsulfonamido)phenyl)boronic acid according to methods described above. MS: 435.3 $[M+H]^+$.

[0695] **Example 212**: 3-(3-(4-(3,5-difluorobenzyl)benzyl)isoxazol-5-yl)pyridin-2-amine

[0696] The compound was synthesized from Intermediate B and (3,5-difluorophenyl)boronic acid according to methods described above. 500 MHz ^{1}H NMR (DMSO-d6) δ 8.08 (dd, J = 4.8, 1.9 Hz, 1H), 7.86 (dd, J = 7.7, 1.9 Hz, 1H), 7.25 (q, J = 8.3 Hz, 4H), 7.06 – 6.93 (m, 3H), 6.80 (s, 1H), 6.69 (dd, J = 7.7, 4.7 Hz, 1H), 6.24 (s, 2H), 3.99 (s, 2H), 3.93 (s, 2H). MS: 377.9 $[M+H]^+$.

[0697] **Example 213**: 3-(3-((6-(3-phenylpropoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0698] The compound was synthesized from Intermediate E and 3-phenylpropan-1-ol according to methods described above. MS: 387.2 $[M+H]^+$.

[0699] **Example 214**: 3-(3-((6-(3-(4-(benzyloxy)phenyl)propoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0700] The compound was synthesized from Intermediate E and 3-(4-(benzyloxy)phenyl)propan-1-ol according to methods described above. MS: 493.1 $[M+H]^+$.

[0701] **Example 215**: 3-(3-((6-(2,2-diphenylethoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0702] The compound was synthesized from Intermediate E and 2,2-diphenylethan-1-ol according to methods described above. MS: 449.3 $[M+H]^+$.

[0703] **Example 216**: 3-(3-(4-(3-fluoro-5-methoxybenzyl)benzyl)isoxazol-5-yl)pyridin-2-amine

[0704] The compound was synthesized from Intermediate B and (3-fluoro-5-methoxyphenyl)boronic acid according to methods described above. MS: 390.0 $[M+H]^+$.

[0705] **Example 217**: 3-(3-((6-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0706] The compound was synthesized from Intermediate E and (3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methanol according to methods described above. MS: 472.3 $[M+H]^+$.

[0707] **Example 218**: 3-(3-((6-((3-chloropyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0708] The compound was synthesized from Intermediate E and (3-chloropyridin-4-yl)methanol according to methods described above. MS: 394.1 $[M+H]^+$.

[0709] **Example 219**: 3-(3-((6-((2,6-dichloropyridin-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0710] The compound was synthesized from Intermediate E and (2,6-dichloropyridin-4-yl)methanol according to methods described above. MS: 428.1 $[M+H]^+$.

[0711] **Example 220**: 3-(3-((6-((2-chlorothiazol-4-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0712] The compound was synthesized from Intermediate E and (2-chlorothiazol-4-yl)methanol according to methods described above. MS: 399.9 $[M+H]^+$.

[0713] **Example 221**: 3-(3-((6-((5-chlorothiophen-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0714] The compound was synthesized from Intermediate E and (5-chlorothiophen-2-yl)methanol according to methods described above. MS: 398.9 $[M+H]^+$.

[0715] **Example 222**: 3-(3-((6-((6-chloropyridin-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0716] The compound was synthesized from Intermediate E and (6-chloropyridin-2-yl)methanol according to methods described above. MS: 393.8 $[M+H]^+$.

[0717] **Example 223**: 3-(3-((6-((6-bromopyridin-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0718] The compound was synthesized from Intermediate E and (6-bromopyridin-2-yl)methanol according to methods described above. MS: 440.2 $[M+H]^+$.

[0719] **Example 224**:3-((5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)pyridin-2-yl)oxy)propanenitrile

[0720] The compound was synthesized from Intermediate E and 3-hydroxypropanenitrile according to methods described above. MS: 322.2 $[M+H]^+$.

[0721] **Example 225**: 3-(3-((6-(but-3-yn-1-yloxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0722] The compound was synthesized from Intermediate E and but-3-yn-1-ol according to methods described above. MS: 321.2 $[M+H]^+$.

[0723] **Example 226**: 3-(3-((6-((6-fluoropyridin-2-yl)methoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0724] The compound was synthesized from Intermediate E and (6-fluoropyridin-2-yl)methanol according to methods described above. MS: 377.8 $[M+H]^+$.

[0725] **Example 227**: 3-(3-((6-morpholinopyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0726] The compound was synthesized from Intermediate A and 6-Morpholinopyridin-3-ylboronic acid pinacol ester according to methods described above. MS: 338.5 $[M+H]^+$.

[0727] **Example 228**: 3-(3-(4-(morpholinosulfonyl)benzyl)isoxazol-5-yl)pyridin-2-amine

[0728] The compound was synthesized from Intermediate A and 4-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenylsulfonyl)morpholine according to methods described above. MS: 401.4 $[M+H]^+$.

[0729] **Example 229**: 3-(3-((6-(2-phenylpyrrolidin-1-yl)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0730] The compound was synthesized from Intermediate E and 2-phenylpyrrolidine according to methods described above. MS: 398.2 $[M+H]^+$.

[0731] **Example 230**: 3-(3-((6-(piperidin-1-yl)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0732] The compound was synthesized from Intermediate A and 2-(Piperidin-1-yl)pyridine-5-boronic acid pinacol ester according to methods described above. 500 MHz ^{1}H NMR (HCl-salt, DMSO-d6) δ 8.36 (dd, *J* = 7.4, 1.5 Hz, 1H), 8.21 (dd, *J* = 6.1, 1.6 Hz, 1H), 8.12 (*b*s, 2H), 8.01 (d, *J* = 2.2 Hz, 1H), 7.94 (dd, *J* = 9.4, 2.2 Hz, 1H), 7.42 (d, *J* = 9.5 Hz, 1H), 7.08 (s, 1H), 7.05 (dd, *J* = 7.6, 6.1 Hz, 1H), 4.10 (s, 2H), 3.73 (t, *J* = 5.4 Hz, 4H), 1.70 – 1.57 (m, 6H). MS: 336.4 $[M+H]^+$.

[0733] **Example 231**: 3-(3-(4-(((3-azidophenyl)amino)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine

[0734] The compound was synthesized from Intermediate B and 3-azidoaniline according to methods described above. 500 MHz ^{1}H NMR ($CDCl_3$) δ 8.14 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.70 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.30 – 7.23 (m, 2H), 7.12 (t, *J* = 8.0 Hz, 1H), 6.70 (dd, *J* = 7.7, 4.9 Hz, 1H), 6.43 – 6.37 (m, 2H), 6.28 – 6.21 (m, 2H), 5.39 (s, 2H), 4.30 (s, 2H), 4.16 (s, 1H), 4.05 (s, 2H). MS: 398.2 $[M+H]^+$.

[0735] **Example 232**: 4-((4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)benzyl)amino)-5-fluoropyrimidin-2(1H)-one

[0736] The compound was synthesized from Intermediate B and Flucytosine according to methods described above. MS: 393.3 $[M+H]^+$.

[0737] **Example 233**: (E)-3-(3-(4-(3-fluorostyryl)benzyl)isoxazol-5-yl)pyridin-2-amine

[0738] The compound was synthesized from Example 97 according to methods described for Example 99, but using 1-fluoro-3-vinylbenzene. MS: 371.9 $[M+H]^+$.

[0739] **Example 234**: 3-(3-(4-((6-chloropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine

[0740] The compound was synthesized from Intermediate C and 2,6-dichloropyridine according to methods described above. MS: 378.9 $[M+H]^+$.

[0741] **Example 235**: 3-(3-(4-((3-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine

[0742] The compound was synthesized from Intermediate C and 2,3-difluoropyridine according to methods described above. MS: 363.1 $[M+H]^+$.

[0743] **Example 236**: 3-(3-(4-((5-chloro-3-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine

[0744] The compound was synthesized from Intermediate C and 5-chloro-2,3-difluoropyridine according to methods described above. MS: 397.1 $[M+H]^+$.

[0745] **Example 237**: 5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(2,6-difluorophenyl)pyridin-2-amine

[0746] The compound was synthesized from Intermediate E and 2,6-difluoroaniline according to methods described above. MS: 380.2 $[M+H]^+$.

[0747] **Example 238**: 5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(3,5-difluorophenyl)pyridin-2-amine

[0748] The compound was synthesized from Intermediate E and 3,5-difluoroaniline according to methods described above. MS: 380.0 $[M+H]^+$.

[0749] **Example 239**: 3-(3-(4-((4,6-difluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine

[0750] The compound was synthesized from Intermediate C and 2,4,6-trifluoropyridine according to methods described above. MS: 380.9 $[M+H]^+$.

[0751] **Example 240**: 3-(3-(4-((4-chlorothiazol-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine

[0752] The compound was synthesized from Intermediate C and 2,4-dichlorothiazole according to methods described above. MS: 385.1 $[M+H]^+$.

[0753] **Example 241**: 3-(3-(4-((3,5,6-trifluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine

[0754] The compound was synthesized from Intermediate C and 2,3,5,6-tetrafluoropyridine according to methods described above. MS: 398.9 $[M+H]^+$.

[0755] **Example 242**: 3-(3-(4-((3,5-difluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine

[0756] The compound was synthesized from Intermediate C and 2,3,5-trifluoropyridine according to methods described above. MS: 380.9 $[M+H]^+$.

[0757] **Example 243**: 3-(3-(4-(pyrimidin-2-yloxy)benzyl)isoxazol-5-yl)pyridin-2-amine

[0758] The compound was synthesized from Intermediate C and 2-chloropyrimidine according to methods described above. MS: 346.0 $[M+H]^+$.

[0759] **Example 244**: 5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(2,5-difluorophenyl)pyridin-2-amine

[0760] The compound was synthesized from Intermediate E and 2,5-difluoroaniline according to methods described above. MS: 380.1 $[M+H]^+$.

[0761] **Example 245**: 5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(2,3,4-trifluorophenyl)pyridin-2-amine

[0762] The compound was synthesized from Intermediate E and 2,3,4-trifluoroaniline according to methods described above. MS: 398.0 $[M+H]^+$.

[0763] **Example 246**: 3-(3-(4-((5-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine

[0764] The compound was synthesized from Intermediate C and 2,5-difluoropyridine according to methods described above. MS: 363.1 $[M+H]^+$.

[0765] **Example 247**: 3-(3-((6-(cyclopropylmethoxy)-5-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0766] The compound was synthesized from Intermediate J and cyclopropylmethanol according to methods described above. MS: 340.7 $[M+H]^+$.

