

PI3K INHIBITORS AND USE THEREOF

RELATED APPLICATIONS

This application claims priority to International Application No. PCT/CN2023/101669, filed
5 on June 21, 2023. The entire contents of the foregoing application are expressly incorporated herein
by reference.

BACKGROUND

PI3Ks are members of a unique and conserved family of intracellular lipid kinases that
10 phosphorylate the 3' -OH group on phosphatidylinositols or phosphoinositides. The PI3K family
comprises 15 kinases with distinct substrate specificities, expression patterns, and modes of regulation
(Katso *et al.*, 2001). The class I PI3Ks (p110 α , p110 β , p110 δ , and p110 γ) are typically activated by
tyrosine kinases or G-protein coupled receptors to generate PIP3, which engages downstream
effectors such as those in the pathways of Akt/PDK1, mTOR, the Tec family kinases, and the Rho
15 family GTPases. The class II and III PI3-Ks play a key role in intracellular trafficking through the
synthesis of PI(3)P and PI(3,4)P₂.

The PI3K isoforms have been implicated, for example, in a variety of human cancers and
disorders. Mutations in the gene coding for PI3K isoforms or mutations which lead to upregulation of
a PI3K isoform are believed to occur in many human cancers. Mutations in the gene coding for a
20 PI3K isoform are point mutations clustered within several hotspots in helical and kinase domains.
Because of the high rate of PI3K mutations, targeting of this pathway may provide valuable
therapeutic opportunities.

Genetic alterations in genes in PI3K signaling are believed to be involved in a range of
cancers such as endometrial cancer, breast cancer, esophageal squamous-cell cancer, cervical
25 squamous-cell carcinoma, cervical adenocarcinoma, colorectal adenocarcinoma, bladder urothelial
carcinoma, glioblastoma, ovarian cancer, non-small-cell lung cancer, esophagogastric cancer, nerve-
sheath tumor, head and neck squamous-cell carcinoma, melanoma, esophagogastric adenocarcinoma,
soft-tissue sarcoma, prostate cancer, fibrolamellar carcinoma, hepatocellular carcinoma, diffuse
glioma, colorectal cancer, pancreatic cancer, cholangiocarcinoma, B-cell lymphoma, mesothelioma,
30 adrenocortical carcinoma, renal non- clear-cell carcinoma, renal clear-cell carcinoma, germ-cell
carcinoma, thymic tumor, pheochromocytoma, miscellaneous neuroepithelial tumor, thyroid cancer,
leukemia, and encapsulated glioma (Goncalves MD, Hopkins BD, Cantiey LC. Phosphatidylinositol
3-Kinase, Growth Disorders, and Cancer. N Engl J Med. 2018 Nov 22;379(21):2052-2062).

The alpha (α) isoform of PI3K has been implicated, for example, in a variety of human
35 cancers. Angiogenesis has been shown to selectively require the α isoform of PI3K in the control of
endothelial cell migration. (Graupera *et al*, Nature 2008; 453; 662-6). Mutations in the gene coding
for PI3K α or mutations which lead to upregulation of PI3K α are believed to occur in many human

cancers such as lung, stomach, endometrial, ovarian, bladder, breast, colon, brain, prostate, and skin cancers. Mutations in the gene coding for PI3K α are point mutations clustered within several hotspots in helical and kinase domains, such as E542K, E545K, and H1047R. Many of these mutations have been shown to be oncogenic gain-of-function mutations. Because of the high rate of PI3K α mutations, targeting of this pathway may provide valuable therapeutic opportunities. While other PI3K isoforms such as PI3K δ or PI3K γ are expressed primarily in hematopoietic cells, PI3K α , along with PI3K β , is expressed constitutively.

Due to the central role of PI3K α in regulating organismal glucose homeostasis, PI3K inhibition in patients often gives rise to hyperglycemia and/or hyperinsulinemia (Busaidy NL, *et al*, Management of metabolic effects associated with anticancer agents targeting the PI3K-Akt- mTOR pathway. J. Clin. Oncol. 2012;30:2919-28). High levels of circulating insulin could potentially be mitogenic and/or antiapoptotic for cancer cells and thus negate the antiproliferative effects of PI3K inhibitors (Blouin M-J, *et al*, Abstract 4615: the hyperinsulinemia caused by PI3K inhibitors attenuates their antineoplastic efficacy, but can be minimized by co administration of metformin. Cancer Res 2013;73:4615).

In the setting of cancer with mutated PI3K α , one way to overcome the problem of compensatory production of insulin and/or glucose upon systemic PI3K α inhibition would be to develop inhibitors with enhanced selectivity for mutant PI3K α over wild-type PI3K α . This would create an increased window for drug dosing to selectively inhibit the pathologic signaling of mutant PI3K α in the cancer cells without affecting the wild-type PI3K α in the host tissues that control systemic metabolism (Okkenhaug K, Graupera M, Vanhaesebroeck B. Targeting PI3K in Cancer: Impact on Tumor Cells, Their Protective Stroma, Angiogenesis, and Immunotherapy. Cancer Discov. 2016 Oct;6(10): 1090-1105), thus limiting toxicities and permitting higher doses and more complete inhibition of the drug target (Ariella B. Hanks, *et al*, Challenges for the clinical development of PI3K inhibitors: Strategies to improve their impact in solid tumors. Cancer Discov. 2019 Apr; 9(4): 482-491).

Currently PI3K α inhibitors are nearly equipotent to wild-type and mutant PI3K α . Mutant selective inhibitors have been elusive due to the PI3K α mutations location far from the active site. As such, inhibitors which target a second, peripheral binding pocket near a known mutation (*e.g.*, H1047R) may provide a route to selective PI3K α inhibition. Thus, targeting a mutated, peripheral binding pocket of PI3K α , may in turn provide a valuable therapeutic target for drug development.

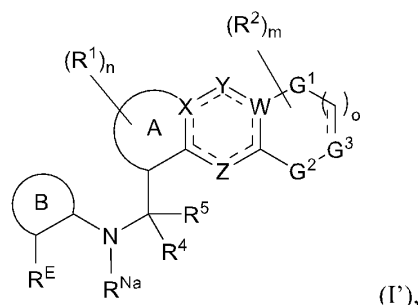
Therefore, it remains a need to discover PI3K inhibitors having novel activity profiles, in particular those specifically or selectively targeting mutated PI3K α .

SUMMARY

Described herein are compounds of Formula (I'), pharmaceutically acceptable salts, or

stereoisomers thereof that inhibit the activity of PI3K α , in particular, selectively inhibit PI3K α mutation (*e.g.*, H1047R and H1047L).

In one aspect, the present disclosure provides a compound of Formula (I'), a pharmaceutically acceptable salt, or a stereoisomer thereof:



wherein Rings A and B, and the variables W, X, Y, Z, G¹, G², G³, R¹, R², R⁴, R⁵, R^E, R^{Na}, n, m, and o are as defined herein.

Also provided are pharmaceutical compositions comprising a compound of Formula (I) or (I'), a pharmaceutically acceptable salt, or a stereoisomer thereof and a pharmaceutically acceptable carrier or excipient.

The present disclosure further provides methods of inhibiting PI3K α in a patient, comprising administering to the patient a compound of Formula (I'), or a pharmaceutically acceptable salt, or a stereoisomer thereof.

The present disclosure also provides methods of treating a disease or condition modulated at least in part by PI3K α in a subject, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I'), a pharmaceutically acceptable salt, or a stereoisomer thereof.

The present disclosure further provides a method of treating cancer or a disorder in a patient in need thereof, comprising administering to the patient an effective amount of (1) a compound of Formula (I'), a pharmaceutically acceptable salt, or a stereoisomer thereof; or (2) a pharmaceutically acceptable composition comprising a compound of Formula (I'), a pharmaceutically acceptable salt, or a stereoisomer thereof, and a pharmaceutically acceptable carrier.

In certain embodiments, the cancer is treatable by inhibiting PI3K α (*e.g.*, PI3K α mutation), such as a cancer selected from the group consisting of: breast cancer (such as hormone receptor positive, HER2 negative breast cancer, HER2 positive breast cancer and triple negative breast cancer), endometrial cancer, uterine cancer, gastric cancer, leukemia, lymphoma, sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, head and neck cancer, brain cancer, or prostate cancer.

In certain embodiments, the disorder is CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome) or PIK3CA-related overgrowth syndrome (PROS).

In certain embodiments of the methods of the present disclosure, the cancer can be treated by inhibiting the activity of PI3K α (e.g., PI3K α mutation).

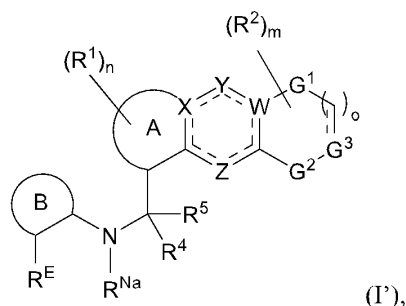
In certain embodiments of the methods of the present disclosure, the compounds of the present disclosure are administered with any one of a second therapeutic agent as described herein that also treats the same cancer.

The present disclosure also provides a use of a compound of Formula (I'), a pharmaceutically acceptable salt, or a stereoisomer thereof or a pharmaceutical composition comprising the same in any of the methods described herein. In one embodiment, provided is a compound of Formula (I') or a pharmaceutically acceptable salt or a stereoisomer thereof or a pharmaceutical composition comprising the same for use in any of the methods described herein. In another embodiment, provided is use of a compound of Formula (I') or a pharmaceutically acceptable salt or a stereoisomer thereof or a pharmaceutical composition comprising the same for the manufacture of a medicament for any of the methods described herein.

DETAILED DESCRIPTION

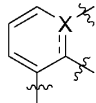
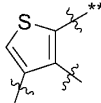
1. Compounds

In a first aspect, the present disclosure provides a compound represented by Formula (I'):



or a pharmaceutically acceptable salt thereof, wherein:

==== is a single bond or a double bond as valency permits;

Ring A is  or , wherein ** is the attachment point to Y;

(i) when W is C and Y is N or CR^{Z1}, then X is C, and Z is N or CR^{Z1};

(ii) when W is C and Y is C(O), then X is C or N, and Z is CR^{Z1}, N, NR^{N1}, or O;

(iii) when W is N, then Y is C(O), X is C, and Z is N or CR^{Z1};

G¹, G², and G³ are each, independently, C(R^{G2})₂, NR^{N2}, or O;

n is 0, 1, 2, or 3;

m is 0, 1, 2, 3, or 4;

o is 0, 1, 2, 3, or 4;

R^{Na} is H;

R^{N1} is H, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C(O)R^{1a}$, C_{3-6} cycloalkyl, phenyl, or 5-to 6-membered heteroaryl, wherein the phenyl and 5-to 6-membered heteroaryl represented by R^{N1} are each optionally substituted with one to three substituents selected from halo, C_{1-3} alkyl, and C_{1-3} haloalkyl;

5 R^{Z1} is H, halo, cyano, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxylalkyl, C_{1-6} alkoxylalkyl, C_{1-6} hydroxyalkoxy, $NR^{N1a}R^{N1b}$, $-C(O)R^{1a}$, $-C(O)OR^{O1a}$, $-C(O)NR^{N1a}R^{N1b}$, $-OR^{O1a}$, 3-12 membered carbocyclyl, phenyl, 5- or 6-membered heteroaryl, or 4-12 membered heterocyclyl, wherein the carbocyclyl, phenyl, 5- or 6-membered heteroaryl, or 4-12 membered heterocyclyl represented by R^{Z1} are each optionally substituted by one to four R^{1b} ;

10 each R^1 is, independently, halo, cyano, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxylalkyl, C_{1-6} alkoxylalkyl, C_{1-6} hydroxyalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, $NR^{N1a}R^{N1b}$, $-C(O)R^{1a}$, $-C(O)OR^{O1a}$, $-C(O)NR^{N1a}R^{N1b}$, $-OR^{O1a}$, $-(CH_2)_{0 \text{ or } 1-3-12}$ membered carbocyclyl, $-(CH_2)_{0 \text{ or } 1-4-12}$ membered heterocyclyl, $-(CH_2)_{0 \text{ or } 1-6-10}$ membered aryl, or $-(CH_2)_{0 \text{ or } 1-5-10}$ membered heteroaryl, wherein the C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl represented by R^1 are each
15 optionally substituted by one to four R^{1b} ;

R^{1a} , R^{O1a} , R^{N1a} , and R^{N1b} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, or 4-6 membered heterocyclyl;

each R^{1b} is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxylalkyl, C_{1-6} alkoxylalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkoxy, $-C(O)R^{1a}$, $-C(O)OR^{O1a}$,
20 $-C(O)NR^{N1a}R^{N1b}$, $-SO_2R^{1a}$, $-NR^{N1a}R^{N1b}$, $-NR^{N1a}C(O)R^{1a}$, $-NR^{N1a}C(O)OR^{O1a}$, $-NR^{N1a}SO_2R^{1a}$, $-NR^{N1a}SO_2NR^{N1a}R^{N1b}$, cyano, NO_2 , or OR^{O1a} ;

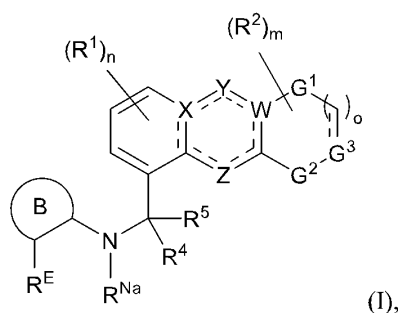
R^{N2} is H, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C(O)R^{2a}$, C_{3-6} cycloalkyl, phenyl, or 5-to 6-membered heteroaryl, wherein the phenyl and 5-to 6-membered heteroaryl represented by R^{N2} are each optionally substituted with one to three substituents selected from halo, C_{1-3} alkyl, and C_{1-3} haloalkyl;

25 each R^{G2} is, independently, H, halo, cyano, oxo (as appropriate), NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, $*=CH-R^7$ (as appropriate), C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} hydroxylalkyl, C_{1-6} alkoxylalkyl, C_{1-6} hydroxyalkoxy, $-C(O)R^{2a}$, $-C(O)OR^{O2a}$, $-C(O)NR^{N2a}R^{N2b}$, OR^{O2a} , $NR^{N2a}R^{N2b}$, SO_2R^{2a} , $-NR^{N2a}C(O)R^{2a}$, $-NR^{N2a}C(O)OR^{O2a}$, $-NR^{N2a}SO_3R^{2a}$, $-NR^{N2a}SO_3NR^{N2a}R^{N2a}$, $-(CH_2)_{0 \text{ or } 1-3-12}$ membered carbocyclyl, $-(CH_2)_{0 \text{ or } 1-4-12}$ membered heterocyclyl,
30 $-(CH_2)_{0 \text{ or } 1-6-10}$ membered aryl, or $-(CH_2)_{0 \text{ or } 1-5-10}$ membered heteroaryl, wherein the carbocyclyl, heterocyclyl, aryl, or heteroaryl represented by R^{G2} are each optionally substituted by one to four halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxylalkyl, C_{1-6} alkoxylalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkoxy, $-C(O)R^{2a}$, $-C(O)OR^{O2a}$, $-C(O)NR^{N2a}R^{N2b}$, cyano, NO_2 , OR^{O2a} , $NR^{N2a}R^{N2b}$, SO_3R^{2a} , $-NR^{N2a}C(O)R^{2a}$, $-NR^{N2a}C(O)OR^{O2a}$, $-NR^{N2a}SO_3R^{2a}$, or $-NR^{N2a}SO_3NR^{N2a}R^{N2a}$, and wherein the
35 C_{2-6} alkenyl is optionally substituted with phenyl or 5- to 6-membered heteroaryl;

each R^2 is independently halo, cyano, oxo (as appropriate), NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, $*=CH-R^7$ (as appropriate), C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} hydroxylalkyl, C_{1-6} alkoxylalkyl,

- C_{1-6} hydroxyalkoxy, $-C(O)R^{2a}$, $-C(O)OR^{O2a}$, $-C(O)NR^{N2a}R^{N2b}$, OR^{O2a} , $NR^{N2a}R^{N2b}$, SO_2R^{2a} ,
 $-NR^{N2a}C(O)R^{2a}$, $-NR^{N2a}C(O)OR^{2a}$, $-NR^{N2a}SO_3R^{2a}$, $-NR^{N2a}SO_3NR^{N2a}R^{N2a}$, $-(CH_2)_{0 \text{ or } 1-3-12}$ membered
 carbocyclyl, $-(CH_2)_{0 \text{ or } 1-4-12}$ membered heterocyclyl, $-(CH_2)_{0 \text{ or } 1-6-10}$ membered aryl, or
 $-(CH_2)_{0 \text{ or } 1-5-10}$ membered heteroaryl, wherein the carbocyclyl, heterocyclyl, aryl, or heteroaryl
 5 represented by R^2 are each optionally substituted by one to four halo, C_{1-6} alkyl, C_{1-6} haloalkyl,
 C_{1-6} hydroxylalkyl, C_{1-6} alkoxylalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkoxy, $-C(O)R^{2a}$,
 $-C(O)OR^{O2a}$, $-C(O)NR^{N2a}R^{N2b}$, cyano, NO_2 , OR^{O2a} , $NR^{N2a}R^{N2b}$, SO_3R^{2a} , $-NR^{N2a}C(O)R^{2a}$,
 $-NR^{N2a}C(O)OR^{2a}$, $-NR^{N2a}SO_3R^{2a}$, or $-NR^{N2a}SO_3NR^{N2a}R^{N2a}$, and wherein the C_2 alkenyl is optionally
 substituted with phenyl or 5- to 6-membered heteroaryl; or
 10 two R^2 , two R^{G2} , one R^2 and one R^{N2} , one R^2 and one R^{G2} , or one R^{G2} and one R^{N2} , together
 with the atoms to which they are connected, form 3- to 12 membered carbocyclyl, 4- to 12 membered
 heterocyclyl, phenyl, naphthyl or 5- to 10-membered heteroaryl, each of which is optionally
 substituted by one to four R^6 ;
 R^{2a} and R^{O2a} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, or
 15 4-6 membered heterocyclyl;
 R^{N2a} and R^{N2b} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{O2a} , or C_{3-6} cycloalkyl;
 * is the connection point to the tricyclic core ring;
 R^7 is C_{1-4} alkyl, 3- to 12 membered carbocyclyl, 4- to 12 membered heterocyclyl, phenyl,
 naphthyl, or 5- to 10-membered heteroaryl, each of which is optionally substituted by one to four
 20 halo, $-OH$, $-NH_2$, cyano, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, or heteroaryl;
 each R^6 is independently halo, cyano, oxo (as appropriate), NO_2 , C_{1-6} alkyl, C_{2-6} alkenyl,
 C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} hydroxylalkyl, C_{1-6} alkoxylalkyl, C_{1-6} hydroxyalkoxy, $-C(O)R^{6a}$,
 $-C(O)OR^{O6a}$, $-C(O)NR^{N6a}R^{N6b}$, OR^{O6a} , $NR^{N6a}R^{N6b}$, SO_2R^{6a} , $-NR^{N6a}C(O)R^{6a}$, $-NR^{N6a}C(O)OR^{6a}$,
 $-NR^{N6a}SO_3R^{6a}$, $-NR^{N6a}SO_3NR^{N6a}R^{N6a}$, $-(CH_2)_{0 \text{ or } 1-3-12}$ membered carbocyclyl, $-(CH_2)_{0 \text{ or } 1-4-12}$
 25 membered heterocyclyl, $-(CH_2)_{0 \text{ or } 1-6-10}$ membered aryl, or $-(CH_2)_{0 \text{ or } 1-5-10}$ membered heteroaryl,
 wherein the carbocyclyl, heterocyclyl, aryl, or heteroaryl represented by R^6 are each optionally
 substituted by one to four halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxylalkyl, C_{1-6} alkoxylalkyl,
 C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkoxy, $-C(O)R^{6a}$, $-C(O)OR^{O6a}$, $-C(O)NR^{N6a}R^{N6b}$, cyano, NO_2 ,
 OR^{O6a} , $NR^{N6a}R^{N6b}$, SO_3R^{6a} , $-NR^{N6a}C(O)R^{6a}$, $-NR^{N6a}C(O)OR^{6a}$, $-NR^{N6a}SO_3R^{6a}$, or
 30 $-NR^{N6a}SO_3NR^{N6a}R^{N6a}$,
 or two R^6 , together with the atoms to which they are attached, form C_{3-6} cycloalkyl;
 R^{6a} and R^{O6a} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, or
 4-6 membered heterocyclyl;
 R^{N6a} and R^{N6b} are each independently H, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{O6a} , or
 35 C_{3-6} cycloalkyl;
 Ring B is phenyl or 5- to 10-membered monocyclic or bicyclic heteroaryl, each of which is
 substituted with R^E ortho to the $N(R^{Na})$ substituent, and optionally substituted with one to four R^3 ;

- each R^3 is independently halo, cyano, NO_2 , C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} hydroxylalkyl, C_{1-6} alkoxylalkyl, C_{1-6} hydroxyalkoxy, $-C(O)R^{3a}$, $-C(O)OR^{O3a}$, $-C(O)NR^{N3a}R^{N3b}$, OR^{O3a} , $NR^{N3a}R^{N3b}$, SO_2R^{3a} , $-NR^{N3a}C(O)R^{3a}$, $-NR^{N3a}C(O)OR^{3a}$, $-NR^{N3a}SO_3R^{3a}$, $-NR^{N3a}SO_3NR^{N3a}R^{N3a}$, $-(CH_2)_{0 \text{ or } 1-3-12}$ membered carbocyclyl, $-(CH_2)_{0 \text{ or } 1-4-12}$ membered heterocyclyl, $-(CH_2)_{0 \text{ or } 1-6-10}$ membered aryl, or $-(CH_2)_{0 \text{ or } 1-5-10}$ membered heteroaryl, wherein the carbocyclyl, heterocyclyl, aryl, or heteroaryl represented by R^3 are each optionally substituted by one to four halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxylalkyl, C_{1-6} alkoxylalkyl, C_{1-6} hydroxyalkoxy, $-C(O)R^{3a}$, $-C(O)OR^{O3a}$, $-C(O)NR^{N3a}R^{N3b}$, cyano, NO_2 , OR^{O3a} , $NR^{N3a}R^{N3b}$, SO_3R^{3a} , $-NR^{N3a}C(O)R^{3a}$, $-NR^{N3a}C(O)OR^{3a}$, $-NR^{N3a}SO_3R^{3a}$, or $-NR^{N3a}SO_3NR^{N3a}R^{N3a}$,
- R^E is H, cyano, C_{1-4} alkyl, $-C(O)R^8$, $-C(NH)NR^{N3E}R^{N3E}$, $-S(O_2)NR^{N3E}R^{N3E}$, $-C(O)OR^{O3a}$, $-C(O)NR^{N3a}R^{N3b}$, phenyl, 5- to 10-membered heteroaryl, or 4- to 12-membered heterocyclyl, wherein the C_{1-4} alkyl is optionally substituted by one to four R^{Ea} , and the phenyl, 5- to 10-membered heteroaryl, and 4- to 12-membered heterocyclyl are each optionally substituted with one or two R^{Eb} ; or R^E and R^3 , together with the atoms to which they are attached, form a 5- to 6-membered monocyclic heterocyclyl;
- R^8 is H, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-4} thioalkyl, C_{1-4} thiohaloalkyl, or SH;
- each R^{Ea} is, independently halo, cyano, OH, or $NR^{N3E}R^{N3E}$;
- each R^{Eb} is, independently, oxo, =S, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, cyano, C_{1-3} alkoxy, -OH, or $-C(O)NR^{N3E}R^{N3E}$, wherein the C_{1-3} alkyl represented by R^{Eb} is optionally substituted by 4- to 6-membered heterocyclyl optionally substituted with C_{1-3} alkyl;
- each R^{N3E} is, independently, H, OH or C_{1-3} alkyl;
- R^{3a} and R^{O3a} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, or 4-6 membered heterocyclyl, wherein the C_{1-6} alkyl represented by R^{3a} or R^{O3a} is optionally substituted by a 4-6 membered heterocyclyl;
- R^{N3a} and R^{N3b} are each independently H, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{O3a} , $-SO_2C_{1-4}$ alkyl, or C_{3-6} cycloalkyl, wherein the C_{1-6} alkyl represented by R^{N3a} or R^{N3b} is optionally substituted by C_{1-3} alkoxy or a 5- to 6-membered heteroaryl;
- R^4 is C_{1-3} alkyl and
- R^5 is H.
- In a second aspect, the present disclosure provides a compound according to the first aspect, wherein the compound is represented by Formula (I):



a pharmaceutically acceptable salt, wherein:

- each R^6 is independently halo, cyano, oxo (as appropriate), NO_2 , C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} hydroxylalkyl, C_{1-6} alkoxylalkyl, C_{1-6} hydroxyalkoxy, $-\text{C}(\text{O})\text{R}^{6a}$, $-\text{C}(\text{O})\text{OR}^{6a}$, $-\text{C}(\text{O})\text{NR}^{N6a}\text{R}^{N6b}$, OR^{6a} , $\text{NR}^{N6a}\text{R}^{N6b}$, SO_2R^{6a} , $-\text{NR}^{N6a}\text{C}(\text{O})\text{R}^{6a}$, $-\text{NR}^{N6a}\text{C}(\text{O})\text{OR}^{6a}$, $-\text{NR}^{N6a}\text{SO}_3\text{R}^{6a}$, $-\text{NR}^{N6a}\text{SO}_3\text{NR}^{N6a}\text{R}^{N6a}$, $-(\text{CH}_2)_{0 \text{ or } 1-3-12}$ membered carbocyclyl, $-(\text{CH}_2)_{0 \text{ or } 1-4-12}$ membered heterocyclyl, $-(\text{CH}_2)_{0 \text{ or } 1-6-10}$ membered aryl, or $-(\text{CH}_2)_{0 \text{ or } 1-5-10}$ membered heteroaryl, wherein the carbocyclyl, heterocyclyl, aryl, or heteroaryl represented by R^6 are each optionally substituted by one to four halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxylalkyl, C_{1-6} alkoxylalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkoxy, $-\text{C}(\text{O})\text{R}^{6a}$, $-\text{C}(\text{O})\text{OR}^{6a}$, $-\text{C}(\text{O})\text{NR}^{N6a}\text{R}^{N6b}$, cyano, NO_2 , OR^{6a} , $\text{NR}^{N6a}\text{R}^{N6b}$, SO_3R^{6a} , $-\text{NR}^{N6a}\text{C}(\text{O})\text{R}^{6a}$, $-\text{NR}^{N6a}\text{C}(\text{O})\text{OR}^{6a}$, $-\text{NR}^{N6a}\text{SO}_3\text{R}^{6a}$, or $-\text{NR}^{N6a}\text{SO}_3\text{NR}^{N6a}\text{R}^{N6a}$,

- R^7 is 3- to 12 membered carbocyclyl, 4- to 12 membered heterocyclyl, phenyl, naphthyl, or 5- to 10-membered heteroaryl, each of which is optionally substituted by one to four halo, $-\text{OH}$, $-\text{NH}_2$, cyano, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, or heteroaryl;

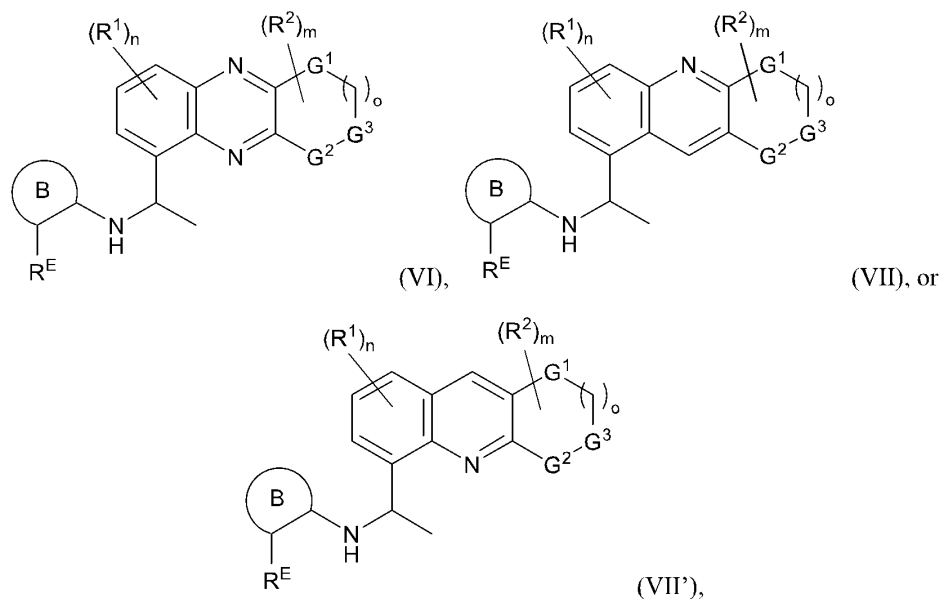
R^E is $-\text{C}(\text{O})\text{OR}^{O3a}$ or $-\text{C}(\text{O})\text{NR}^{N3a}\text{R}^{N3b}$,

R^{3a} and R^{O3a} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, or 4-6 membered heterocyclyl; and

- R^{N3a} and R^{N3b} are each independently H, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{O3a} , or C_{3-6} cycloalkyl. The definitions of the remaining variables are provided in the first aspect.

In one aspect, R^4 is $-\text{CH}_3$ or $-\text{CH}_2\text{CH}_3$. In another aspect, R^4 is $-\text{CH}_3$.