[0767] **Example 248**: 3-(3-((2-(3,5-difluorophenoxy)pyrimidin-5-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0768] 3,5-difluorophenol (109mg, 0.834mmol) was dissolved in DMF (0.5mL) and KOtBu (1M in THF, 730µL, 0.730mmol) was added dropwise. The mixture was stirred for 5min and a solution of 3-(3-((2-chloropyrimidin-5-yl)methyl)isoxazol-5-yl)pyridin-2-amine (Intermediate L, 30mg, 0.104mmol) in DMF (0.5mL) was added. The resulting mixture was stirred for 1h at 60°C and directly purified by flash chromatography to give 3-(3-((2-(3,5-difluorophenoxy)pyrimidin-5-yl)methyl)isoxazol-5-yl)pyridin-2-amine (17mg, 0.045mmol, 42.8 % yield). 500 MHz ^{1}H NMR (DMSO-d6) δ 8.70 (s, 2H), 8.10 (dd, *J* =

4.8, 1.8 Hz, 1H), 7.86 (dd, J = 7.7, 1.9 Hz, 1H), 7.21 – 7.06 (m, 3H), 6.89 (s, 1H), 6.71 (dd, J = 7.7, 4.8 Hz, 1H), 6.28 (s, 2H), 4.10 (s, 2H). MS: 382.0 $[M+H]^+$.

[0769] **Example 249**: 3-(3-((2-((3-fluorobenzyl)oxy)pyrimidin-5-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0770] The compound was synthesized from Intermediate L and according to methods described above. MS: 378.1 $[M+H]^+$.

[0771] **Example 250**: 5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-3-fluoro-N-(2-fluorophenyl)pyridin-2-amine

[0772] The compound was synthesized from Intermediate J and 2-fluoroaniline according to methods described above. MS: 380.0 $[M+H]^+$.

[0773] **Example 251**: 3-(3-((5-fluoro-6-((3-fluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0774] The compound was synthesized from Intermediate J and (3-fluorophenyl)methanol according to methods described above. MS: 394.7 $[M+H]^+$.

[0775] **Example 252**: 3-(3-((6-(3,5-difluorophenoxy)-5-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0776] The compound was synthesized from Intermediate J and 3,5-difluorophenol according to methods described above. MS: 398.5 $[M+H]^+$.

[0777] **Example 253**: 5-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-N-(2,6-difluorophenyl)-3-fluoropyridin-2-amine

[0778] The compound was synthesized from Intermediate J and 2,6-difluoroaniline according to methods described above. MS: 398.0 $[M+H]^+$.

[0779] **Example 254**: 3-(3-((5-fluoro-6-(2-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0780] The compound was synthesized from Intermediate J and 2-fluorophenol according to methods described above. MS: 380.9 $[M+H]^+$.

[0781] **Example 255**: 3-(3-((5-fluoro-6-phenoxypyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0782] The compound was synthesized from Intermediate J and phenol according to methods described above. MS: 362.7 $[M+H]^+$.

[0783] **Example 256**: 3-(3-((5-fluoro-6-(3-fluorophenoxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0784] The compound was synthesized from Intermediate J and 3-fluorophenol according to methods described above. MS: 380.8 $[M+H]^+$.

[0785] **Example 257**: 3-(3-((6-(benzyloxy)-5-fluoropyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0786] The compound was synthesized from Intermediate J and benzyl alcohol according to methods described above. MS: 376.6 $[M+H]^+$.

[0787] **Example 258**: 3-(3-(3-fluoro-4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine

[0788] 4-((5-(2-aminopyridin-3-yl)isoxazol-3-yl)methyl)-2-fluorophenol (Intermediate K, 100mg, 0.351mmol) was dissolved in DMF (1mL) and potassium 2-methylpropan-2-olate (1M in THF, 421μL, 0.421mmol) was added dropwise. The mixture was stirred for 5min and a solution of 2,6-difluoropyridine (81mg, 0.701mmol) in DMF (0.5mL) was added. The resulting mixture was stirred for 16h at 60 °C and directly purified by flash chromatography to give 3-(3-(3-fluoro-4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine. 500 MHz ^{1}H NMR (DMSO-d6) δ 8.10 (dd, J = 4.8, 1.8 Hz, 1H), 8.05 (q, 1H), 7.89 (dd, J = 7.6, 1.8 Hz, 1H), 7.40 (dd, J = 11.6, 2.0 Hz, 1H), 7.33 (t, 1H), 7.23 (ddd, J = 8.3, 1.9, 0.8 Hz, 1H), 7.04 (dd, J = 7.9, 1.5 Hz, 1H), 6.94 – 6.85 (m, 2H), 6.71 (dd, J = 7.7, 4.8 Hz, 1H), 6.29 (s, 2H), 4.11 (s, 2H). MS: 380.9 $[M+H]^+$.

[0789] **Example 259**: 3-(3-(3-fluoro-4-(pyrimidin-2-yloxy)benzyl)isoxazol-5-yl)pyridin-2-amine

[0790] The compound was synthesized from Intermediate K and 2-chloropyrimidine according to methods described above. MS: 363.9 $[M+H]^+$.

[0791] **Example 260**: 3-(3-((5-fluoro-6-((2-fluorobenzyl)oxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine

[0792] The compound was synthesized from Intermediate J and (2-fluorophenyl)methanol according to methods described above. MS: 394.7 $[M+H]^+$.

[0793] **Example 261**: 3-(3-(4-((2,6-difluoropyridin-4-yl)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine

[0794] The compound was synthesized from Intermediate B and (2,6-difluoropyridin-4-yl)boronic acid according to methods described above. MS: 379.3 $[M+H]^+$.

[0795] **Examples 262-495** can be synthesized as described in any of the examples above.

[0796] **Example 496:** Evaluation of compound activity against *C. neoformans* and *C. gattii* isolates

[0797] In this study, compound activity against *C. neoformans* and *C. gattii* isolates were evaluated. N-phosphonooxymethyl prodrugs of these molecules were synthesized and two of these prodrugs were evaluated in a disseminated *C. neoformans* infection model where 100 mg/kg ABT had been administered orally 2 h prior to therapy.

[0798] Cryptococcal meningitis (CM), caused primarily by *Cryptococcus neoformans*, is uniformly fatal if not treated. Treatment options are limited especially in resource-poor geographical regions, and mortality rates remain high despite current therapies. Here, the *in vitro* and *in vivo* activity of several compounds including **Compound 2** and its prodrug **Compound 1** were evaluated. These compounds target the conserved Gwt1 enzyme that is required for the localization of glycosylphosphatidyl inositol (GPI)-anchored cell wall mannoproteins in fungi.

[0799] The Gwt1 inhibitors had low MIC values, ranging from 0.004 μg/mL to 0.5 μg/mL against both *C. neoformans* and *C. gattii*. **Compound 2** and 3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-2-amine demonstrated *in vitro* synergy with fluconazole (FICI 0.37). In a CM model, **Compound 1** and fluconazole each, alone, reduced $\log_{10}$ colony forming units (CFU)/g brain (0.78 and 1.04, respectively), whereas the combination resulted in a reduction of 3.52 $\log_{10}$ CFU/g brain.

[0800] Efficacy as measured by a reduction in brain and lung fungal burden was also observed for another Gwt1 inhibitor prodrug, (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-

yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate, where dose dependent reductions in fungal burden ranged between 5.91 and 1.79 $\log_{10}$ CFU/g lung and between 7.00 and 0.92 $\log_{10}$ CFU/g brain, representing near or complete sterilization of lung and brain tissue at the higher doses. These data support further clinical evaluation of this new class of antifungal agents for CM.

In vitro* activity of Gwt1 inhibitors vs *Cryptococcus

[0801] Antifungal susceptibility profile. Several compounds were highly active against all 4 fungal strains evaluated (**Table 3**), with MIC or MEC values ranging from 0.004 to 0.25 μg/mL against *C. neoformans, C. gattii, Candida albicans* and *Aspergillus fumigatus*. When compared to the MIC values of **Compound 2** vs *Cryptococcus,* 3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-2-amine and 3-(3-((6-(benzyloxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine demonstrated 4 to 8-fold lower MIC values, whereas 3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine demonstrated 32-fold lower MIC values. (**Table 3**).

Table 3. *In vitro* susceptibility profiles of Gwt1 Inhibitors

Compound	Prodrug	MIC[2] (μg/mL)			MIC or MEC[2] (μg/mL)
		C. neoformans H99	*C. gattii* WM276	*C. albicans* 90028	*A. fumigatus* MYA3626
Compound 2	Compound 1	0.25	0.125	0.008	0.008
Ex. 185	Ex. 173	0.031	0.031	0.016	0.016
Ex. 111	Ex. 172	0.008	0.004	0.031	0.063
Ex. 142	Ex. 174	0.031	0.016	0.031	0.008
AMB	--	0.25	0.25	1	1
FLC	--	2	1	0.5	>16
CAS	--	ND[1]	ND	0.5	0.25

[0802] Gwt1 inhibitors are synergistic with FLC. The synergy of **Compound 2** and 3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-2-amine in combination with FLC using standard microtiter dilution techniques was evaluated. Synergy (FICI values <0.5) was observed for both compounds *vs C. neoformans* H99: FLC/ **Compound 2** (0.37), FLC/3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-2-amine (0.37). Importantly, no antagonism was observed.

[0803] The activity of Gwt1 inhibitors against susceptible and FLC non-susceptible/resistant strains. The activities of **Compound 2**, 3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-2-amine, 3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine, 3-(3-((6-(benzyloxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine, AMB and FLC were examined against a collection of susceptible and FLC nonsusceptible/resistant (MIC ≥16 μg/mL) strains of *C. neoformans* and *C. gattii*. 3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine was the most active compound tested with MIC values ranging between 0.004 to 0.031 μg/mL against all 18 strains tested, followed by

3-(3-((6-(benzyloxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine (range 0.016 to 0.125 μg/mL), 3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-2-amine (range 0.031 to 0.25 μg/mL), and **Compound 2** (range 0.125 to 0.5 μg/mL) (**Table 2**). Consistent with different mechanisms of action, the activities of the exemplary compounds as well as AMB were unchanged for FLC-resistant strains DUMC118 and RSA-MW-3615, relative to susceptible strains (**Table 2**). FLC-resistant *C. neoformans* DUMC158.03 demonstrated somewhat higher MIC values for the four exemplary compounds as well as AMB, suggesting that additional non-target-based mutations may be present in this strain.