In a third aspect, the present disclosure provides a compound according to the first or second aspect, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by Formula (VI), (VII), or (VII'):

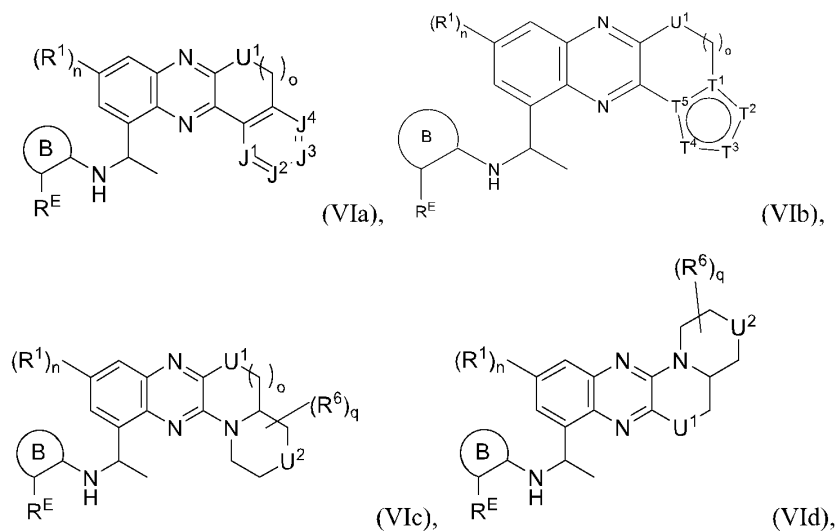


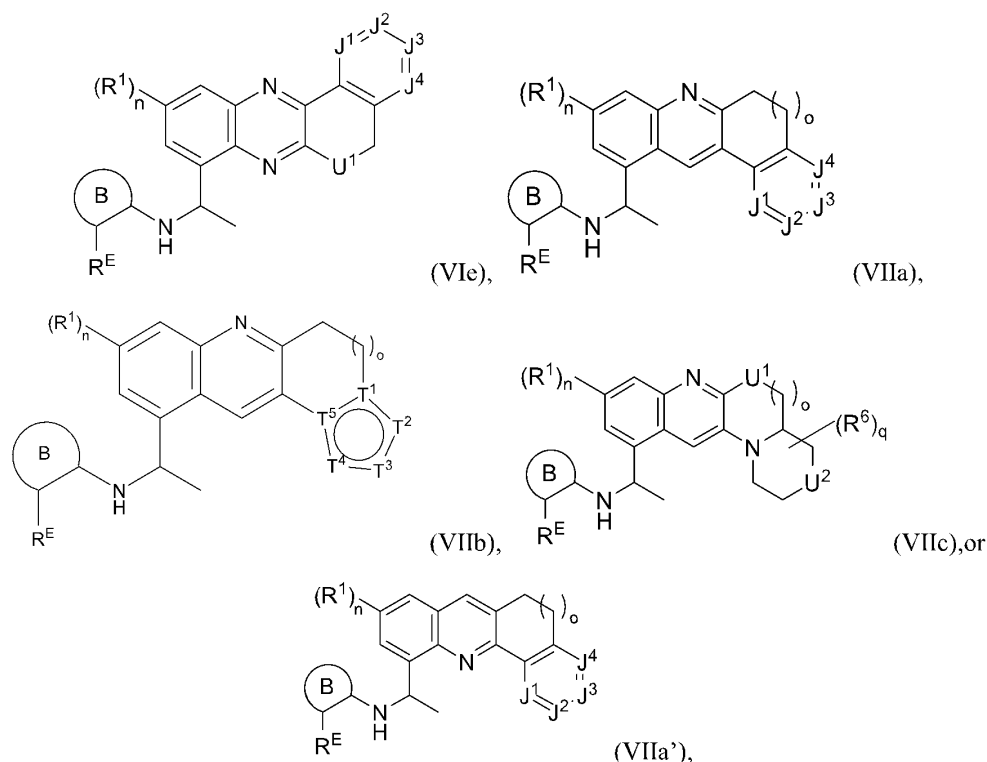
wherein m and n are each, independently, 0, 1 or 2; and o is 0 or 1. The definitions of the remaining variables are provided in the first or second aspect.

- 5 In an alternative of the third aspect, the compound is represented by Formula (VI). In another alternative of the third aspect, the compound is represented by Formula (VII). In another alternative of the third aspect, the compound is represented by Formula (VII').

In a fourth aspect, the present disclosure provides a compound according to the third aspect, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by Formula (VIa),

- 10 (VIb), (VIc), (VIId), (VIe), (VIIa), (VIIb), (VIIc), or (VIIa'):





wherein:

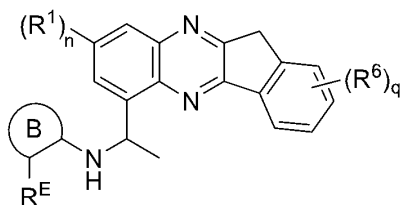
- 5 n and o, are each, independently 0 or 1;
 q is 0, 1, or 2;
 J¹, J², J³, and J⁴, are each, independently, N, CH, or CR⁶;
 T¹ and T⁵, are each, independently, N or C;
 T², T³, and T⁴, are each, independently, N, NR^{N6}, O, S, CH, or CR⁶;
 10 R^{N6} is H, C₁₋₃alkyl, C₁₋₃haloalkyl, C₃₋₆cycloalkyl, phenyl, or 5- to 6-membered heteroaryl,
 wherein the phenyl and 5- to 6-membered heteroaryl represented by R^{N6} are each optionally
 substituted by one to three halo, C₁₋₃alkyl, C₁₋₃haloalkyl, cyano, OH, C₁₋₃alkoxy, or C₁₋₃haloalkoxy;
 U¹ is NR^{N2}, CH₂, or O;
 U² is absent, NR^{N6}, CH₂, or O. The definitions of the remaining variables are provided in the
 15 third aspect.

- In an alternative of the fourth aspect, the compound is represented by Formula (VIa). In
 another alternative of the fourth aspect, the compound is represented by Formula (VIb). In another
 alternative of the fourth aspect, the compound is represented by Formula (VIc). In another alternative
 of the fourth aspect, the compound is represented by Formula (VIId). In another alternative of the
 20 fourth aspect, the compound is represented by Formula (VIe). In another alternative of the fourth
 aspect, the compound is represented by Formula (VIIa). In another alternative of the fourth aspect, the
 compound is represented by Formula (VIIb). In another alternative of the fourth aspect, the compound

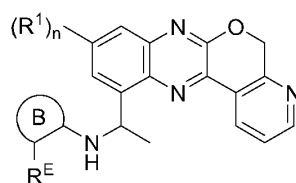
is represented by Formula (VIIc). In another alternative of the fourth aspect, the compound is represented by Formula (VIIa').

In a fifth aspect, the present disclosure provides a compound according to the fourth aspect, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by Formula (VIa-1),

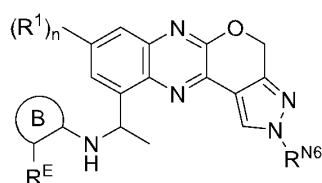
5 (VIa-2), (VIb-1), (VIc-1), (VIc-2), (VIc-3), (VIc-4), (VIId-1), (VIId-2), (VIId-1), (VIId-2), (VIId-1), or (VIIc-1):



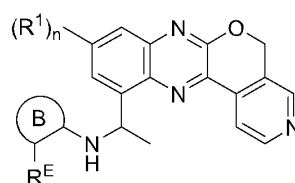
(VIa-1),



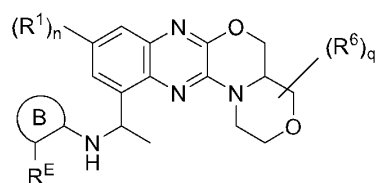
(VIa-2),



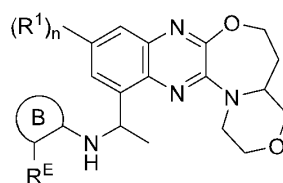
(VIb-1),



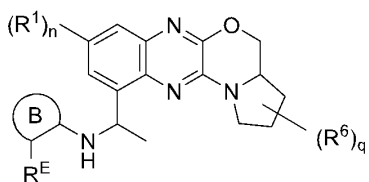
(VIa-3),



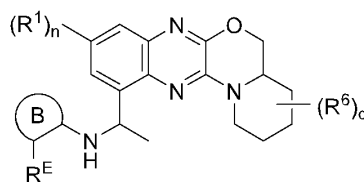
(VIc-1),



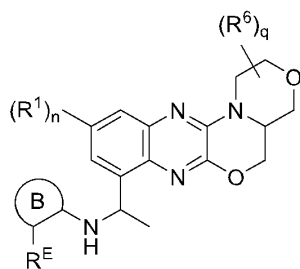
(VIc-2),



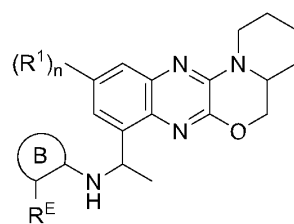
(VIc-3),



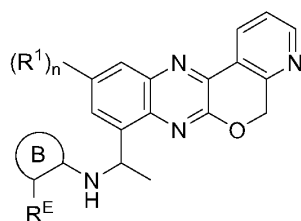
(VIc-4),



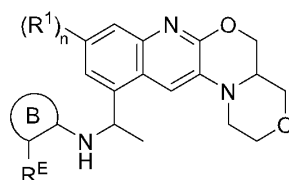
(VIId-1),



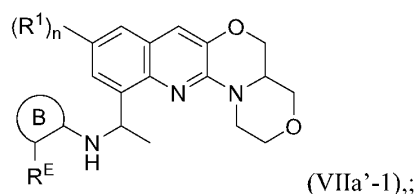
(VIId-2),



(VIId-1),



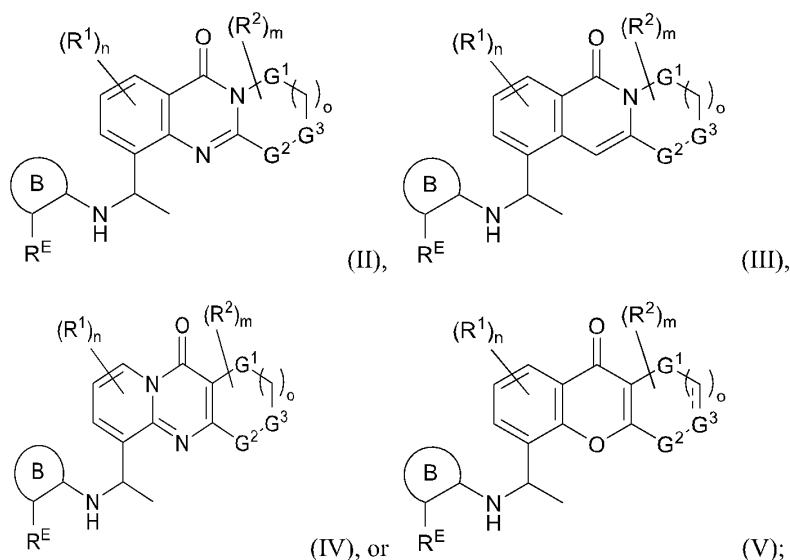
(VIIc-1), or



wherein n is 0 or 1 and q is 0, 1, or 2. The definitions of the remaining variables are provided in the fourth aspect.

In an alternative of the fifth aspect, the compound is represented by Formula (VIa-1). In another alternative of the fifth aspect, the compound is represented by Formula (VIa-2). In another alternative of the fifth aspect, the compound is represented by Formula (VIb-1). In another alternative of the fifth aspect, the compound is represented by Formula (VIc-1). In another alternative of the fifth aspect, the compound is represented by Formula (VIc-2). In another alternative of the fifth aspect, the compound is represented by Formula (VIc-3). In another alternative of the fifth aspect, the compound is represented by Formula (VIc-4). In another alternative of the fifth aspect, the compound is represented by Formula (VId-1). In another alternative of the fifth aspect, the compound is represented by Formula (VId-2). In another alternative of the fifth aspect, the compound is represented by Formula (VIe-1).

In a sixth aspect, the present disclosure provides a compound according to the first or second aspect, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by Formula (II), (III), (IV), or (V):



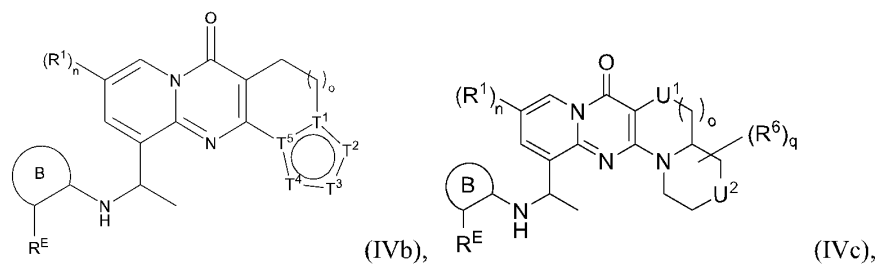
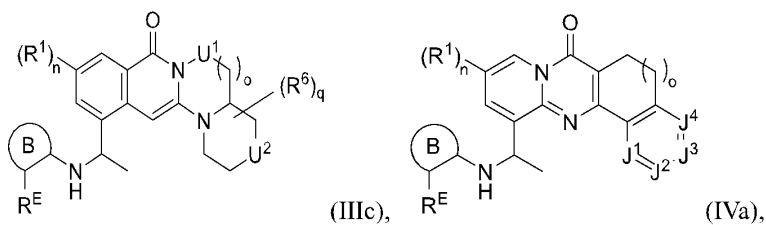
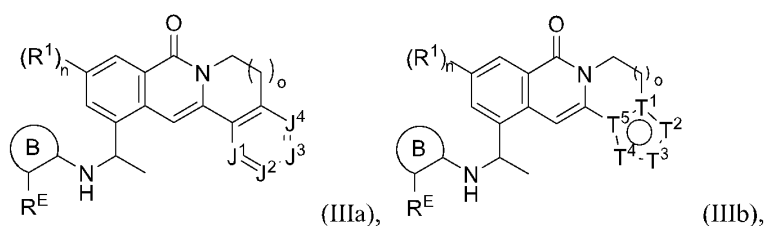
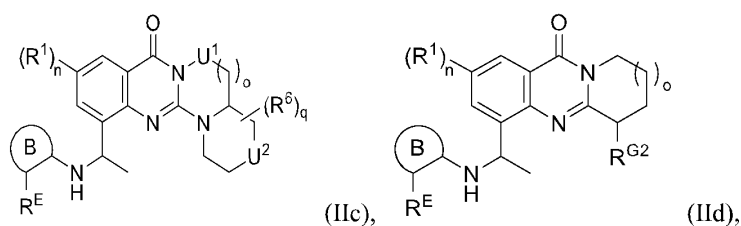
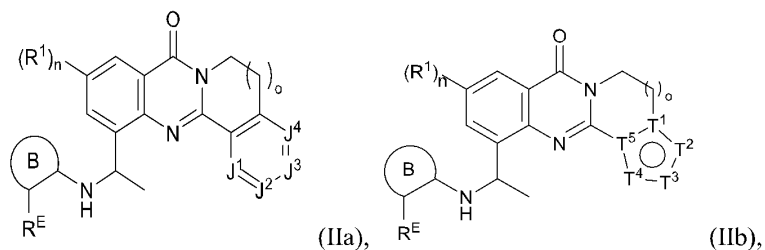
wherein m and n are each, independently, 0, 1, or 2; o is 0 or 1. The definitions of the remaining variables are provided in the first or second aspect.

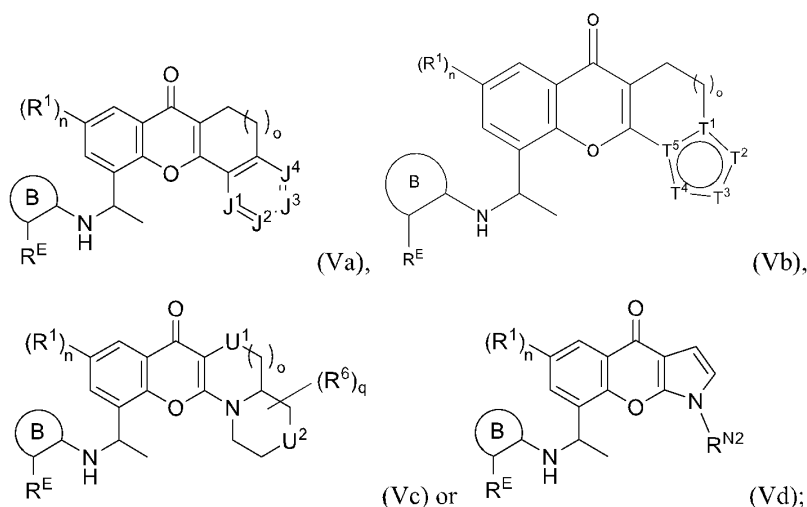
In an alternative of the sixth aspect, the compound is represented by Formula (II). In another alternative of the sixth aspect, the compound is represented by Formula (III). In another alternative of

the sixth aspect, the compound is represented by Formula (IV). In another alternative of the sixth aspect, the compound is represented by Formula (V).

In a seventh aspect, the present disclosure provides a compound according to the sixth aspect, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by Formula (IIa),

5 (IIb), (IIc), (IIId), (IIIa), (IIIb), (IIIc), (IVa), (IVb), (IVc), (Va), (Vb), (Vc), or (Vd):





wherein:

n and o, are each, independently, 0 or 1;

5 q is 0, 1, or 2;

J¹, J², J³, and J⁴, are each, independently, N, CH, or CR⁶;

T¹ and T⁵, are each, independently, N or C;

T², T³, and T⁴, are each, independently, N, NR^{N6}, O, S, CH, or CR⁶;

10 R^{N6} is H, C₁₋₃alkyl, C₁₋₃haloalkyl, C₃₋₆cycloalkyl, phenyl, naphthyl, or 5- to 6-membered heteroaryl, wherein the phenyl, naphthyl, and 5- to 6-membered heteroaryl represented by R^{N6} are each optionally substituted by one to three halo, C₁₋₃alkyl, C₁₋₃haloalkyl, cyano, OH, C₁₋₃alkoxy, or C₁₋₃haloalkoxy;

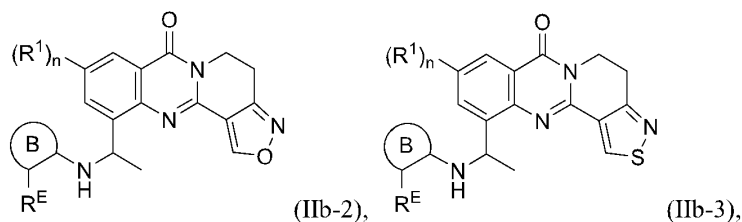
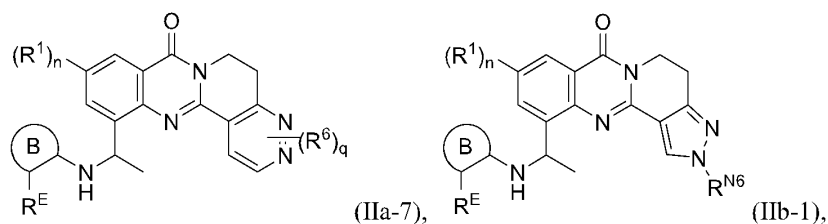
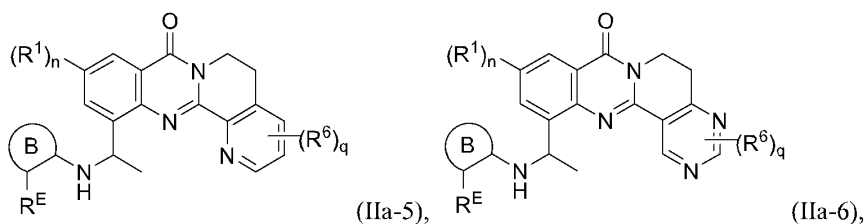
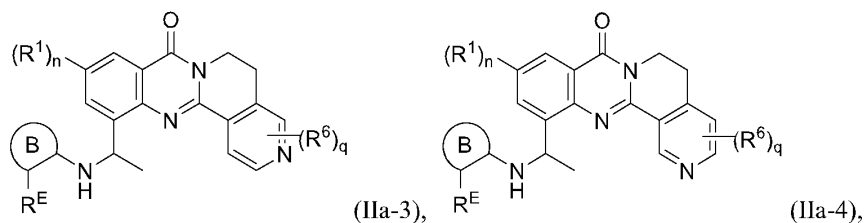
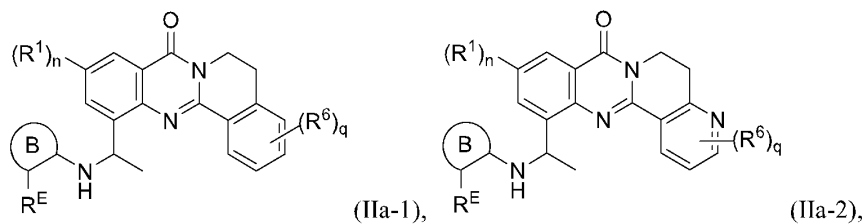
U¹ is NR^{N2}, CH₂, or O;

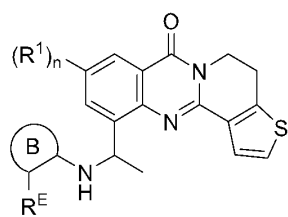
15 U² is NR^{N6}, CH₂, or O. The definitions of the remaining variables are provided in the sixth aspect.

In an alternative of the seventh aspect, the compound is represented by Formula (IIa). In another alternative of the seventh aspect, the compound is represented by Formula (IIb). In another alternative of the seventh aspect, the compound is represented by Formula (IIc). In another alternative of the seventh aspect, the compound is represented by Formula (IId). In another alternative of the seventh aspect, the compound is represented by Formula (IIIa). In another alternative of the seventh aspect, the compound is represented by Formula (IIIb). In another alternative of the seventh aspect, the compound is represented by Formula (IIIc). In another alternative of the seventh aspect, the compound is represented by Formula (IVa). In another alternative of the seventh aspect, the compound is represented by Formula (IVb). In another alternative of the seventh aspect, the compound is represented by Formula (IVc). In another alternative of the seventh aspect, the compound is represented by Formula (Va). In another alternative of the seventh aspect, the compound

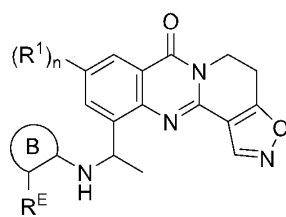
is represented by Formula (Vb). In another alternative of the seventh aspect, the compound is represented by Formula (Vc).

- In an eighth aspect, the present disclosure provides a compound according to the seventh aspect, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by
- 5 Formula (IIa-1), (IIa-2), (IIa-3), (IIa-4), (IIa-5), (IIa-6), (IIa-7), (IIb-1), (IIb-2), (IIb-3), (IIb-4), (IIb-5), (IIb-6), (IIb-7), (IIb-8), (IIb-9), (IIb-10), (IIb-11), (IIc-1), (IIIa-1), (IIIb-1), (IIIc-1), (IVc-1), (Va-1), (Va-2), (Va-3), or (Vc-1):

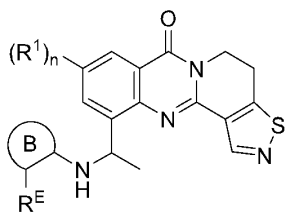




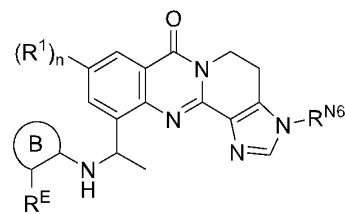
(IIb-4),



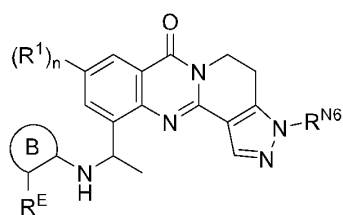
(IIb-5),



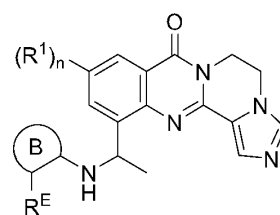
(IIb-6),



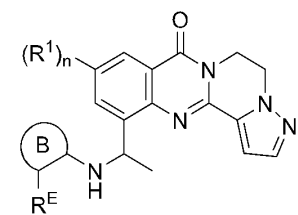
(IIb-7),



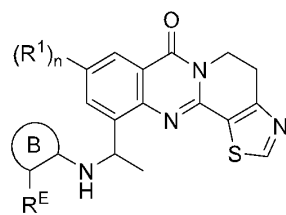
(IIb-8),



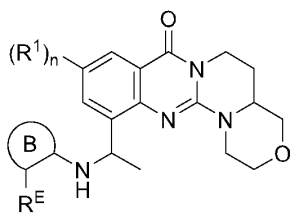
(IIb-9),



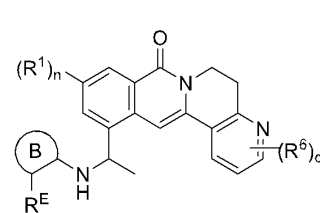
(IIb-10),



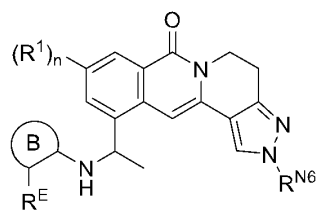
(IIb-11),



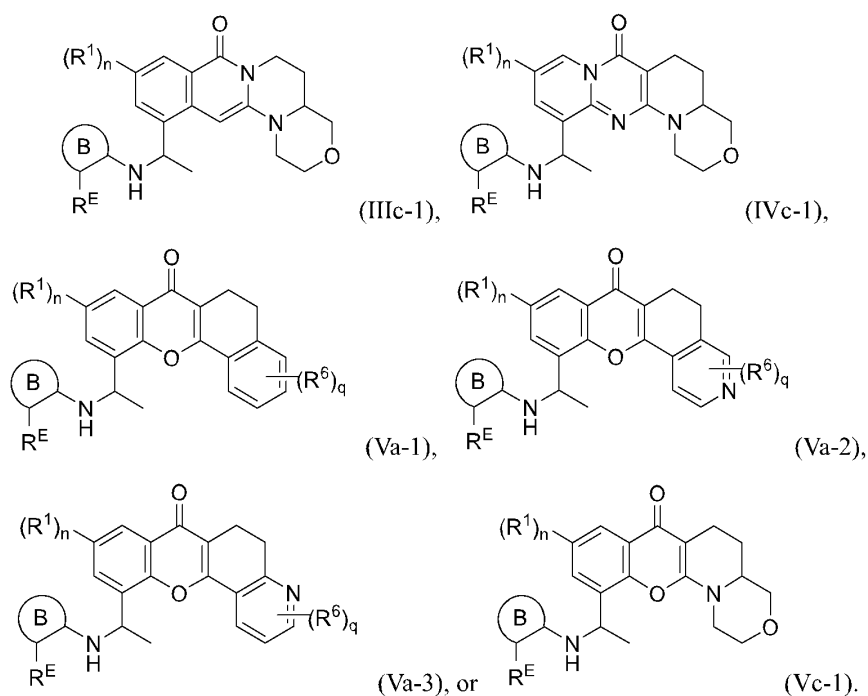
(IIc-1),



(IIIa-1),



(IIIb-1),

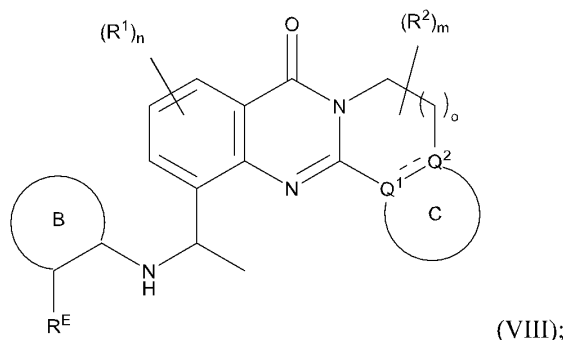


The definitions of the remaining variables are provided in the seventh aspect.

- 5 In an alternative of the eighth aspect, the compound is represented by Formula (IIa-1). In another alternative of the eighth aspect, the compound is represented by Formula (IIa-2). In another alternative of the eighth aspect, the compound is represented by Formula (IIa-3). In another alternative of the eighth aspect, the compound is represented by Formula (IIa-4). In another alternative of the eighth aspect, the compound is represented by Formula (IIa-5). In another alternative of the eighth aspect, the compound is represented by Formula (IIa-6). In another alternative of the eighth aspect, the compound is represented by Formula (IIa-7). In another alternative of the eighth aspect, the compound is represented by Formula (IIb-1). In another alternative of the eighth aspect, the compound is represented by Formula (IIb-2). In another alternative of the eighth aspect, the compound is represented by Formula (IIb-3). In another alternative of the eighth aspect, the compound is represented by Formula (IIb-4). In another alternative of the eighth aspect, the compound is represented by Formula (IIb-5). In another alternative of the eighth aspect, the compound is represented by Formula (IIb-6). In another alternative of the eighth aspect, the compound is represented by Formula (IIb-7). In another alternative of the eighth aspect, the compound is represented by Formula (IIb-8). In another alternative of the eighth aspect, the compound is represented by Formula (IIb-9). In another alternative of the eighth aspect, the compound is represented by Formula (IIb-10). In another alternative of the eighth aspect, the compound is represented by Formula (IIb-11). In another alternative of the eighth aspect, the compound is represented by Formula (IIc-1). In another alternative of the eighth aspect, the compound is represented by Formula (IIIa-1). In another
- 10
- 15
- 20

alternative of the eighth aspect, the compound is represented by Formula (IIIb-1). In another alternative of the eighth aspect, the compound is represented by Formula (IIIc-1). In another alternative of the eighth aspect, the compound is represented by Formula (IVc-1). In another alternative of the eighth aspect, the compound is represented by Formula (Va-1). In another alternative of the eighth aspect, the compound is represented by Formula (Va-2). In another alternative of the eighth aspect, the compound is represented by Formula (Va-3). In another alternative of the eighth aspect, the compound is represented by Formula (Vc-1).