In vivo* activity of Gwt1 inhibitors vs *C. neoformans

[0804] Efficacy of Compound 1 alone and in combination with FLC in a murine model of cryptococcal meningitis. The efficacy of **Compound 1** and FLC were evaluated in a well-established mouse CM model. Since *Cryptococcus* infections can be hematogenously disseminated to other organs, both lung and brain CFU were evaluated. Male CD-1 mice were infected with 5.9×10^4 CFU *C. neoformans* strain H99 via lateral tail vein injection. Mice were assigned to four groups (n=10) consisting of: a) treatment with **Compound 1**; b) treatment with **Compound 1** plus FLC, c) treatment with FLC, or d) no treatment control. Treatment was initiated within 1 h after infection. **Compound 1** was administered by oral gavage at a dose of 390 mg/kg thrice daily, roughly eight hours apart. ABT was not used in this model, thus TID dosing of **Compound 1** was necessitated by the short half-life of **Compound 2** in mice (1.40 to 2.75 h) (34). FLC (2 mg/mL, Sagent Pharmaceuticals, Schaumburg, IL) was administered at a dose of 80 mg/kg/day intraperitoneally (IP).

[0805] The mean $\log_{10}$ CFU/g brain and lung counts in untreated control mice were 7.81 ± 0.19 and 5.97 ± 0.47, respectively. Significant differences ($P = <0.05$) in lung fungal burden were observed in all treatment groups (**Compound 1**, FLC, and **Compound 1** plus FLC) as compared to the untreated control. In lung, the $\log_{10}$ CFU/g reductions in fungal burden were similar for all three treatments groups as compared to the untreated control: **Compound 1** (1.50), FLC (1.30) and combined therapy (1.84), with no statistically significant differences between the treatment groups.

[0806] In brain, mice treated with **Compound 1** demonstrated a reduction of 0.78 $\log_{10}$ CFU/g fungal burden versus the control group, which was not significantly different. However, significant reductions in $\log_{10}$ CFU/g fungal burden versus the control group were observed for FLC alone (1.04) and the combination of **Compound 1** and FLC (3.51) (P <0.01 and P <0.001, respectively).

[0807] Effect of ABT on the pharmacokinetics of exemplary compounds.

[0808] The PK of **Compound 2**, 3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine, 3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-2-amine and 3-(3-((6-(benzyloxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine were compared in male CD-1 mice after the administration of 26 mg/kg of the corresponding prodrug (**Compound 1**, (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate, (2-amino-3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate, (2-amino-3-(3-((6-(benzyloxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate) either orally or by IP injection (**Table 4**). In half of the cohorts, 100 mg/kg ABT was administered 2 h prior to

compound administration. Although the AUC values of the analytes differed up to 4-fold after oral administration of the four prodrugs, the addition of ABT resulted in similar exposures for **Compound 2**, 3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-2-amine and 3-(3-((6-(benzyloxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine. The resulting exposure for 3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine was approximately 2-fold higher than the three other compounds evaluated. The addition of ABT resulted in 8.6 to 15-fold increased exposure after oral administration of the prodrugs.

Table 4. Exposures of Gwt1 Inhibitors Following Oral or IP Dosing of Prodrugs in the Presence or Absence of 100 mg/kg ABT Pre-Treatment

Prodrug	Analyte	Average AUC[1] (μg·h/mL) resulting from 26 mg/kg dose				Ratio +ABT/ -ABT (PO)	Ratio +ABT/ -ABT (IP)
		PO	IP	PO + ABT	IP + ABT		
Compd. 1	Compd. 2	2.76 ± 0.23	4.36 ± 0.11	41.50 ± 8.09	24.28 ± 17.74	15.0	5.6
Ex. 172	Ex. 111	10.66 ± 0.48	11.75 ± 1.83	91.28 ± 20.75	97.25 ± 12.61	8.6	8.3
Ex. 173	Ex. 185	4.49 ± 2.32	4.31 ± 0.96	41.94 ± 6.41	35.61 ± 28.22	9.3	8.3
Ex. 174	Ex. 142	3.49 ± 0.27	4.68 ± 0.73	49.92 ± 10.34	72.62 ± 9.07	14.3	15.5

[0809] When the prodrugs were administered IP, similar exposures were obtained for the analytes **Compound 2**, 3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-2-amine and 3-(3-((6-(benzyloxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine, while 3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine demonstrated an approximately 2-fold higher AUC than the other compounds evaluated (**Table 4**). The addition of ABT prior to IP drug administration increased exposures from 5.6 to 15.5-fold. IP dosing was chosen as the route of administration for **Compound 1**, (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate and (2-amino-3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate in the CM model.

[0810] Efficacy of exemplary compounds in a murine model of cryptococcal meningitis when dosed in the presence of the pan-CYP inhibitor ABT. In a preliminary experiment, the efficacies of **Compound 1**, (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate and (2-amino-3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate were evaluated in the disseminated model of CM (n=5 mice/cohort). 100 mg/kg ABT was administered orally to male CD-1 mice 2 h prior to compound administration. Mice were injected with 6.9×10^4 CFU *C. neoformans* strain H99 per mouse via lateral tail vein at T= 0 h. Treatment with each prodrug was initiated about 1 h post-infection by IP administration and continued daily for 7 days with

100 mg/kg ABT administered orally 2 h prior to each dose of compound . The mean log_{10} CFU/g brain and lung counts in untreated control mice were 7.83 ± 0.09 and 4.67 ± 0.88, respectively **(FIG. 1)**.

[0811] In lung, neither the 34 mg/kg or the 85 mg/kg dose of **Compound 1** achieved a statistically significant reduction in log_{10} CFU/g tissue vs the untreated control. Of note is that 390 mg/kg **Compound 1** dosed orally TID results in higher AUC values than 85 mg/kg **Compound 1** dosed IP QD with ABT **(FIG. 2)**, thus better efficacy in lung was observed with **Compound 1** monotherapy. In lung, administration of 60 mg/kg or 34 mg/kg (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate reduced tissue burdens below the limit of detection (approximately 4.67 log_{10} CFU/g lung tissue). For (2-amino-3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate, the reduction of CFU in lung was 3.28 log_{10} CFU/g (85 mg/kg QD) and 1.07 log_{10} CFU/g (34 mg/kg QD).

[0812] In brain, administration of 60 mg/kg or 34 mg/kg (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate resulted in a reduction of 7.13 and 7.05 log_{10} CFU/g brain tissue, respectively. For (2-amino-3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate, the reduction of CFU in brain was 2.72 log_{10} CFU/g (85 mg/kg QD) and 1.66 log_{10} CFU/g (34 mg/kg QD). Administration of 85 mg/kg **Compound 1** demonstrated a modest reduction in log_{10} CFU/g (0.85), which did not, however, achieve statistical significance.

[0813] A dose response study was performed with (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate and (2-amino-3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate to confirm the observed activity. In this study, QD doses of 7.5, 20 and 60 mg/kg were evaluated in conjunction with the administration of ABT. A 60 mg/kg dose QD without ABT was also evaluated as a control.

[0814] The mean log_{10} CFU/g tissue counts in untreated control mice were 7.83 ± 0.07 (brain) and 5.91 ± 0.24 (lung) **(FIG. 2)**. Control animals which received daily doses of 100 mg/kg ABT without compound had log_{10} CFU/g tissue values of 8.07 ± 0.28 (brain) and 7.04 ± 0.34 (lung).

[0815] Both (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate and (2-amino-3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate demonstrated a dose response in the reduction of log_{10} CFU/g brain and lung tissue when ABT was utilized. Cohorts which received 60 mg/kg/day of exemplary compounds without ABT showed either a numerical but non-significant reduction in lung burden of 0.74 log_{10} CFU/g ((2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate) or no reductions in log_{10} CFU/g mouse tissue, consistent with a shorter half-life and lower exposure.

[0816] For (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate with ABT, dose dependent reductions in log_{10} CFU/g ranged between 5.91 to 1.79 for lung and between 7.00 to 0.92 for brain. All ABT plus (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate treatment cohorts

demonstrated reductions in fungal lung burden that were statistically significant from the ABT-administered control group ($P \leq 0.05$). The two highest ABT plus (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate dosing levels also showed reductions in brain fungal burden, ranging from 6.99 to 2.95 $\log_{10}$ CFU/g ($P \leq 0.05$)

[0817] For (2-amino-3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate, dose dependent changes in $\log_{10}$ CFU/g ranged between a reduction of 1.55 $\log_{10}$ CFU/g to an increase of 1.20 for lung and between a reduction of 1.45 to an increase of 0.24 for brain. However, none of these reductions reached statistical significance vs the ABT-administered control group. Statistical significance was also not achieved when these cohorts were evaluated versus the no ABT vehicle control.

[0818] The results of the dose response experiment were consistent with the preliminary finding that (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate demonstrated near or complete sterilization of lung and brain tissue at doses of 34 and 60 mg/kg (plus ABT).

[0819] **Analysis of AUC values vs change in $\log_{10}$ CFU/g tissue.** The three compounds evaluated in the efficacy model had MIC values for the infecting strain (*C. neoformans* H99) that differed by 8 to 32-fold: **Compound 2** (0.25 μg/mL), 3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-2-amine (0.031 μg/mL), and 3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine (0.008 μg/mL) (**Table 1**). The data in **Table 4** show that AUC values after IP dosing (plus ABT) ranged from 24.3 to 97.3 μg·h/mL, representing a 4-fold difference. To understand the influence of AUC vs MIC differences, the magnitude of $\log_{10}$ CFU/g tissue changes across the three experiments were assessed.

[0820] AUC values across the three experiments for **Compound 1** (with or without ABT) ranged from 7.0 μg·h/mL (7.5 mg/kg **Compound 1** QD plus ABT) to 196.3 μg·h/mL (390 mg/kg TID). At an AUC of 196.3 μg·h/mL, a modest but significant reduction in lung burden was observed (1.5 $\log_{10}$ CFU/g). Lower AUC values were not efficacious. AUC values ranged from 10.0 to 116.4 μg·h/mL for (2-amino-3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate, and from 27 to 224.3 μg·h/mL for (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate. The efficacy of the three compounds at a dose that gave rise to similar AUC values were compared.