In a ninth aspect, the present disclosure provides a compound according to the first or second aspect, wherein the compound is represented by Formula (VIII):



or a pharmaceutically acceptable salt thereof, wherein:

n is 0, 1, or 2;

m is 0, 1, or 2;

o is 0 or 1;

- each R^1 is, independently, halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-NR^{N1a}R^{N1b}$, $-C(O)R^{1a}$, $-C(O)OR^{O1a}$, $-C(O)NR^{N1a}R^{N1b}$, OR^{O1a} , C_{3-6} cycloalkyl, phenyl, or 5-to 6-membered monocyclic heteroaryl, wherein the C_{3-6} cycloalkyl, phenyl, and 5-to 6-membered monocyclic heteroaryl represented by R^1 are each optionally substituted by one to three halo, C_{1-3} alkyl, C_{1-3} haloalkyl, OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, $-C(O)R^{1a}$, $-C(O)OR^{O1a}$, or $-C(O)NR^{N1a}R^{N1b}$,
- each R^2 is independently halo, oxo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, $-NR^{N2a}R^{N2b}$, $-C(O)R^{2a}$, $-C(O)OR^{O2a}$, $-C(O)NR^{N2a}R^{N2b}$, OR^{O2a} , C_{3-6} cycloalkyl, phenyl, or 5-to 6-membered monocyclic heteroaryl, wherein the C_{3-6} cycloalkyl, phenyl, and 5-to 6-membered monocyclic heteroaryl represented by R^2 are each optionally substituted by one to three halo, C_{1-3} alkyl, C_{1-3} haloalkyl, OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, $-C(O)R^{2a}$, $-C(O)OR^{O2a}$, or $-C(O)NR^{N2a}R^{N2b}$,
- R^{2a} , R^{O2a} , R^{N2a} , and R^{N2b} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, or 4-6 membered heterocyclyl;

Ring B is phenyl or 5- to 6-membered monocyclic heteroaryl, each of which is substituted with R^E ortho to the NH substituent, and one to three R^3 ;

- each R^3 is independently halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, $-NR^{N3a}R^{N3b}$, $-C(O)R^{3a}$, $-C(O)OR^{O3a}$, $-C(O)NR^{N3a}R^{N3b}$, OR^{O3a} , C_{3-6} cycloalkyl, phenyl, or 5-to 6-membered monocyclic

heteroaryl, wherein the C₃₋₆cycloalkyl, phenyl, and 5-to 6-membered monocyclic heteroaryl represented by R³ are each optionally substituted by one to three halo, C₃₋₃alkyl, C₃₋₃haloalkyl, OH, C₁₋₃alkoxy, C₁₋₃haloalkoxy, -C(O)R^{3a}, -C(O)OR^{3a}, or -C(O)NR^{N3a}R^{N3b};

R^{3a}, R^{3b}, R^{N3a}, and R^{N3b} are each independently H, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, or 4-6 membered heterocyclyl;

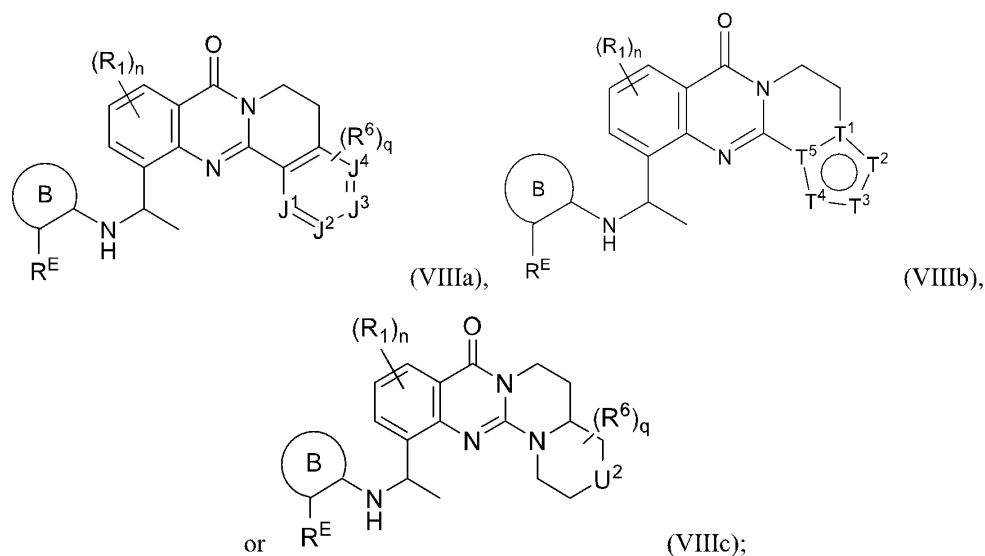
Ring C is 6-membered monocyclic heterocyclyl, phenyl, or 5- to 6-membered monocyclic heteroaryl, each of which is optionally substituted with one to three R⁶;

Q¹ and Q² are each, independently, C, CH, or N, provided that at least one of Q¹ or Q² is C or CH;

each R⁶ is, independently, halo, oxo, cyano, C₁₋₆alkyl, C₁₋₆haloalkyl, -NR^{N6a}R^{N6b}, -C(O)R^{6a}, -C(O)OR^{6a}, -C(O)NR^{N6a}R^{N6b}, OR^{6a}, C₁₋₆cycloalkyl, phenyl, or 5-to 6-membered monocyclic heteroaryl, wherein the C₁₋₆cycloalkyl, phenyl, and 5-to 6-membered monocyclic heteroaryl represented by R⁶ are each independently substituted by one to three halo, OH, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, -C(O)R^{6a}, -C(O)OR^{6a}, or -C(O)NR^{N6a}R^{N6b};

R^{6a}, R^{6b}, R^{N6a}, and R^{N6b} are each independently H, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆cycloalkyl, or 4-6 membered heterocyclyl. The definitions of the remaining variables are provided in the first or second aspect.

In a tenth aspect, the present disclosure provides a compound according to the ninth aspect, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by Formula (VIIIa), (VIIIb), or (VIIIc):



wherein:

n is 0 or 1;
q is 0, 1, or 2;
U² is NR^{N6}, CH₂, or O;

J^1 , J^2 , J^3 , and J^4 , are each, independently, N or CH, wherein at least one of J^1 , J^2 , J^3 , and J^4 is CH;

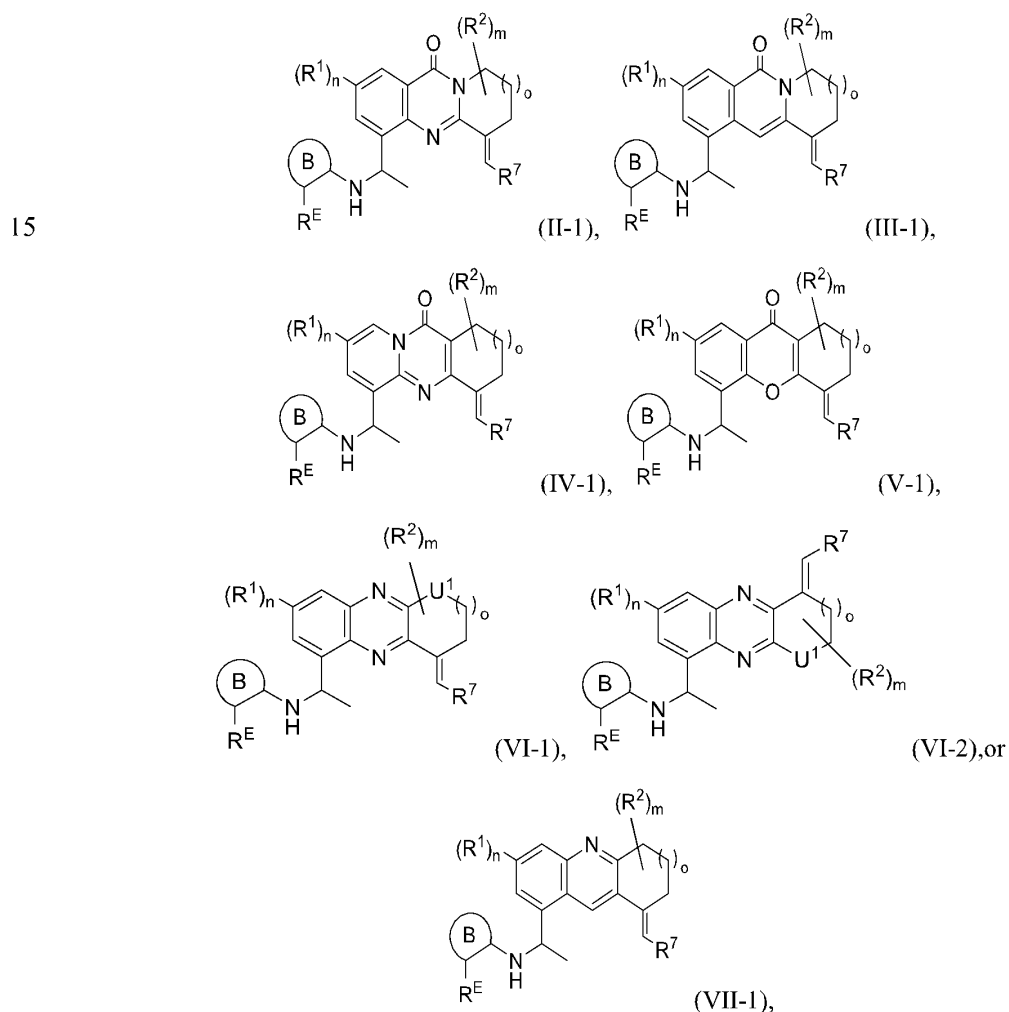
T^1 and T^5 , are each, independently, N or C;

T^2 , T^3 , and T^4 , are each, independently, N, NR^{N6} , O, S, or CH;

- 5 R^{N6} is H, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{3-6} cycloalkyl, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl represented by R^{N6} are each optionally substituted by one to three halo, C_{1-3} alkyl, C_{1-3} haloalkyl, cyano, OH, C_{1-3} alkoxy, or C_{1-3} haloalkoxy. The definitions of the remaining variables are provided in the ninth aspect.

- 10 In an alternative tenth aspect, the compound is of Formula (VIIIa). In another alternative of the tenth aspect, the compound is of Formula (VIIIb). In another alternative of the tenth aspect, the compound is of Formula (VIIIc).

In an eleventh aspect, the present disclosure provides a compound according to the first aspect, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by Formula (II-1), (III-1), (IV-1), (V-1), (VI-1), (VI-2), or (VII-1):



wherein

m, n, and o, are each, independently 0 or 1;

U¹ is NR^{N2}, CH₂, or O;

R⁷ is C₁₋₄alkyl, 5- or 6-membered heterocyclyl, phenyl, or 5- or 6-membered heteroaryl,

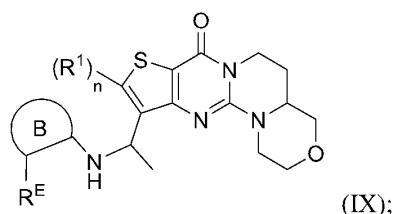
5 wherein the 5- or 6-membered heterocyclyl, phenyl, or 5- or 6-membered heteroaryl are each optionally substituted by one to two halo, -OH, -NH₂, cyano, C₁₋₃alkyl, C₁₋₃alkyl-OR^{O7a}, C₃₋₆cycloalkyl, C₁₋₃haloalkyl, or 4-to 6 membered heterocyclyl;

R^{O7a} is H or C₁₋₃alkyl. The definitions of the remaining variables are provided in the first aspect.

10 In an alternative of the eleventh aspect, the compound is of Formula (II-1). In another alternative of the eleventh aspect, the compound is of Formula (III-1). In another alternative of the eleventh aspect, the compound is of Formula (IV-1). In another alternative of the eleventh aspect, the compound is of Formula (V-1). In another alternative of the eleventh aspect, the compound is of Formula (VI-1). In another alternative of the eleventh aspect, the compound is of Formula (VI-2). In
15 another alternative of the eleventh aspect, the compound is of Formula (VII-1).

In a twelfth aspect, the present disclosure provides a compound according to the eleventh aspect, or a pharmaceutically acceptable salt thereof, wherein R⁷ is C₁₋₃alkyl, phenyl, pyridyl, isoxazolyl, pyrazolyl, imidazolyl, tetrahydrofuranyl, or tetrahydro-2H-pyranyl, wherein the phenyl, pyridyl, isoxazolyl, pyrazolyl, imidazolyl, tetrahydrofuranyl, and tetrahydro-2H-pyranyl are each
20 optionally substituted by one to two halo, -OH, C₁₋₃alkoxy, -NH₂, cyano, C₁₋₃alkyl, C₁₋₃haloalkyl, C₁₋₃alkyl-OR^{O7a}, or cyclopropyl, or morpholinyl; R^{O7a} is H or C₁₋₃alkyl. The definitions of the remaining variables are provided in the eleventh aspect.

In a thirteenth aspect, the present disclosure provides a compound according to the first aspect, wherein the compound is represented by Formula (IX):



25

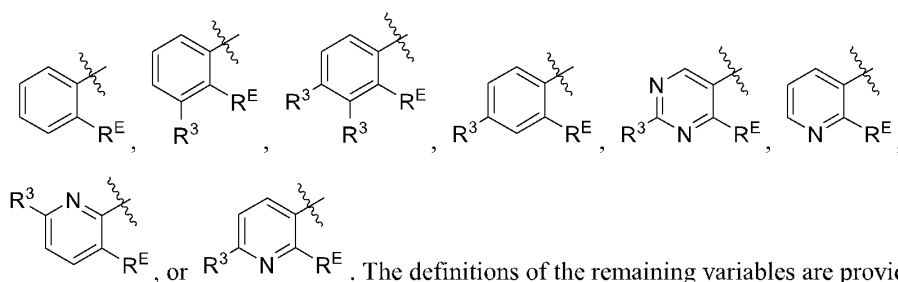
or a pharmaceutically acceptable salt thereof. The definitions of the remaining variables are provided in the first aspect.

In a fourteenth aspect, the present disclosure provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, or thirteenth aspect,
30 or a pharmaceutically acceptable salt thereof, wherein Ring B is phenyl or 6-membered monocyclic heteroaryl, each of which is substituted with R^E ortho to the NR^{Na} substituent, and further optionally

substituted with one or two R^3 . The definitions of the remaining variables are provided in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, or thirteenth aspect.

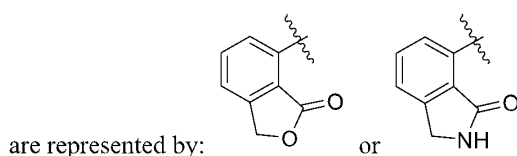
In a fifteenth aspect, the present disclosure provides a compound according to the fourteenth aspect, or a pharmaceutically acceptable salt thereof, wherein Ring B is phenyl, pyrimidinyl, or pyridinyl, each of which is substituted with R^E ortho to the NR^{Na} substituent, and further optionally substituted with one or two R^3 . The definitions of the remaining variables are provided in the fourteenth aspect.

In a sixteenth aspect, the present disclosure provides a compound according to the fifteenth aspect, or a pharmaceutically acceptable salt thereof, wherein Ring B and R^E , together with optionally substituted R^3 , are represented by:



The definitions of the remaining variables are provided in the fifteenth aspect.