[0821] *AUC values of approximately 80 μg·h/mL.* In the presence of ABT, doses of 20 mg/kg (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate, 60 mg/kg (2-amino-3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate, and 80 mg/kg **Compound 1** resulted in very similar AUC values of 74.8, 82.1, and 79.4 μg·h/mL respectively. However, $\log_{10}$ CFU/g brain reductions were 2.95, 1.45 and 0.85, respectively and $\log_{10}$ CFU/g lung reductions were 3.69, 1.55 and 0.9. Thus, despite the same AUC values for the 3 compounds, better efficacy was associated with lower MIC values (0.008 μg/mL, 0.031 μg/mL and 0.25 μg/mL, respectively) suggesting that improved microbiological activity largely accounts for improved efficacy

[0822] Efficacy of (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate and AMB in a delayed model of cryptococcal meningitis. A delayed treatment model was used to compare the efficacy of once daily treatment using 60 mg/kg (IP) (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate, 3 mg/kg (IP) AMB vs vehicle control (IP 5% dextrose). As in the previous mouse model, 100 mg/kg ABT (PO) was administered 2 h prior to each (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate dose (n=5 mice/cohort). Infection was initiated on Day 1 and treatment was initiated 24 h later (Day 2) rather than 1 h. Treatments were administered for 7 days (final dose on Day 8) and mice were sacrificed on Day 9 for CFU enumeration.

[0823] The mean $\log_{10}$ CFU/g tissue counts in untreated control mice were 8.15 ± 0.24 (brain) and 6.22 ± 0.93 (lung) **(FIG. 3).** Both (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate and AMB demonstrated a statistically significant reduction of $\log_{10}$ CFU/g lung (4.59 and 4.02, respectively) vs the untreated control group ($P \leq 0.05$). (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate also showed a reduction of 6.84 $\log_{10}$ CFU/g brain vs the untreated control, which was significant ($P \leq 0.01$). These data are very similar to the reductions observed in the 60 mg/kg (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate plus ABT cohort shown **FIG. 2**, demonstrating the reproducibility of these findings. Although AMB demonstrated a 4.40 $\log_{10}$ CFU/g brain reduction, this did not meet statistical significance.

[0824] Two additional compounds, 3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-2-amine and 3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine, demonstrated 8 to 32-fold improved anti-*C. neoformans* H99 activity with MIC values of 0.031 and 0.008 μg/mL, respectively compared to **Compound 2**. This difference in activity was also seen against a larger panel of 18 isolates where MIC_{90} values were 0.5 μg/mL (**Compound 2**), 0.25 μg/mL (3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-2-amine) and 0.031 μg/mL (3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine) (**Table 4**). These values compare favorably to other drugs in clinical use for CM. In a global study that evaluated antifungal activity versus 46 strains of *C. neoformans,* MIC_{90} values for the azoles range from 0.06 μg/mL (isavuconazole) to 4 μg/mL (FLC), whereas the echinocandins were largely inactive with MIC_{90} values ≥ 16 μg/mL (35). Similarly, in a study of US isolates, MIC_{90} values versus *C. neoformans* were: AMB (2 μg/mL), and 5-flucytosine (8 μg/mL), with only itraconazole (0.125 μg/mL) and ketoconazole (0.06 μg/mL) demonstrating low MIC_{90} values.

Table 4. Activity of Gwt1 Inhibitors vs Susceptible and FLC Non-Susceptible/Resistant Strains of *Cryptococcus*

Species	Isolate	MIC (μg/mL)					
		001A	2020	2039	2041	AMB	FLC
C. neoformans	H99	0.125	0.031	0.004	0.031	0.25	1

Species	Isolate	MIC (μg/mL)					
		001A	2020	2039	2041	AMB	FLC
C. neoformans	DUMC 118.00	0.25	0.063	0.016	0.063	0.25	64
C. neoformans	DUMC 158.03	0.25	0.25	0.031	0.125	1	32
C. neoformans	MYA-4564	0.125	0.063	0.004	0.016	0.25	4
C. neoformans	MYA-4565	0.5	0.25	0.031	0.125	0.125	1
C. neoformans	MYA-4566	0.25	0.125	0.008	0.063	0.25	2
C. neoformans	MYA-4567	0.25	0.063	0.016	0.031	0.25	1
C. neoformans	14116	0.125	0.031	0.004	0.016	0.25	4
C. neoformans	76484	0.125	0.063	0.004	0.016	0.25	4
C. gattii	RSA-MW-3615	0.125	0.031	0.004	0.016	0.25	64
C. gattii	MYA-4877	0.25	0.063	0.008	0.016	0.25	4
C. gattii	MYA-4093	0.5	0.125	0.016	0.125	0.25	2
C. gattii	MYA-4094	0.25	0.25	0.016	0.063	0.25	2
C. gattii	MYA-4560	0.25	0.063	0.008	0.016	0.063	1
C. gattii	MYA-4561	0.5	0.125	0.016	0.031	0.25	4
C. gattii	MYA-4562	0.25	0.125	0.016	0.031	0.25	2
C. gattii	MYA-4563	0.5	0.125	0.016	0.031	0.125	4
C. gattii	MYA-4560	0.25	0.063	0.008	0.016	0.063	1
GEOMEAN		0.241	0.085	0.010	0.034	0.215	3.564
MIC_{90}		0.5	0.25	0.031	0.125	0.25	64

[0825] In this study, a collection of clinically isolated FLC-susceptible and FLC-nonsusceptible/resistant strains of *C. neoformans* and *C. gattii* were examined. Consistent with a different mechanism of action, the potency of the four Gwt1 compounds relative to FLC was maintained, although one strain (DUMC 158.03) had higher MIC values for the exemplary compounds as well as AMB, suggesting that additional non-target-based mutations may be present in this strain. Despite the elevated MIC values for this strain, it is anticipated that appropriate clinical exposures may still be achieved for coverage of these types of strains.

[0826] Standard microtiter checkerboard dilution experiments demonstrated that both **Compound 2** and 3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-2-amine are synergistic with FLC *vs C. neoformans* H99. These data are consistent with previous reports of **Compound 2** synergy with FLC against 9 of 10 *Candida tropicalis* strains and 2 of 20 strains of *C. albicans*. Importantly, no antagonism was observed.

Improved activity in combination with FLC was also observed in the CM mouse model. Monotherapy of **Compound 1** or FLC resulted in a reduction of 0.78 and 1.04 $\log_{10}$ CFU/g brain tissue vs the untreated control, whereas the combination of **Compound 1** and FLC resulted in a reduction of 3.52 $\log_{10}$ CFU/g brain tissue as compared to control. This combination therapy was significantly more active in the reduction of fungal burden in the brain than monotherapy with **Compound 1**.

[0827] ABT has been used to increase exposure of drugs in other therapeutic animal models; however, the use of ABT for improving efficacy in infectious disease models has not been widespread. Two studies utilized ABT in short-term models, where $\log_{10}$ CFU/g tissue were examined after 24 to 48 h. The antibacterial efficacy of experimental adenosine analogs targeting DNA ligase were evaluated at 24 h post-infection in a thigh model in which mice received a single dose of 100 mg/kg ABT 2 h prior to infection to reduce the high hepatic clearance. The efficacy of **Compound 1** was examined after ABT administration in disseminated *Candida* infection models where *C. albicans* kidney burdens were reduced 6.0 ± 0.1 $\log_{10}$ CFU/g kidney after 48 h. Since efficacy models can require treatments lasting 7 days or longer, the ability to maintain good drug exposures by administration of ABT over the treatment period is important. One study examined the pharmacokinetic parameters of antipyrine in mice administered as a 14-day continuous infusion of 20 or 60 mg ABT per ALZET osmotic pump. In that study AUC values increased 3 to 4-fold when antipyrine was dosed intravenously (IV) and 8 to 10-fold after oral administration, demonstrating the feasibility of long-term ABT administration. Here, it was shown that 7 days of daily administration of 100 mg/kg ABT 2 h prior to treatment with exemplary compounds dramatically increased the efficacy of three Gwt1 inhibitors. Pharmacokinetic studies demonstrated that ABT increased exposures 5.6 to 15.5-fold when exemplary molecules were dosed orally, and 8.6 to 15-fold, when exemplary molecules were dosed IP. These data support the use of ABT in infectious disease animal models for analysis of both clinical candidates and early discovery molecules, where proof-of-concept data are required.

[0828] Clinical studies have clearly shown that rapid killing of cryptococcal cells in the CNS is associated with an improved host outcome. The animal model data of the present disclosure provide evidence of effective brain penetration, one of the key factors in the choice of a drug for the treatment of CM. These data are consistent with ^{14}C- **Compound 1** distribution studies which demonstrated significant radioactivity in tissues associated with invasive fungal infections, including brain tissue; whereas poor CNS penetration has been observed for the echinocandins. Notably, (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate significantly reduced lung and brain tissue fungal burden in a murine CM model, where in past experience, only AMB has shown a similar reduction in CFU in this model. In the current study, (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate was at least comparable to or better than AMB in a delayed treatment model. Thus, an oral agent, with the potential to kill yeasts rapidly in the CNS of a host, such as (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate, is of significant interest. Further pharmacodynamics studies will be performed after the optimal Gwt1 inhibitor is identified.

[0829] **Example 497**: Materials and Methods

[0830] **Isolates tested.** *C. neoformans* strains H99, DUMC 118.00, DUMC 158.03 and *C. gattii* strains R272, and RSA-MW-3515 were obtained from Duke University. *C. albicans* 90028, *A. fumigatus* MYA3626, *C. neoformans* 14116, *C. neoformans* 76484 and the pathogenic *Cryptococcus* reference strains panel (ATCC MP-11) were obtained from American Type Culture Collection (ATCC, Manassas, VA, USA). The MP-11 panel consists of strains representing eight molecular types and three subtypes of *C. neoformans* and *C. gattii*.

[0831] **Antifungal agents.** All drug stock solutions were prepared at 10 mg/mL in 100% dimethyl sulfoxide (DMSO) and aliquots stored at -20°C: AMB (VWR, Radnor, PA, USA), FLC, (Alfa Aesar, Tewksbury, MA, USA or Sagent Pharmaceuticals, Schaumburg, IL), caspofungin (Sigma, St. Louis, MO, USA), **Compound 2**, 3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-2-amine 3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine, 3-(3-((6-(benzyloxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine.

[0832] For pharmacokinetic and efficacy studies, the prodrugs **Compound 1**, (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate, (2-amino-3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate, (2-amino-3-(3-((6-(benzyloxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate were used. **Compound 1**, the N-phosphonooxymethyl prodrug, is soluble in water. On adding **Compound 1** to water, the pH is less than 7.0. Sodium hydroxide was added to bring pH back to a neutral range, maintain solubility, and allow dosing of the formulated material. Prodrugs (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate, (2-amino-3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate and (2-amino-3-(3-((6-(benzyloxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate were formulated similarly to enable oral and IP dosing of compounds for pharmacokinetic and efficacy studies. Final prodrug solutions were in 5% dextrose and dosed orally (PO) or IP on a per gram mouse body daily weight basis. A 10 mg/mL solution of ABT (Fisher Scientific, Hampton, NH) in water was administered orally 2 h prior to infection as 10 μL per gram mouse body weight resulting in a dose of 100 mg/kg.