In a seventeenth aspect, the present disclosure provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, or thirteenth aspect, or a pharmaceutically acceptable salt thereof, Ring B and R^E , together with optionally substituted R^3 ,



are represented by: The definitions of the remaining variables are provided in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, or thirteenth aspect.

In an eighteenth aspect, the present disclosure provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, or sixteenth aspect, or a pharmaceutically acceptable salt thereof, wherein:

R^E is cyano, C_{1-4} alkyl, $-C(O)R^8$, $-C(NH)NR^{N3E}R^{N3E}$, $-S(O_2)NR^{N3E}R^{N3E}$, $-C(O)OR^{O3a}$, $-C(O)NR^{N3a}R^{N3b}$, phenyl, 5- to 6-membered heteroaryl, or 4- to 10-membered heterocyclyl, wherein the C_{1-4} alkyl is optionally substituted by one to four R^{Ea} , and the phenyl, 5- to 6-membered heteroaryl, and 4- to 10-membered heterocyclyl are each optionally substituted with one or two R^{Eb} ;

R^8 is H, C_{1-3} alkyl, C_{1-3} haloalkyl, or SH;

each R^{Ea} is, independently halo, cyano, OH, or $NR^{N3E}R^{N3E}$;

each R^{Eb} is, independently, oxo, =S, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, cyano, C_{1-3} alkoxy, -OH, or $-C(O)NR^{N3E}R^{N3E}$, wherein the C_{1-3} alkyl is optionally substituted by 4- to 6-membered heterocyclyl optionally substituted with C_{1-3} alkyl;

each R^{N3E} is, independently, H, OH or C_{1-3} alkyl; R^{O3a} is H, C_{1-3} alkyl, or 4-to 6-membered monocyclic heterocyclyl, wherein the C_{1-3} alkyl is optionally substituted by a 4-to 6-membered monocyclic heterocyclyl;

R^{N3a} and R^{N3b} are each independently H, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, -OH, $-S(O)_2C_{1-3}$ alkyl, or cyclopropyl, wherein the C_{1-3} alkyl is optionally substituted by C_{1-3} alkoxy or a 6-membered heteroaryl. The definitions of the remaining variables are provided in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, or sixteenth aspect.

In a nineteenth aspect, the present disclosure provides a compound according to the eighteenth aspect, or a pharmaceutically acceptable salt thereof, wherein:

R^E is cyano, C_{1-4} alkyl, $-C(O)R^8$, $-C(NH)NR^{N3E}R^{N3E}$, $-S(O)_2NR^{N3E}R^{N3E}$, $-C(O)OR^{O3a}$, $-C(O)NR^{N3a}R^{N3b}$, phenyl, pyridinyl, pyrazolyl, oxadiazolyl, imidazolyl, thiazolyl, isothiazolyl, triazolyl, oxazolyl, thiophenyl, morpholinyl, piperdinyl, piperiziny, or 7-oxa-2-azaspiro[3.5]nonanyl, wherein the C_{1-4} alkyl is optionally substituted by one to four R^{Ea} , and the phenyl, pyridinyl, pyrazolyl, oxadiazolyl, imidazolyl, thiazolyl, isothiazolyl, triazolyl, oxazolyl, thiophenyl, morpholinyl, piperdinyl, piperiziny, and 7-oxa-2-azaspiro[3.5]nonanyl are each optionally substituted with one or two R^{Eb} ;

R^8 is H, C_{1-3} alkyl, C_{1-3} haloalkyl, or SH;

each R^{Ea} is, independently halo, cyano, OH, or $NR^{N3E}R^{N3E}$;

each R^{Eb} is, independently, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, cyano, C_{1-3} alkoxy, -OH, or $-C(O)NR^{N3E}R^{N3E}$, wherein the C_{1-3} alkyl is optionally substituted oxetanyl substituted with C_{1-3} alkyl;

each R^{N3E} is, independently, H, OH or C_{1-3} alkyl;

R^{O3a} is H, C_{1-3} alkyl, or tetrahydrofuranyl, wherein the C_{1-3} alkyl is optionally substituted by tetrahydrofuranyl;

R^{N3a} and R^{N3b} are each independently H, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, -OH, $-S(O)_2C_{1-3}$ alkyl, or cyclopropyl, wherein the C_{1-3} alkyl is optionally substituted by C_{1-3} alkoxy or pyridinyl. The definitions of the remaining variables are provided in the eighteenth aspect.

In a twentieth aspect, the present disclosure provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, or sixteenth aspect, or a pharmaceutically acceptable salt thereof, wherein:

R^E is $-C(O)OR^{O3a}$ or $-C(O)NR^{N3a}R^{N3b}$;

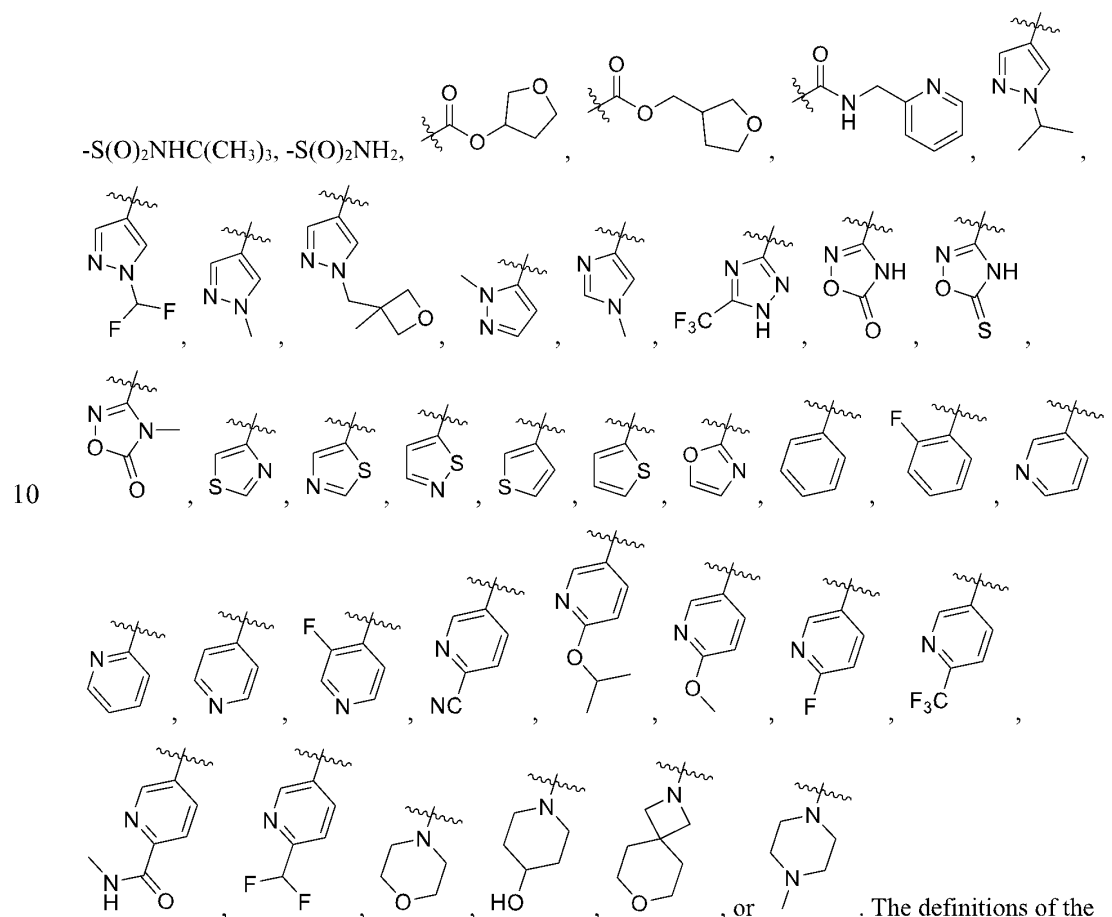
R^{O3a} is H or C_{1-3} alkyl;

R^{N3a} and R^{N3b} are each independently H, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, -OH, or cyclopropyl. The definitions of the remaining variables are provided in the first, second, third, fourth,

fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, or sixteenth aspect aspect.

In a twenty-first aspect, the present disclosure provides a compound according to the eighteenth or nineteenth aspect, or a pharmaceutically acceptable salt thereof, wherein R^E is

- 5 -C(O)OH, -C(O)OCH₃, -C(O)OCH₂CH₃, -C(O)OC(CH₃)₃, -C(O)NH₂, -C(O)NHCH₃,
 -C(O)NHS(O)₂CH₃, -C(O)NHCH₂CH₂OCH₃, -C(O)N(CH₃)OCH₃, cyano, -C(O)H, -C(O)CH₃,
 -C(O)CF₃, -C(O)SH, -CH₃, -C(CH₂CN)₂OH, -C(NH)NHOH, -CH₂OH, -CH(OH)CF₃,



- 15 In a twenty-second aspect, the present disclosure provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, or sixteenth aspect aspect, or a pharmaceutically acceptable salt thereof, wherein R^E is -C(O)OH. The definitions of the remaining variables are provided in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, or sixteenth aspect aspect.

- 20 In a twenty-third aspect, the present disclosure provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth,

fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, or twenty-second aspect, or a pharmaceutically acceptable salt thereof, wherein each R^3 is, independently, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, or 6-membered monocyclic heterocyclyl, wherein the 6-membered monocyclic heterocyclyl is optionally substituted with halo. The definitions of the remaining variables are provided in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, or twenty-second aspect.

In a twenty-fourth aspect, the present disclosure provides a compound according to the twenty-third aspect, or a pharmaceutically acceptable salt thereof, wherein each R^3 is, independently, -Br, -Cl, -F, -CH₃, -CF₃, or pyridinyl, wherein the pyridinyl is optionally substituted with -F. The definitions of the remaining variables are provided in the twenty-third aspect.

In a twenty-fifth aspect, the present disclosure provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, or twenty-fourth aspect, or a pharmaceutically acceptable salt thereof, wherein each R^1 is, independently, CN, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyalkyl, or halo. The definitions of the remaining variables are provided in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, or twenty-fourth aspect.

In a twenty-sixth aspect, the present disclosure provides a compound according to the twenty-fifth aspect, or a pharmaceutically acceptable salt thereof, wherein each R^1 is, independently, C_{1-3} alkyl, C_{1-3} haloalkyl, or halo, preferably wherein R^1 is -CH₃ or -F. The definitions of the remaining variables are provided in the twenty-fifth aspect.

In a twenty-seventh aspect, the present disclosure provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, twenty-fourth, twenty-fifth, or twenty-sixth aspect, or a pharmaceutically acceptable salt thereof, wherein:

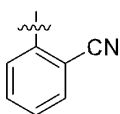
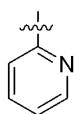
each R^6 is, independently, oxo, halo, cyano, -OH, C_{1-3} alkyl, C_{1-3} alkoxy, -C(O)NH₂, or -NH₂;

or two R^6 , together with the atoms to which they are attached, form cyclopropyl;

R^{N6} is H, C_{1-3} alkyl, phenyl, or pyridinyl, wherein the phenyl is optionally substituted with -CN. The definitions of the remaining variables are provided in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, twenty-fourth, twenty-fifth, or twenty-sixth aspect.

In a twenty-eighth aspect, the present disclosure provides a compound according to the twenty-seventh aspect, or a pharmaceutically acceptable salt thereof, wherein:

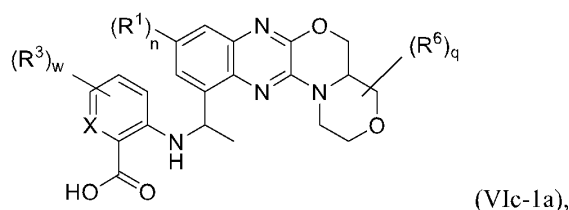
each R^6 is, independently, oxo, -Cl, -F, -OH, -CH₃, -OCH₃, -OCH(CH₃)₃, CN, -C(O)NH₂, or -NH₂;

R^{N6} is H, -CH₃, , or . The definitions of the remaining variables are

provided in the twenty-seventh aspect.

- 5 In a twenty-ninth aspect, the present disclosure provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, or twenty-eighth aspect, or a pharmaceutically acceptable salt thereof, wherein each R^2 is independently halo, C₁₋₃alkyl, or
- 10 C₁₋₃haloalkyl. The definitions of the remaining variables are provided in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, or twenty-eighth aspect.

- In a thirtieth aspect, the present disclosure provides a compound according to the first or
- 15 second aspect, wherein the compound is represented by Formula (VIc-1a):



or a pharmaceutically acceptable salt thereof, wherein:

- X is N or CH;
- n is 0 or 1;
- 20 R^1 is halo or C₁₋₃alkyl;
- w is 0, 1, or 2;
- each R^3 is, independently, halo or C₁₋₃alkyl;
- q is 0, 1, or 2; and
- each R^6 is, independently, halo or C₁₋₃alkyl. The definitions of the remaining variables are
- 25 provided in the first or second aspect.

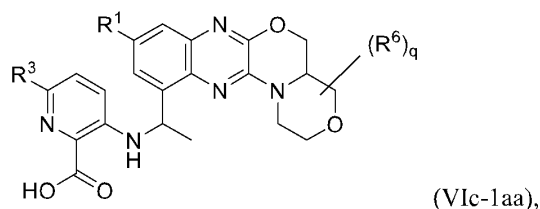
In one aspect, the present disclosure provides a compound according to the thirtieth aspect, or a pharmaceutically acceptable salt thereof, wherein X is N. The definitions of the remaining variables are provided in the thirtieth aspect.

In a thirty-first aspect, the present disclosure provides a compound according to the thirtieth aspect, or a pharmaceutically acceptable salt thereof, wherein R^1 is -F or -CH₃. The definitions of the remaining variables are provided in the thirtieth aspect.

In a thirty-second aspect, the present disclosure provides a compound according to the
 5 thirtieth or thirty-first aspect, or a pharmaceutically acceptable salt thereof, wherein each R^3 is, independently, -F, -Cl, -Br, or -CH₃. The definitions of the remaining variables are provided in the thirtieth or thirty-first aspect.

In one aspect, the present disclosure provides a compound according to the thirtieth, thirty-first, or thirty-second aspect, or a pharmaceutically acceptable salt thereof, wherein w is 1. The
 10 definitions of the remaining variables are provided in the thirtieth, thirty-first, or thirty-second aspect.

In a thirty-third aspect, the present disclosure provides a compound according to the thirtieth, thirty-first, or thirty-second aspect, wherein the compound is represented by Formula (VIc-1aa):



or a pharmaceutically acceptable salt thereof. The definitions of the remaining variables are provided
 15 in the thirtieth, thirty-first, or thirty-second aspect.

In a thirty-fourth aspect, the present disclosure provides a compound according to the thirtieth, thirty-first, thirty-second, or thirty-third aspect, or a pharmaceutically acceptable salt thereof, wherein each R^6 is, independently, C₁₋₃alkyl, preferably wherein each R^6 is -CH₃. The definitions of the remaining variables are provided in the thirtieth, thirty-first, thirty-second, or thirty-third aspect.