[0833] **Antifungal susceptibility testing.** To establish antimicrobial activity, broth microdilution susceptibility testing was performed according to Clinical and Laboratory Standards Institute (CLSI) guidelines M27-A3 for yeasts and M38-A2 for molds. **Compound 2** and analogs were first diluted in DMSO to obtain intermediate dilutions. These were further diluted in microtiter plates to obtain a final concentration of 2 to 0.002 μg/mL. 1 μl of DMSO was added to "No drug" control wells. The solutions were mixed on a plate shaker for 10 mins and plates incubated at 35 °C for 40 to 48 h (*C. albicans*, *A. fumigatus*) and 72 h (*C. neoformans*). The minimum concentration that led to 50% reduction in fungal growth as compared to the control (with the aid of a reading mirror) was determined as the minimum inhibitory concentration (MIC) for *C. albicans* and *C. neoformans*. The minimum concentration that led to shortening of hyphae as compared to hyphal growth in DMSO control wells was determined as the

minimum effective concentration (MEC) for *A. fumigatus* (as read for echinocandins). The use of the MIC and MEC endpoints for **Compound 2** against yeasts and molds, respectively has been described previously. For the cryptococcal synergy studies, **Compound 2** and 3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-2-amine MIC values were read at 50% inhibition.

[0834] Pharmacokinetic analysis. Single dose PK experiments were performed in healthy male CD-1 mice following IP or oral dosing of 26 mg/kg of the prodrugs **Compound 1**, (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate, (2-amino-3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate and (2-amino-3-(3-((6-(benzyloxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate. In half of the cohorts, mice received a single oral dose of 100 mg/kg ABT at 2 h prior to prodrug dosing. Plasma was collected at 0.083, 0.5, 2, 4, 8, and 24 h post-dose (n=3 per time point). AUC is the area under the curve, calculated from T=0 to the last measurable concentration. The active metabolite concentrations in plasma (**Compound 2**, 3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-2-amine, 3-(3-(4-(benzyloxy)benzyl)isoxazol-5-yl)pyridin-2-amine and 3-(3-((6-(benzyloxy)pyridin-3-yl)methyl)isoxazol-5-yl)pyridin-2-amine) were determined by LC-MS/MS. PK parameters were determined using Phoenix WinNonlin (v7.0) and a non-compartmental model. Samples that were below the limit of quantification (0.5 or 1 ng/mL) were not used in the calculation of averages.

[0835] Cryptococcal meningitis model. *C. neoformans* strain H99 was grown in YPD broth at 30 °C on a shaker (220 rpm) for 24 h, centrifuged (1980 rcf) and washed twice in PBS, resuspended in PBS, and quantified by hemacytometric count. CD-1 male mice were infected with ~5 x 10^4 CFU per mouse via lateral tail vein injection of 100μL. Mice were weighed, and treatment was within 1 h after infection. Treatments were administered daily for seven days. Mice were weighed daily and observed for acute and chronic adverse symptoms. Mice were sacrificed on day 8, and brain and left lung were homogenized and cultured for quantitative determination of tissue burden (CFU per gram of tissue). Tissues were homogenized for 25 seconds in 1 mL phosphate buffered saline using two 6.5 mm steel beads and a Mini-Beadbeater 16 (Biospec Products, Inc., Bartlesville, OK), and serially diluted in 10-fold steps. Aliquots (100 μL) of homogenate were plated and incubated for 3 to7 days at 37°C. Fungal burden data were $\log_{10}$ transformed and evaluated using Kruskal-Wallis tests with Dunn's Multiple Comparison Test for Post-hoc analysis (Prism 5; GraphPad Software, Inc., San Diego, CA). A P value of ≤ 0.05 is considered statistically significant.

[0836] Delayed treatment model. The delayed treatment model was similar to the cryptococcal meningitis model with the following exceptions: a) CD-1 male mice were infected with 5.4 x 10^4 CFU per mouse via lateral tail vein injection of 100 μL; b) treatment was initiated 24 h after infection and continued daily for seven days with 100 mg/kg ABT (PO) administered 2 h prior to each (2-amino-3-(3-(4-((6-fluoropyridin-2-yl)oxy)benzyl)isoxazol-5-yl)pyridin-1-ium-1-yl)methyl hydrogen phosphate dose; c) mice were sacrificed 24 h after the last dose, and brain and left lung were homogenized and cultured for quantitative determination of tissue burden (CFU per gram of tissue). Fungal burden data were $\log_{10}$ transformed and evaluated using Kruskal-Wallis tests with Dunn's Multiple Comparison Test for Post-

hoc analysis (Prism 5; GraphPad Software, Inc., San Diego, CA). A *P* value of ≤0.05 is considered statistically significant

Example II: Parenteral Pharmaceutical Composition

[0837] To prepare a parenteral pharmaceutical composition suitable for administration by injection (subcutaneous, intravenous), 1-1000 mg of a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, is dissolved in sterile water and then mixed with 10 mL of 0.9% sterile saline. A suitable buffer is optionally added as well as optional acid or base to adjust the pH. The mixture is incorporated into a dosage unit form suitable for administration by injection

Example III: Oral Solution

[0838] To prepare a pharmaceutical composition for oral delivery, a sufficient amount of a compound described herein, or a pharmaceutically acceptable salt thereof, is added to water (with optional solubilizer(s),optional buffer(s) and taste masking excipients) to provide a 20 mg/mL solution.

Example IV: Oral Tablet

[0839] A tablet is prepared by mixing 20-50% by weight of a compound described herein, or a pharmaceutically acceptable salt thereof, 20-50% by weight of microcrystalline cellulose, 1-10% by weight of low-substituted hydroxypropyl cellulose, and 1-10% by weight of magnesium stearate or other appropriate excipients. Tablets are prepared by direct compression. The total weight of the compressed tablets is maintained at 100 -500 mg.

Example V: Oral Capsule

[0840] To prepare a pharmaceutical composition for oral delivery, 10-500 mg of a compound described herein, or a pharmaceutically acceptable salt thereof, is mixed with starch or other suitable powder blend. The mixture is incorporated into an oral dosage unit such as a hard gelatin capsule, which is suitable for oral administration.

[0841] In another embodiment, 10-500 mg of a compound described herein, or a pharmaceutically acceptable salt thereof, is placed into Size 4 capsule, or size 1 capsule (hypromellose or hard gelatin) and the capsule is closed.

Example VI: Topical Gel Composition

[0842] To prepare a pharmaceutical topical gel composition, a compound described herein, or a pharmaceutically acceptable salt thereof, is mixed with hydroxypropyl celluose, propylene glycol, isopropyl myristate and purified alcohol USP. The resulting gel mixture is then incorporated into containers, such as tubes, which are suitable for topical administration.

Example VII: Inhalation Composition

[0843] To prepare a pharmaceutical composition for inhalation delivery, a compound described herein, or a pharmaceutically acceptable salt thereof, is mixed with anhydrous citric acid and 0.9% sodium chloride solution. The mixture is incorporated into an inhalation delivery unit, such as a nebulizer, which is suitable for inhalation administration.

Example VIII: Ophthalmic Solution Composition

[0844] To prepare a pharmaceutical opthalmic solution composition, a compound described herein, or a pharmaceutically acceptable salt thereof, is mixed with 0.9 g of NaCl in 100 mL of purified water and filterd using a 0.2 micron filter. The resulting isotonic solution is then incorporated into ophthalmic delivery units, such as eye drop containers, which are suitable for ophthalmic administration.

BIOLOGICAL EXAMPLES

Example IX: In vitro Antifungal Assay

[0845] Measurement of antifungal activity: Antifungal activity of the compounds was evaluated in a microdilution broth assay as per Clinical and Laboratory Standard Institute methodology for yeast (for *Candida* and *Cryptococcus*) (1) and molds (for *Aspergillus and Rhizomucor*) (2). *Candida albicans* 90028, *Aspergillus fumigatus* MYA3626, *Rhizomucor pusillus* 46342 and *Cryptococcus neoformans* H99 strains were obtained from American Type Culture Collection (ATCC).

[0846] *Preparation of Fungal Suspension*: C. *albicans* 90028 and *C. neoformans* H99 strains were streaked from frozen stocks at -80 °C onto Sabouraud Dextrose Agar (SDA) plates. These were allowed to grow for 24 h (*C. albicans*) and 48 h (*C. neoformans*) at 35 °C before using them in the assay. 5-6 individual colonies were picked and diluted into sterile water to obtain a fungal suspension. The cell density of the suspension was determined and the culture diluted with RPMI1640 medium to obtain a fungal suspension of 2.5 x 10^3 cells/mL. The suspension was used in the MIC measurement as described below.

[0847] *A. fumigatus* and *R. pusillus* were spread onto Potato Dextrose Agar (PDA) plates spores from -80 °C frozen stocks and incubated for 3-6 days at 30 °C (*A. fumigatus*) and 35 °C (*R. pusillus*). Water containing 1% Tween was directly added to the agar plate and gently agitated to wet and remove the *Aspergillus* conidia. For *R. pusillus*, water was added to the surface and gently massaged to wet and remove the spores. For both species, the conidia or spores and mycelial fragments were collected, followed by removal of mycelium, conidiophores and large clumps of conidia/spores.. The resulting spore suspension was counted and diluted into RPMI1640 medium to adjust to a final suspension of 1-2 x10^4 spores/mL. The suspension was used in the MEC measurement as described below.

[0848] *Preparation of Compound Stocks and Intermediate Dilutions*: The compounds were weighed and DMSO was added to prepare a 10 mg/mL stock. The solutions were mixed by vortexing and sonication at 37 °C for 5-10 mins. The resulting solutions were sterile filtered using a PTFE filter, and aliquoted (12 µL or as needed) and stored at -20 °C. Intermediate compound dilutions were prepared in sterile polypropylene tubes in 100% DMSO. The compound stock solution was first diluted in DMSO to obtain a concentration of 1600 µ g/mL. This was serially 2-fold diluted to obtain a dilution series from 1600 to 0.19 µ g/mL.