In a thirty-fifth aspect, the present disclosure provides a compound according to the thirtieth, thirty-first, thirty-second, or thirty-third aspect, or a pharmaceutically acceptable salt thereof, wherein q is 0. The definitions of the remaining variables are provided in the thirtieth, thirty-first, thirty-second, or thirty-third aspect.

In a thirty-sixth aspect, the present disclosure provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, twenty-eighth, twenty-ninth, thirtieth, thirty-first, thirty-second, thirty-third, thirty-fourth, or thirty-fifth aspect, or a

pharmaceutically acceptable salt thereof, wherein

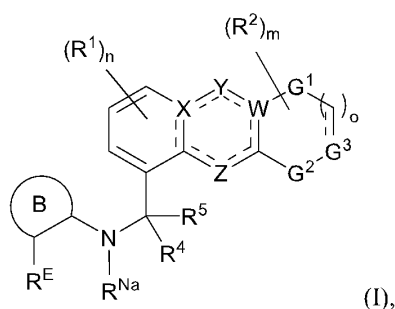
 or

 is

 . The
 30 definitions of the remaining variables are provided in the first, second, third, fourth, fifth, sixth,

seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, twenty-eighth, twenty-ninth, thirtieth, thirty-first, thirty-second, thirty-third, thirty-fourth, or thirty-fifth aspect.

- 5 In addition, in a first embodiment, the present disclosure provides a compound represented by Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

- is a single bond or a double bond as valency permits;
- 10 (i) when W is N, then Y is C(O), X is C, and Z is N or CR^{Z1};
- (ii) when W is C and Y is C(O), then X is C or N, and Z is CR^{Z1}, N, NR^{N1}, or O;
- (iii) when W is C and Y is N or CR^{Z1}, then X is C, and Z is N or CR^{Z1};
- G¹, G², and G³ are each, independently, C(R^{G2})₂, NR^{N2}, or O;
- n is 0, 1, 2, or 3;
- 15 m is 0, 1, 2, 3, or 4;
- o is 0, 1, 2, 3, or 4;
- R^{Nᵃ} is H, C₁₋₆alkyl, or C₁₋₆haloalkyl;
- R^{N1} is H, C₁₋₆alkyl, C₁₋₆haloalkyl, -C(O)R^{1a}, C₃₋₆cycloalkyl, phenyl, or 5-to 6-membered heteroaryl, wherein the phenyl and 5-to 6-membered heteroaryl represented by R^{N1} are each
- 20 optionally substituted with one to three substituents selected from halo, C₁₋₃alkyl, and C₁₋₃haloalkyl;
- R^{Z1} is H, halo, cyano, NO₂, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxylalkyl, C₁₋₆alkoxylalkyl, C₁₋₆hydroxyalkoxy, NR^{N1a}R^{N1b}, -C(O)R^{1a}, -C(O)OR^{O1a}, -C(O)NR^{N1a}R^{N1b}, -OR^{O1a}, 3-12 membered carbocyclyl, phenyl, 5- or 6-membered heteroaryl, or 4-12 membered heterocyclyl, wherein the carbocyclyl, phenyl, 5- or 6-membered heteroaryl, or 4-12 membered heterocyclyl represented by R^{Z1}
- 25 are each optionally substituted by one to four R^{1b};
- each R¹ is, independently, halo, cyano, NO₂, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxylalkyl, C₁₋₆alkoxylalkyl, C₁₋₆hydroxyalkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, NR^{N1a}R^{N1b}, -C(O)R^{1a}, -C(O)OR^{O1a}, -C(O)NR^{N1a}R^{N1b}, -OR^{O1a}, -(CH₂)_{0 or 1-3}-12 membered carbocyclyl, -(CH₂)_{0 or 1-4}-12 membered heterocyclyl, -(CH₂)_{0 or 1-6-10} membered aryl, or -(CH₂)_{0 or 1-5-10} membered heteroaryl, wherein the

C₂₋₆ alkenyl, C₂₋₆ alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl represented by R¹ are each optionally substituted by one to four R^{1b};

R^{1a}, R^{O1a}, R^{N1a}, and R^{N1b} are each independently H, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, or 4-6 membered heterocyclyl;

5 each R^{1b} is independently halo, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxylalkyl, C₁₋₆alkoxylalkyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, C₁₋₆hydroxyalkoxy, -C(O)R^{1a}, -C(O)OR^{O1a}, -C(O)NR^{N1a}R^{N1b}, -SO₂R^{1a}, -NR^{N1a}R^{N1b}, -NR^{N1a}C(O)R^{1a}, -NR^{N1a}C(O)OR^{1a}, -NR^{N1a}SO₂R^{1a}, -NR^{N1a}SO₂NR^{N1a}R^{N1b}, cyano, NO₂, or OR^{O1a};

10 R^{N2} is H, C₁₋₆alkyl, C₁₋₆haloalkyl, -C(O)R^{2a}, C₃₋₆cycloalkyl, phenyl, or 5-to 6-membered heteroaryl, wherein the phenyl and 5-to 6-membered heteroaryl represented by R^{N2} are each optionally substituted with one to three substituents selected from halo, C₁₋₃alkyl, and C₁₋₃haloalkyl;

each R^{G2} is, independently, H, halo, cyano, oxo (as appropriate), NO₂, C₁₋₆alkyl, C₁₋₆haloalkyl, *=-CH-R⁷ (as appropriate), C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆hydroxylalkyl, C₁₋₆alkoxylalkyl, C₁₋₆hydroxyalkoxy, -C(O)R^{2a}, -C(O)OR^{O2a}, -C(O)NR^{N2a}R^{N2b}, OR^{O2a}, NR^{N2a}R^{N2b}, SO₂R^{2a},
15 -NR^{N2a}C(O)R^{2a}, -NR^{N2a}C(O)OR^{2a}, -NR^{N2a}SO₃R^{2a}, -NR^{N2a}SO₃NR^{N2a}R^{N2a}, -(CH₂)_{0 or 1-3-12} membered carbocyclyl, -(CH₂)_{0 or 1-4-12} membered heterocyclyl, -(CH₂)_{0 or 1-6-10} membered aryl, or -(CH₂)_{0 or 1-5-10} membered heteroaryl, wherein the carbocyclyl, heterocyclyl, aryl, or heteroaryl represented by R^{G2} are each optionally substituted by one to four halo, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxylalkyl, C₁₋₆alkoxylalkyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, C₁₋₆hydroxyalkoxy, -C(O)R^{2a},
20 -C(O)OR^{O2a}, -C(O)NR^{N2a}R^{N2b}, cyano, NO₂, OR^{O2a}, NR^{N2a}R^{N2b}, SO₃R^{2a}, -NR^{N2a}C(O)R^{2a}, -NR^{N2a}C(O)OR^{2a}, -NR^{N2a}SO₃R^{2a}, or -NR^{N2a}SO₃NR^{N2a}R^{N2a}, and wherein the C₂alkenyl is optionally substituted with phenyl or 5- to 6-membered heteroaryl;

each R² is independently halo, cyano, oxo (as appropriate), NO₂, C₁₋₆alkyl, C₁₋₆haloalkyl, *=-CH-R⁷ (as appropriate), C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆hydroxylalkyl, C₁₋₆alkoxylalkyl,
25 C₁₋₆hydroxyalkoxy, -C(O)R^{2a}, -C(O)OR^{O2a}, -C(O)NR^{N2a}R^{N2b}, OR^{O2a}, NR^{N2a}R^{N2b}, SO₂R^{2a}, -NR^{N2a}C(O)R^{2a}, -NR^{N2a}C(O)OR^{2a}, -NR^{N2a}SO₃R^{2a}, -NR^{N2a}SO₃NR^{N2a}R^{N2a}, -(CH₂)_{0 or 1-3-12} membered carbocyclyl, -(CH₂)_{0 or 1-4-12} membered heterocyclyl, -(CH₂)_{0 or 1-6-10} membered aryl, or -(CH₂)_{0 or 1-5-10} membered heteroaryl, wherein the carbocyclyl, heterocyclyl, aryl, or heteroaryl represented by R² are each optionally substituted by one to four halo, C₁₋₆alkyl, C₁₋₆haloalkyl,
30 C₁₋₆hydroxylalkyl, C₁₋₆alkoxylalkyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, C₁₋₆hydroxyalkoxy, -C(O)R^{2a}, -C(O)OR^{O2a}, -C(O)NR^{N2a}R^{N2b}, cyano, NO₂, OR^{O2a}, NR^{N2a}R^{N2b}, SO₃R^{2a}, -NR^{N2a}C(O)R^{2a}, -NR^{N2a}C(O)OR^{2a}, -NR^{N2a}SO₃R^{2a}, or -NR^{N2a}SO₃NR^{N2a}R^{N2a}, and wherein the C₂alkenyl is optionally substituted with phenyl or 5- to 6-membered heteroaryl; or

two R², two R^{G2}, one R² and one R^{N2}, one R² and one R^{G2}, or one R^{G2} and one R^{N2}, together
35 with the atoms to which they are connected, form 3- to 12 membered carbocyclyl, 4- to 12 membered heterocyclyl, phenyl, naphthyl or 5- to 10-membered heteroaryl, each of which is optionally substituted by one to four R⁶;

R^{2a} and R^{O2a} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, or 4-6 membered heterocyclyl;

R^{N2a} and R^{N2b} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{O2a} , or C_{3-6} cycloalkyl;

* is the connection point to the tricyclic core ring;

- 5 R^7 is 3- to 12 membered carbocyclyl, 4- to 12 membered heterocyclyl, phenyl, naphthyl, or 5- to 10-membered heteroaryl, each of which is optionally substituted by one to four halo, -OH, -NH₂, cyano, NO₂, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, or heteroaryl;

- each R^6 is independently halo, cyano, oxo (as appropriate), NO₂, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} hydroxylalkyl, C_{1-6} alkoxylalkyl, C_{1-6} hydroxyalkoxy, -C(O) R^{6a} ,
 10 -C(O) OR^{O6a} , -C(O) $NR^{N6a}R^{N6b}$, OR^{O6a} , $NR^{N6a}R^{N6b}$, SO_2R^{6a} , - $NR^{N6a}C(O)R^{6a}$, - $NR^{N6a}C(O)OR^{6a}$,
 - $NR^{N6a}SO_3R^{6a}$, - $NR^{N6a}SO_3NR^{N6a}R^{N6a}$, -(CH₂)_{0 or 1-3-12} membered carbocyclyl,
 -(CH₂)_{0 or 1-4-12} membered heterocyclyl, -(CH₂)_{0 or 1-6-10} membered aryl, or -(CH₂)_{0 or 1-5-10}
 membered heteroaryl, wherein the carbocyclyl, heterocyclyl, aryl, or heteroaryl represented by R^6 are
 each optionally substituted by one to four halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxylalkyl,
 15 C_{1-6} alkoxylalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkoxy, -C(O) R^{6a} , -C(O) OR^{O6a} ,
 -C(O) $NR^{N6a}R^{N6b}$, cyano, NO₂, OR^{O6a} , $NR^{N6a}R^{N6b}$, SO_3R^{6a} , - $NR^{N6a}C(O)R^{6a}$, - $NR^{N6a}C(O)OR^{6a}$,
 - $NR^{N6a}SO_3R^{6a}$, or - $NR^{N6a}SO_3NR^{N6a}R^{N6a}$,

R^{6a} and R^{O6a} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, or 4-6 membered heterocyclyl;

- 20 R^{N6a} and R^{N6b} are each independently H, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{O6a} , or C_{3-6} cycloalkyl;

Ring B is phenyl or 5- to 10-membered monocyclic or bicyclic heteroaryl, each of which is substituted with R^E ortho to the $N(R^{Na})$ substituent, and optionally substituted with one to four R^3 ;

- each R^3 is independently halo, cyano, NO₂, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl,
 25 C_{1-6} hydroxylalkyl, C_{1-6} alkoxylalkyl, C_{1-6} hydroxyalkoxy, -C(O) R^{3a} , -C(O) OR^{O3a} , -C(O) $NR^{N3a}R^{N3b}$,
 OR^{O3a} , $NR^{N3a}R^{N3b}$, SO_2R^{3a} , - $NR^{N3a}C(O)R^{3a}$, - $NR^{N3a}C(O)OR^{3a}$, - $NR^{N3a}SO_3R^{3a}$, - $NR^{N3a}SO_3NR^{N3a}R^{N3a}$,
 -(CH₂)_{0 or 1-3-12} membered carbocyclyl, -(CH₂)_{0 or 1-4-12} membered heterocyclyl,
 -(CH₂)_{0 or 1-6-10} membered aryl, or -(CH₂)_{0 or 1-5-10} membered heteroaryl, wherein the carbocyclyl,
 heterocyclyl, aryl, or heteroaryl represented by R^3 are each optionally substituted by one to four halo,
 30 C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxylalkyl, C_{1-6} alkoxylalkyl, C_{1-6} hydroxyalkoxy, -C(O) R^{3a} ,
 -C(O) OR^{O3a} , -C(O) $NR^{N3a}R^{N3b}$, cyano, NO₂, OR^{O3a} , $NR^{N3a}R^{N3b}$, SO_3R^{3a} , - $NR^{N3a}C(O)R^{3a}$,
 - $NR^{N3a}C(O)OR^{3a}$, - $NR^{N3a}SO_3R^{3a}$, or - $NR^{N3a}SO_3NR^{N3a}R^{N3a}$,

R^E is -C(O) OR^{O3a} or -C(O) $NR^{N3a}R^{N3b}$;

- 35 R^{3a} and R^{O3a} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, or 4-6 membered heterocyclyl;

R^{N3a} and R^{N3b} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{O3a} , or C_{3-6} cycloalkyl;

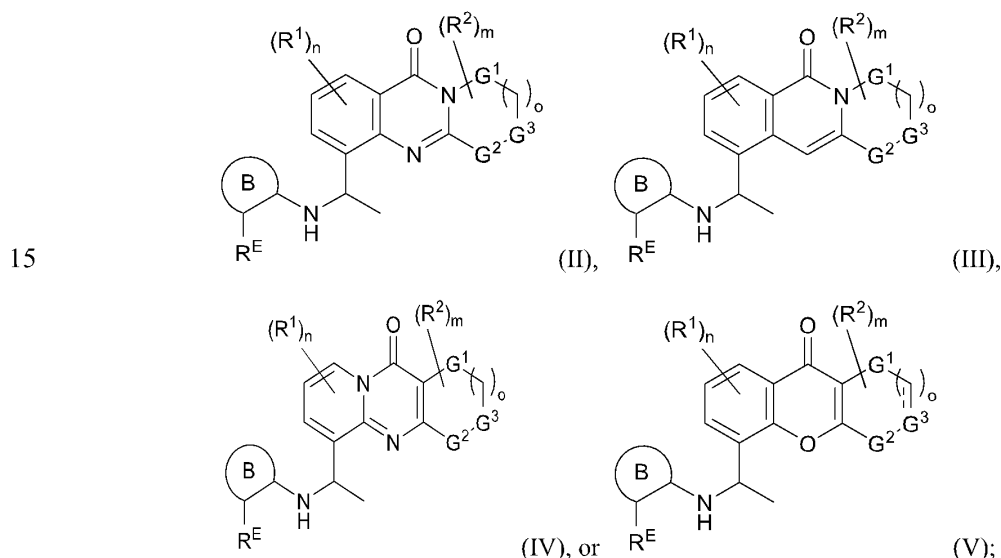
R^4 and R^5 are each, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, or C_{1-6} alkoxyalkyl; or

R^4 and R^5 , together with the carbon to which they are attached, form C_{3-6} cycloalkyl or 4-6 membered oxygen-containing only heterocycl.