[0849] *MIC/MEC Measurement:* 99 µL l of the fungal suspension in RPMI1640 prepared as above was added to each well of a 96-well round bottom assay plate. 1 µ L of the intermediate compound dilutions (200-0.19 µ g/mL) were added to wells of the plate. This led to a 100-fold dilution of the intermediate

dilutions resulting in a final compound concentration of 2-0.0019 μg/mL in the plate. 1 μL of DMSO was added to "No drug" control wells. The solutions were mixed by shaking on a plate shaker for 10 mins and plates incubated at 35 °C for 40-48 h (*C. albicans*, *A. fumigatus, R. pusillus*) and 72h (*Cryptococcus*). The minimum concentration that clearly inhibited fungal growth (≥50% inhibition) as compared to the control by visual inspection was determined as the minimum inhibitory concentration (MIC) for *C. albicans* and *C. neoformans* (as read for echinocandins). This was validated by thorough mixing and reading at 600 nm on a microplate reader. The minimum concentration that led to shortening of hyphae as compared to hyphal growth in DMSO control wells was determined as the minimum effective concentration (MEC) for *A. fumigatus* and *R. pusillus* (as read for echinocandins). The use of the MIC and MEC endpoints against yeasts and molds, respectively has been described by Pfaller MA, Duncanson F, Messer SA, Moet GJ, Jones RN, Castanheira M. Antimicrob Agents Chemother. 2011. 55(11):5155-8. In vitro activity of a novel broad-spectrum antifungal, E1210, tested against Aspergillus spp. determined by CLSI and EUCAST broth microdilution methods. Results are shown in **Table 2**, and the letters indicate the following ranges in μg/mL:

A: MEC or MIC ≤ 0.010; B: 0.010 < MEC or MIC ≤ 0.10; C: 0.10 < MEC or MIC ≤ 1.0;

D: MEC or MIC > 1.0; NT: Not tested

Table 2.

Ex.	*Aspergillus fumigatus* MEC	*Candida albicans* MIC	*Rhizomucor pusillus* MEC	*Cryptococcus neoformans* MIC	*Cryptococcus gattii* MIC
B	C	D	D	NT	NT
C	C	D	D	NT	NT
E	D	D	D	NT	NT
1	C	B	D	C	B
2	C	D	D	D	NT
3	C	C	D	NT	NT
4	B	C	C	C	C
5	C	C	C	C	C
6	D	D	D	NT	NT
7	C	C	D	NT	NT
8	C	C	C	B	A
9	C	B	C	C	B
10	C	C	D	C	C
11	B	C	D	C	C
12	B	C	D	C	C
13	C	C	D	NT	NT
14	B	C	C	C	C
15	A	B	C	B	B
16	C	C	C	NT	NT
17	B	B	C	B	B
18	B	B	C	C	C
19	B	B	C	B	B
20	B	C	C	B	B
21	C	C	D	NT	NT
22	C	C	D	C	B
23	C	C	C	C	B
24	D	D	D	NT	NT
25	D	D	D	NT	NT
26	B	C	D	C	C

Ex.	*Aspergillus fumigatus* MEC	*Candida albicans* MIC	*Rhizomucor pusillus* MEC	*Cryptococcus neoformans* MIC	*Cryptococcus gattii* MIC
27	D	C	D	C	C
28	C	C	D	C	C
29	C	C	D	NT	NT
30	D	C	C	D	D
31	B	B	C	C	C
32	B	B	C	C	C
33	D	D	D	NT	NT
34	C	B	C	D	C
35	B	B	D	B	B
36	B	B	D	B	B
37	B	B	D	A	A
38	B	C	C	C	C
39	C	C	D	C	C
40	B	C	C	B	B
41	B	B	C	B	B
42	B	B	C	B	B
43	B	C	C	B	B
44	D	C	D	NT	NT
45	C	C	D	NT	NT
46	C	C	D	C	C
47	C	B	C	C	C
48	B	B	C	B	B
49	D	D	D	NT	NT
50	C	C	D	C	C
51	B	C	C	C	C
52	C	C	D	NT	NT
53	C	C	C	C	C
54	B	B	D	B	A
55	C	C	D	C	C
56	C	C	D	NT	NT
57	B	B	C	B	A
58	C	B	C	C	B
59	C	C	D	NT	NT
60	C	B	D	B	B
61	B	B	D	C	B
62	B	C	D	D	D
63	NT	C	D	NT	NT
64	NT	C	D	NT	NT
65	B	C	D	C	C
66	C	C	D	NT	NT
67	C	C	D	NT	NT
68	C	C	D	NT	NT
69	B	B	C	B	B
70	B	C	D	C	C
71	D	D	D	NT	NT
72	C	B	C	B	C
73	C	B	D	D	D
74	C	B	D	B	B
75	B	B	C	B	C
76	C	D	C	NT	NT
77	C	B	C	B	B
78	C	B	C	B	B
79	C	B	C	B	C
80	A	A	C	B	B
81	B	B	C	A	B
82	B	C	D	B	B

Ex.	*Aspergillus fumigatus* MEC	*Candida albicans* MIC	*Rhizomucor pusillus* MEC	*Cryptococcus neoformans* MIC	*Cryptococcus gattii* MIC
83	B	B	D	A	B
84	B	B	C	B	C
85	B	B	C	NT	NT
86	B	B	D	NT	NT
87	B	C	D	NT	NT
88	C	C	D	NT	NT
89	D	D	D	NT	NT
90	D	C	D	NT	NT
91	NT	NT	D	NT	NT
92	NT	NT	C	NT	NT
93	D	D	D	NT	NT
94	D	D	D	NT	NT
95	D	D	D	NT	NT
96	D	D	D	NT	NT
97	C	D	D	NT	NT
98	C	C	D	NT	NT
99	C	D	D	C	C
100	C	C	D	C	C
101	C	C	D	B	B
102	D	D	D	NT	NT
103	C	C	D	NT	NT
104	D	D	D	D	NT
105	C	B	D	C	B
106	B	B	C	C	B
107	B	B	B	B	B
108	B	B	C	C	C
109	D	D	D	NT	NT
110	B	B	C	B	A
111	B	B	C	A	A
112	B	C	C	B	B
113	C	D	D	NT	NT
114	B	C	D	C	C
115	B	C	D	C	C
116	B	D	D	NT	NT
117	B	C	D	B	A
118	C	C	D	C	C
119	D	D	D	NT	NT
120	A	B	C	B	B
121	A	B	B	B	B
122	A	A	B	B	B
123	B	B	D	C	B
124	B	B	B	B	B
125	C	C	D	D	D
126	D	D	D	NT	NT
127	A	B	C	B	B
128	C	D	D	NT	NT
129	D	D	D	NT	NT
130	B	B	C	A	B
131	B	B	C	B	B
132	A	B	C	B	B
133	C	C	C	NT	NT
134	C	C	C	B	B
135	B	C	C	B	C
136	B	C	B	C	C
137	B	B	D	C	B
138	B	B	C	B	A

Ex.	*Aspergillus fumigatus* MEC	*Candida albicans* MIC	*Rhizomucor pusillus* MEC	*Cryptococcus neoformans* MIC	*Cryptococcus gattii* MIC
139	C	B	D	B	A
140	B	A	C	B	B
141	B	B	C	B	B
142	A	B	C	B	B
143	B	C	C	B	A
144	B	B	C	B	B
145	D	D	D	NT	NT
146	D	C	D	C	C
147	D	D	D	NT	NT
148	B	B	C	B	B
149	B	B	D	B	C
150	C	C	D	C	C
151	C	C	C	NT	NT
152	B	B	D	NT	NT
153	B	C	D	NT	NT
154	B	B	C	B	B
155	D	D	D	NT	NT
156	D	C	D	C	D
157	C	D	C	C	C
158	C	C	D	NT	NT
159	C	C	D	NT	NT
160	B	C	C	C	C
161	B	B	C	B	B
162	C	B	D	NT	NT
163	C	D	C	NT	NT
164	C	D	D	NT	NT
165	B	C	C	B	B
166	B	C	C	NT	NT
167	B	C	C	NT	NT
168	B	B	C	C	B
169	B	B	C	B	B
170	C	C	C	NT	NT
171	C	B	C	NT	NT
172	NT	NT	NT	NT	NT
173	NT	NT	NT	NT	NT
174	NT	NT	NT	NT	NT
175	NT	NT	NT	NT	NT
176	NT	NT	NT	NT	NT
177	NT	NT	NT	NT	NT
178	NT	NT	NT	NT	NT
179	NT	NT	NT	NT	NT
180	NT	NT	NT	NT	NT
181	NT	NT	NT	NT	NT
182	NT	NT	NT	NT	NT
183	NT	NT	NT	NT	NT
184	NT	NT	NT	NT	NT
185	C	C	C	B	B
186	B	B	D	C	B
187	C	C	C	C	B
188	D	D	C	D	D
189	B	B	D	B	C
190	C	C	D	C	C
191	B	C	C	C	C
192	C	C	D	NT	NT
193	B	C	C	C	C
194	C	D	D	NT	NT

Ex.	*Aspergillus fumigatus* MEC	*Candida albicans* MIC	*Rhizomucor pusillus* MEC	*Cryptococcus neoformans* MIC	*Cryptococcus gattii* MIC
195	C	C	D	B	B
196	C	B	C	B	C
197	NT	NT	NT	NT	NT
198	D	C	C	C	D
199	D	D	D	D	D
200	D	D	D	D	D
201	C	C	D	C	D
202	D	D	D	D	D
203	D	D	D	C	C
204	D	D	D	D	D
205	D	C	C	C	D
206	D	D	D	D	D
207	B	C	D	B	C
208	B	B	C	B	B
209	D	D	D	D	D
210	D	D	D	NT	NT
211	D	D	D	NT	NT
212	C	C	C	B	B
213	C	C	D	C	C
214	D	D	D	NT	NT
215	D	D	D	NT	NT
216	C	C	D	C	C
217	D	D	NT	D	D
218	C	C	D	D	D
219	C	D	NT	D	D
220	C	C	C	C	C
221	B	C	C	B	C
222	B	B	D	B	C
223	B	B	D	C	C
224	D	D	D	D	D
225	B	C	C	C	C
226	B	B	D	B	C
227	D	D	D	NT	NT
228	D	D	D	NT	NT
229	D	D	D	NT	NT
230	C	C	D	NT	NT
231	B	C	C	B	B
232	D	D	NT	NT	NT
233	C	D	NT	D	D
234	B	B	C	A	A
235	B	B	C	A	A
236	C	C	C	C	C
237	C	B	D	B	B
238	D	D	NT	C	C
239	C	C	C	B	B
240	C	C	C	B	B
241	B	C	C	B	B
242	B	B	C	B	A
243	C	C	D	C	C
244	C	C	D	C	C
245	C	C	D	C	C
246	B	C	C	B	C
247	B	B	NT	C	D
248	C	D	NT	D	D
249	B	C	NT	C	D
250	B	B	C	B	C

Ex.	*Aspergillus fumigatus* MEC	*Candida albicans* MIC	*Rhizomucor pusillus* MEC	*Cryptococcus neoformans* MIC	*Cryptococcus gattii* MIC
251	B	C	NT	C	C
252	C	C	NT	C	C
253	C	C	D	C	C
254	B	B	NT	C	D
255	B	B	NT	C	D
256	C	B	NT	C	D
257	B	B	C	C	D
258	B	C	C	B	C
259	B	D	NT	C	D
260	C	C	NT	C	D
261	C	C	C	C	C

Example X: Systemic Candidal Infection Model in Mice

Preparation of Fungal Inoculant

[0850] *C.* albicans is subcultured in brain heart infusion broth and grown at 37 °C overnight. Cells are collected by centrifugation and washed three times with sterilized physiological saline and counted with a hemocytometer. The suspension is adjusted to 2×10^7 cells/mL with sterilized physiological saline to serve as the fungal inoculum.

Infection

[0851] 8-week-old BALB/c mice weighing ~20g are rendered neutropenic by receiving 150 mg/kg and 100 mg/kg of cyclophosphamide via IP injection on day -4 and day -1 prior to infection, respectively. The fungal inoculum is used in the amounts of 0.2 mL (4×10^6 cells/mouse).

Treatment

[0852] From 0.5 to 1 hour after fungal inoculation, 0.2 mL of agent solution containing a compound described herein (dissolved or suspended in sterilized physiological saline containing 6.5% dimethyl sulfoxide and 3.5% Tween 80 or another appropriate vehicle) is administered into orally using a peroral probe, 3 times every 4 hours. The agent concentration ranges from 1 mg/kg to 500 mg/kg, and the number of animals in one group ranges from 5 to 10 animals.

Determination of Effects

[0853] Animals are sacrificed after 48 hrs and organs such as kidney and brain are harvested. Colony forming units/gram of tissue are determined in order to assess the protective efffect of a compound vs a no drug (vehicle) control

Example XI: Murine Model of Cryptococcal Meningitis

Preparation of Fungal Inoculant

[0854] Cryptococcus neoformans strain H99 was grown in YPD broth at 30 °C on a shaker (220 rpm) for 24 hours, centrifuged (1980 rcf) and washed twice in PBS, resuspended in PBS, and quantified by hemacytometric, count.

Infection and treatment

[0855] CD-1 male mice are infected with ~6 x 10^4 colony forming units (CFU) per mouse via lateral tail vein injection of 100μL. Compounds are administed by oral, intraperitoneal or intravenous routes from 1 to 3 times daily. Treatments were given for seven days.

Determination of Effects

[0856] Mice are sacrificed on day 8, and brain and left lung are homogenized and cultured for quantitative determination of tissue burden (CFU per gram of tissue). Colony forming units/gram of tissue are determined in order to assess the protective efffect of a compound vs a no drug (vehicle) control.

Example XII: Clinical Trial of a Compound Described Herein in Patients with a Fungal Infection

The purpose of this study is to investigate whether a compound described herein can treat patients with fungal infections. Another purpose of this study is to assess the safety, tolerability, pharmacokinetics, bioavailability and food effect of single doses of a compound described herein administered intravenously and orally, followed by an evaluation of the safety, tolerability, pharmacokinetics and drug-drug interaction potential of multiple doses of a compound described herein administered orally.

Study Type:

Interventional

[0857] Study Design:

Allocation: Randomized

Interventional Model: Crossover Assignment

Masking: Double (Participant Investigator)

Primary Purpose: Treatment

Primary Outcome Measures:

Safety and tolerability of single and multiple oral doses of whether a compound described herein as measured by adverse events (AEs), physical examinations (PE), vital signs (VS), laboratory safety tests, urinalysis and 12-lead electrocardiograms (ECG). Time Frame: 21 days

Secondary Outcome Measures:

- Pharmacokinetics of single and multiple doses of a compound described herein as measured by maximum observed concentration (Cmax). Time Frame: 21 days
- Pharmacokinetics of single and multiple dose of a compound described herein as measured by area under the curve (AUC). Time Frame: 21 days
- Pharmacokinetics of single and multiple doses of a compound described herein as measured by terminal half life (t1/2). Time Frame: 21 days
- Pharmacokinetics of single and multiple doses of a compound described herein as measured by volume of distribution (Vd). Time Frame: 21 days
- Pharmacokinetics of single and multiple doses of a compound described herein as measured by elimination rate constant (Kel). Time Frame: 21 days

- Pharmacokinetics of single and multiple doses of a compound described herein as measured by accumulation ratio. Time Frame: 21 days
- **Eligibility:**

Ages Eligible for Study: 18 Years to 55 Years (Adult)

Sexes Eligible for Study: All

Accepts Healthy Volunteers: Yes

Inclusion Criteria:

- Women of childbearing potential must agree to avoid pregnancy during the study and to use contraception at least 2 weeks before the start of the study until 3 months after the last dose of study drug.
- Males with partner(s) of childbearing potential must agree to use appropriate barrier contraception from the screening period until 3 months after the last dose of study drug.
- Screening hematology, clinical chemistry, coagulation and urinalysis consistent with overall good health.
- No significantly abnormal findings on physical examination, ECG and vital signs.
- Willing and able to provide written informed consent.

Exclusion Criteria:

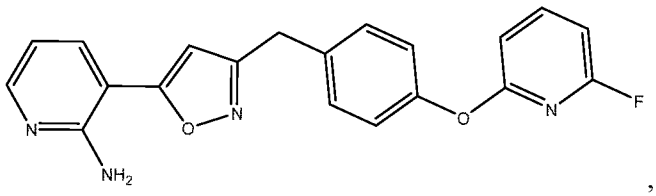
- Any uncontrolled or active major systemic disease including, but not limited to: cardiovascular, pulmonary, gastrointestinal, metabolic, urogenital, neurological, immunological, psychiatric, or neoplastic disorder with metastatic potential.
- History or presence of malignancy within the past year. Subjects who have been successfully treated with no recurrence of basal cell carcinoma of the skin or carcinoma in-situ of the cervix may be enrolled.
- Use of prescription medication within 14 days prior to the first dose of study drug and throughout the study.
- Use of non-prescription or over-the-counter medications within 7 days prior to the first dose of study drug and throughout the study.

[0858] Although the invention has been described with reference to the above example, it will be understood that modifications and variations are encompassed within the spirit and scope of the invention. Accordingly, the invention is limited only by the following claims.

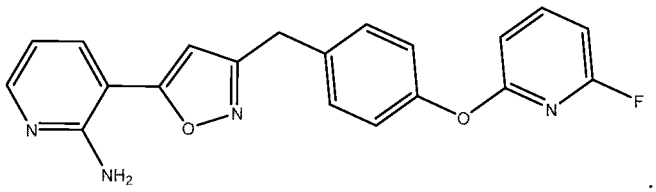
CLAIMS

WHAT IS CLAIMED IS:

1. A compound



, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof.

2. A compound  .

3. A pharmaceutical composition, comprising:
   the compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, a stereoisomer, mixture of stereoisomers, or an isotopic variant thereof; and
   at least one pharmaceutically acceptable excipient.

4. A pharmaceutical composition, comprising:
   the compound of claim 2; and
   at least one pharmaceutically acceptable excipient.

5. A method of treating a fungal disease in a subject in need thereof, the method comprising:
   administering to the subject a therapeutically effective amount of a compound of claim 1 or claim 2, or the pharmaceutical composition of claim 3 or claim 4.

6. The method of claim 5, wherein the fungal disease is selected from the group consisting of: aspergillosis, blastomycosis, candidiasis, coccidioidomycosis (Valley Fever), cryptococcosis, fungal eye infection, histoplasmosis, mucormycosis, *Pneumocystis* pneumonia (PCP), ringworm, sporotrichosis, and talaromycosis.

7. The method of claim 5 or claim 6, wherein the fungal disease is caused by a fungal species selected the group consisting of: *Aspergillus fumigatus, Aspergillus flavus*, *Blastomyces dermatitidis, Ajellomyces dermatitidis, Candida albicans, Candida glabrata*, *Candida rugosa*,

Candida auris, Coccidioides immitis, *Coccidioides posadasii, Cryptococcus neoformans*, *Cryptococcus gattii, Histoplasma capsulatum, Rhizopus stolonifer, Rhizopus arrhizus, Mucor indicus, Cunninghamella bertholletiae, Apophysomyces elegans, Absidia species, Saksenaea species, Rhizomucor pusillus, Entomophthora species, Conidiobolus species, Basidiobolus species, Sporothrix schenckii, Pneumocystis jirovecii*, *Talaromyces marneffei, Asclepias albicans*, *Fusarium solani, Scedosporium apiospermum, and Rhizomucor pusillus*.

8. The method of any one of claims 5 to 7, wherein the subject is immunocompromised.

9. The method of claim of any one of claims 5 to 8, wherein the subject has received chemotherapy treatment.

10. The method of claim of any one of claims 5 to 9, wherein the subject is infected with HIV/AIDS.

11. The method of claim of any one of claims 5 to 10, wherein the fungal disease is caused by *Cryptococcus neoformans* or *Cryptococcus gattii.*

12. Use of the compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or an isotopic variant thereof, in the manufacture of a medicament for treating a fungal disease in a subject in need thereof.

13. Use of the compound of claim 2, in the manufacture of a medicament for treating a fungal disease in a subject in need thereof.

14. The use of claim 12 or claim 13, wherein the fungal disease is selected from the group consisting of: aspergillosis, blastomycosis, candidiasis, coccidioidomycosis (Valley Fever), cryptococcosis, fungal eye infection, histoplasmosis, mucormycosis, *Pneumocystis* pneumonia (PCP), ringworm, sporotrichosis, and talaromycosis.

15. The use of any one of claims 12 to 14, wherein the fungal disease is caused by a fungal species selected from the group consisting of: *Aspergillus fumigatus, Aspergillus flavus*, *Blastomyces dermatitidis, Ajellomyces dermatitidis, Candida albicans, Candida glabrata*, *Candida rugosa*, *Candida auris, Coccidioides immitis*, *Coccidioides posadasii, Cryptococcus neoformans*, *Cryptococcus gattii, Histoplasma capsulatum, Rhizopus stolonifer, Rhizopus arrhizus, Mucor indicus, Cunninghamella bertholletiae, Apophysomyces elegans, Absidia species, Saksenaea species, Rhizomucor pusillus, Entomophthora species, Conidiobolus species, Basidiobolus*

species, Sporothrix schenckii, Pneumocystis jirovecii, Talaromyces marneffei, Asclepias albicans, Fusarium solani, Scedosporium apiospermum, and Rhizomucor pusillus.

16. The use of any one of claims 12 to 15, wherein the subject is immunocompromised.

17. The use of any one of claims 12 to 16, wherein the subject has received chemotherapy treatment.

18. The use of any one of claims 12 to 17, wherein the subject is infected with HIV/AIDS.

19. The use of any one of claims 12 to 18, wherein the fungal disease is caused by *Cryptococcus neoformans* or *Cryptococcus gattii*.

FIG. 1

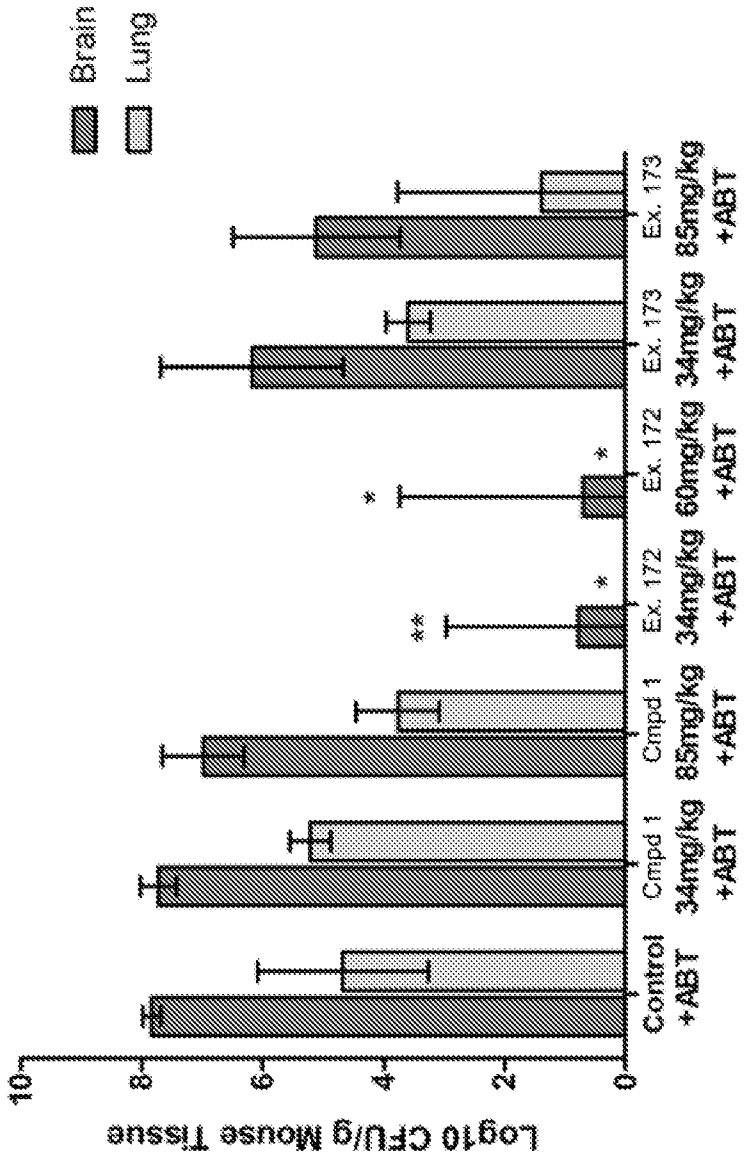

Brain
Lung
Log10 CFU/g Mouse Tissue
10
8
6
4
2
0
Control +ABT
Cmpd 1 34mg/kg +ABT
Cmpd 1 85mg/kg +ABT
Ex. 172 34mg/kg +ABT
Ex. 172 60mg/kg +ABT
Ex. 173 34mg/kg +ABT
Ex. 173 85mg/kg +ABT
*
**
*
*
*

FIG. 2

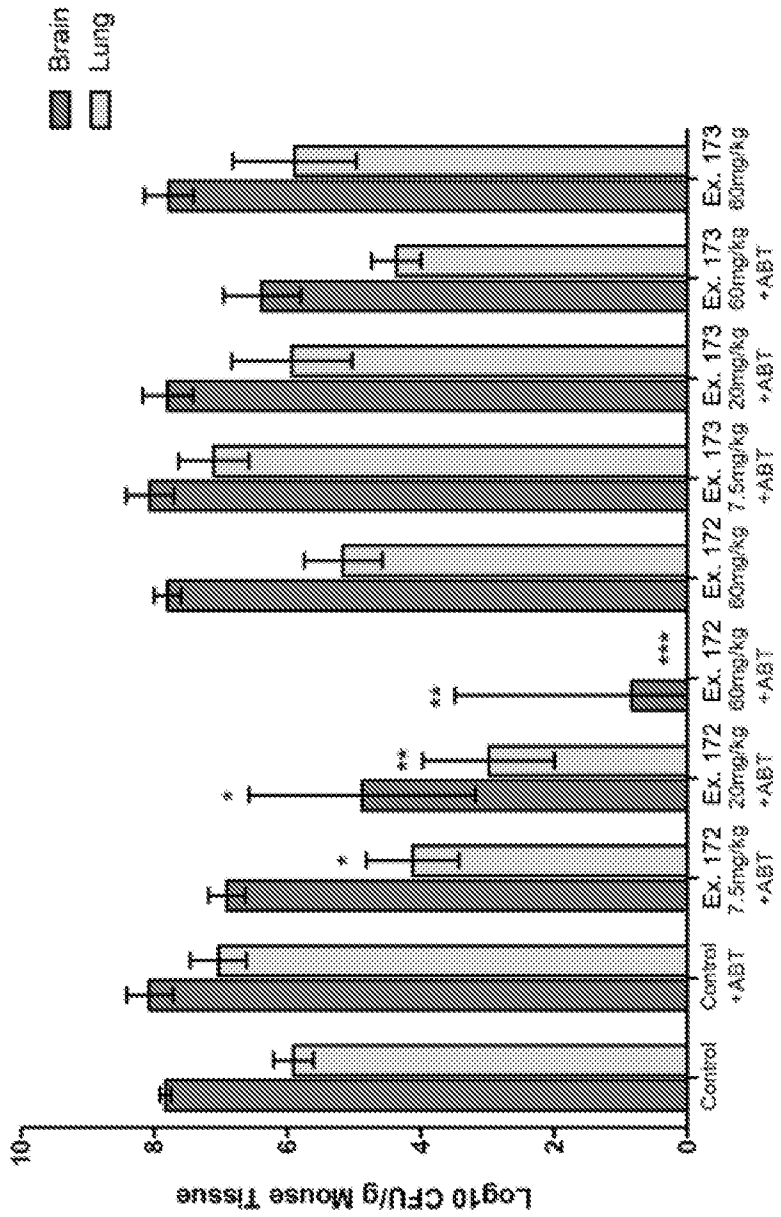
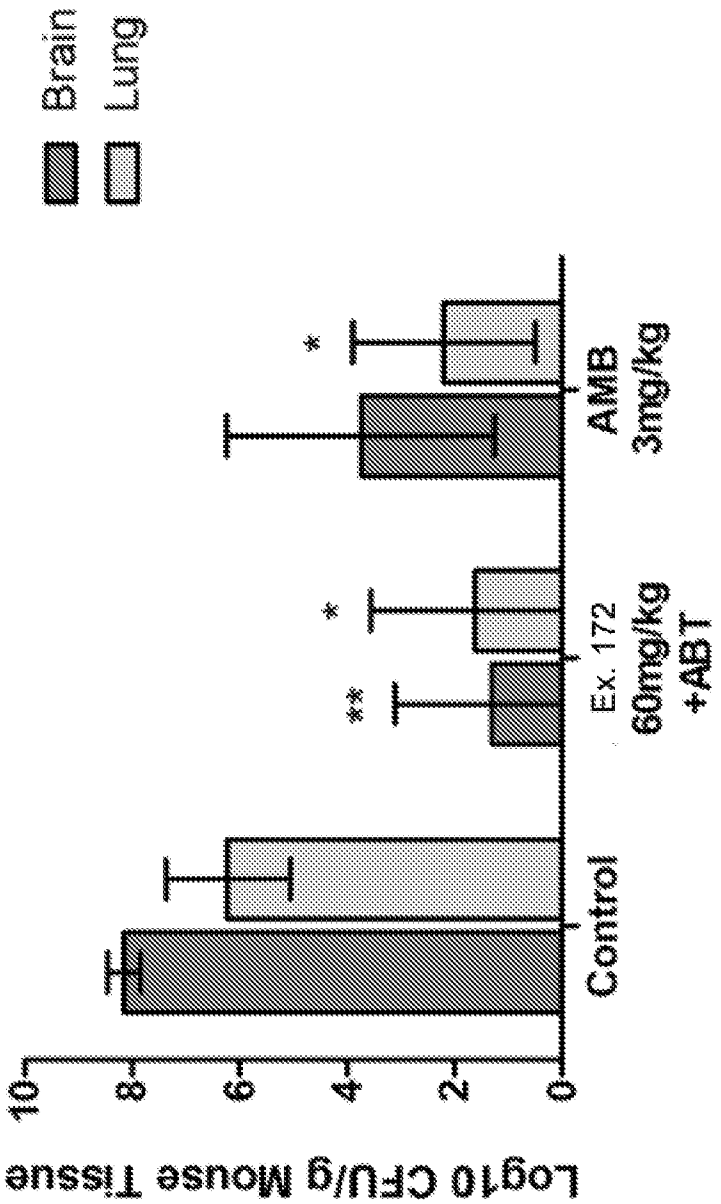

Brain
Lung
Log10 CFU/g Mouse Tissue
10
8
6
4
2
0
*
*
**
**
***
Control
Control +ABT
Ex. 172 7.5mg/kg +ABT
Ex. 172 20mg/kg +ABT
Ex. 172 60mg/kg +ABT
Ex. 172 60mg/kg
Ex. 173 7.5mg/kg +ABT
Ex. 173 20mg/kg +ABT
Ex. 173 60mg/kg +ABT
Ex. 173 60mg/kg

FIG. 3


Brain
Lung
Log10 CFU/g Mouse Tissue
0
2
4
6
8
10
Control
Ex. 172 60mg/kg +ABT
AMB 3mg/kg
**
*
*