5 In a second embodiment, the present disclosure provides a compound according to the first embodiment, a pharmaceutically acceptable salt thereof, wherein R^{Na} is H. The definitions of the remaining variables are provided in the first embodiment.

In a third embodiment, the present disclosure provides a compound according to the first or second embodiment, a pharmaceutically acceptable salt thereof, wherein R^4 is
10 C_{1-3} alkyl and R^5 is H. The definitions of the remaining variables are provided in the first or second embodiment.

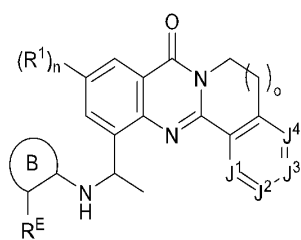
In a fourth embodiment, the present disclosure provides a compound according to the first, second, or third embodiment, a pharmaceutically acceptable salt thereof, wherein the compound is represented by Formula (II), (III), (IV), or (V):



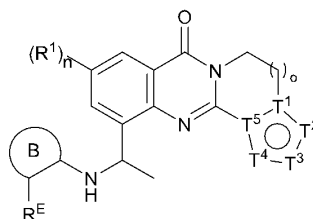
wherein m and n are each, independently, 0, 1, or 2, and o is 0 or 1. The definitions of the remaining variables are provided in the first, second, or third embodiment.

In an alternative of the fourth embodiment, the compound is of Formula (II). In another
20 alternative of the fourth embodiment, the compound is of Formula (III). In another alternative of the fourth embodiment, the compound is of Formula (IV). In another alternative of the fourth embodiment, the compound is of Formula (V).

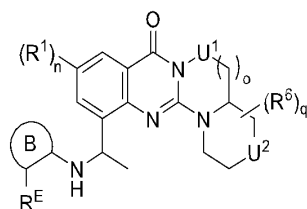
In a fifth embodiment, the present disclosure provides a compound according to the fourth embodiment, a pharmaceutically acceptable salt thereof, wherein the compound is represented by
25 Formula (IIa), (IIb), (IIc), (IId), (IIIa), (IIIb), (IIIc), (IVa), (IVb), (IVc), (Va), (Vb), (Vc), or (Vd):



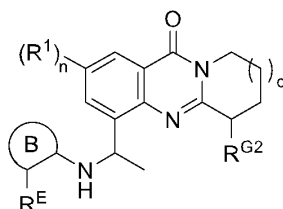
(IIa),



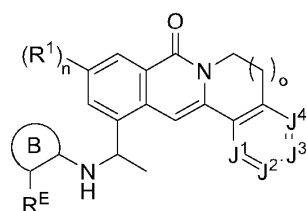
(IIb),



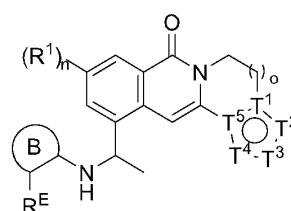
(IIc),



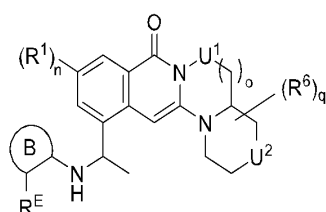
(IId),



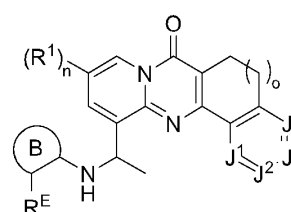
(IIIa),



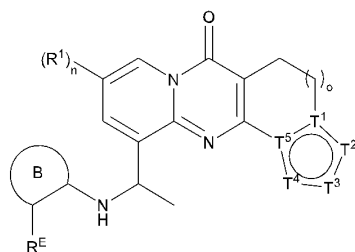
(IIIb),



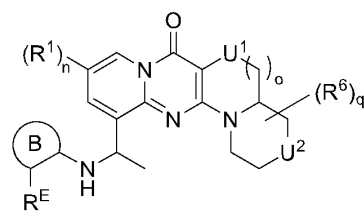
(IIIc),



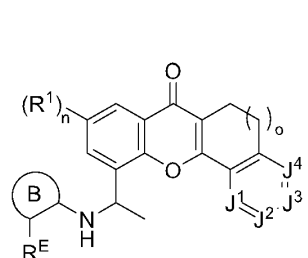
(IVa),



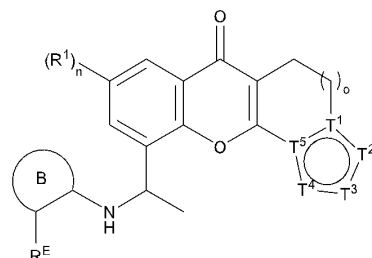
(IVb),



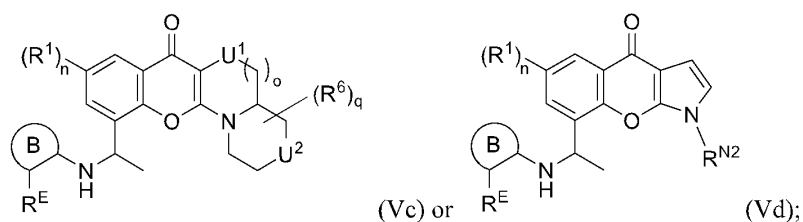
(IVc),



(Va),



(Vb),



wherein:

n and o, are each, independently, 0 or 1;

q is 0, 1, or 2;

5 J¹, J², J³, and J⁴, are each, independently, N, CH, or CR⁶;

T¹ and T⁵, are each, independently, N or C;

T², T³, and T⁴, are each, independently, N, NR^{N6}, O, S, CH, or CR⁶;

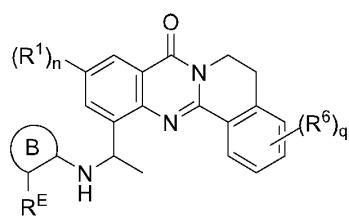
R^{N6} is H, C₁₋₃alkyl, C₁₋₃haloalkyl, C₃₋₆cycloalkyl, phenyl, naphthyl, or 5- to 6-membered heteroaryl, wherein the phenyl, naphthyl, and 5- to 6-membered heteroaryl represented by R^{N6} are
 10 each optionally substituted by one to three halo, C₁₋₃alkyl, C₁₋₃haloalkyl, cyano, OH, C₁₋₃alkoxy, or C₁₋₃haloalkoxy;

U¹ is NR^{N2}, CH₂, or O;

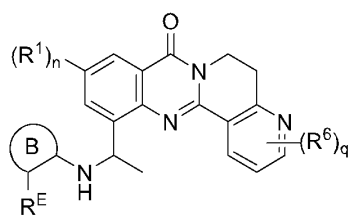
U² is NR^{N6}, CH₂, or O. The definitions of the remaining variables are provided in the fourth embodiment.

15 In an alternative of the fifth embodiment, the compound is of Formula (IIa). In another alternative of the fifth embodiment, the compound is of Formula (IIb). In another alternative of the fifth embodiment, the compound is of Formula (IIc). In another alternative of the fifth embodiment, the compound is of Formula (IId). In another alternative of the fifth embodiment, the compound is of Formula (IIIa). In another alternative of the fifth embodiment, the compound is of Formula (IIIb). In
 20 another alternative of the fifth embodiment, the compound is of Formula (IIIc). In another alternative of the fifth embodiment, the compound is of Formula (IVa). In another alternative of the fifth embodiment, the compound is of Formula (IVb). In another alternative of the fifth embodiment, the compound is of Formula (IVc). In another alternative of the fifth embodiment, the compound is of Formula (Va). In another alternative of the fifth embodiment, the compound is of Formula (Vb). In
 25 another alternative of the fifth embodiment, the compound is of Formula (Vc). In another alternative of the fifth embodiment, the compound is of Formula (Vd).

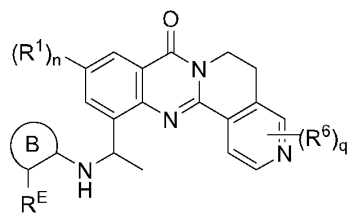
In a sixth embodiment, the present disclosure provides a compound according to the fifth embodiment, a pharmaceutically acceptable salt thereof, wherein the compound is represented by
 30 Formula (IIa-1), (IIa-2), (IIa-3), (IIa-4), (IIa-5), (IIa-6), (IIa-7), (IIb-1), (IIb-2), (IIb-3), (IIb-4), (IIb-5), (IIb-6), (IIb-7), (IIb-8), (IIb-9), (IIb-10), (IIb-11), (IIc-1), (IIIa-1), (IIIc-1), (IVc-1), (Va-1), (Va-2), (Va-3), or (Vc-1):



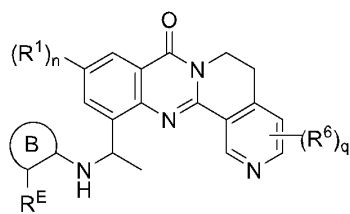
(IIa-1),



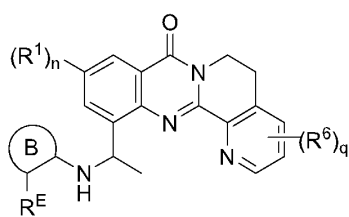
(IIa-2),



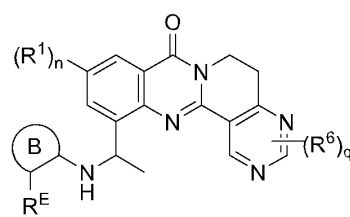
(IIa-3),



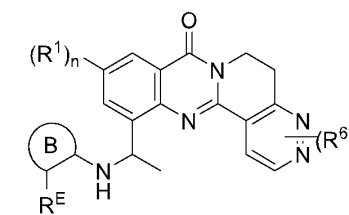
(IIa-4),



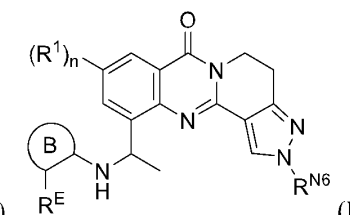
(IIa-5),



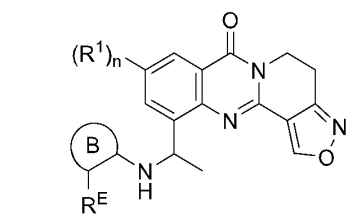
(IIa-6),



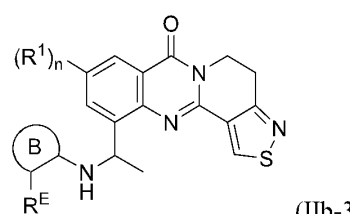
(IIa-7),



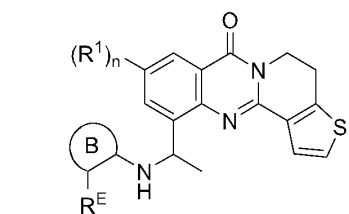
(IIb-1),



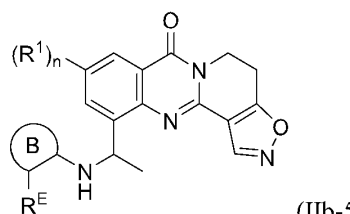
(IIb-2),



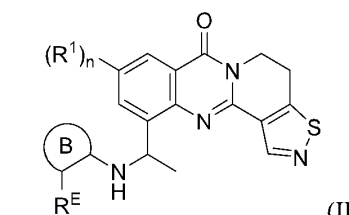
(IIb-3),



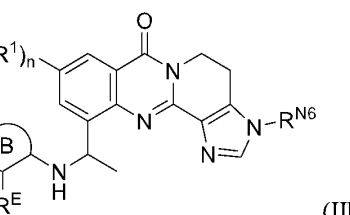
(IIb-4),



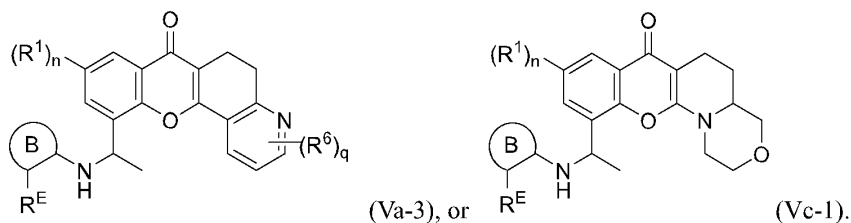
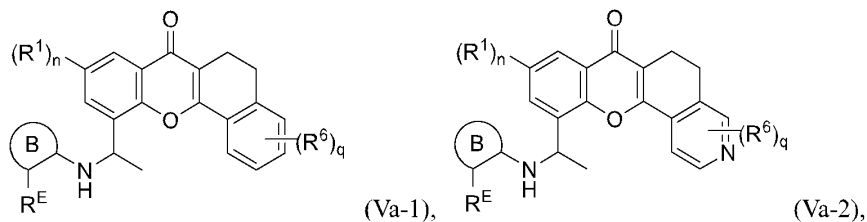
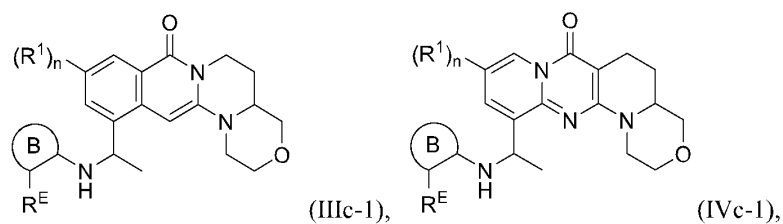
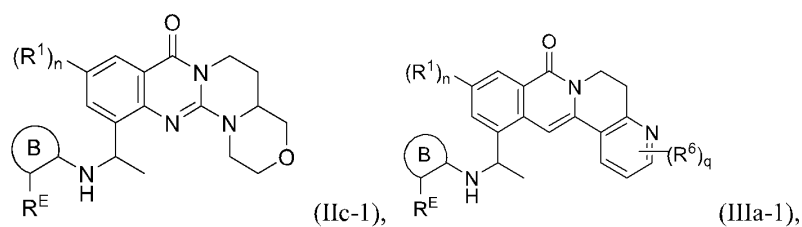
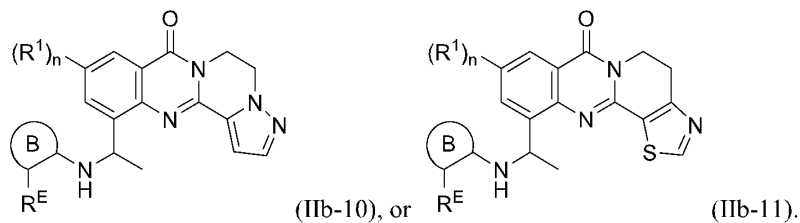
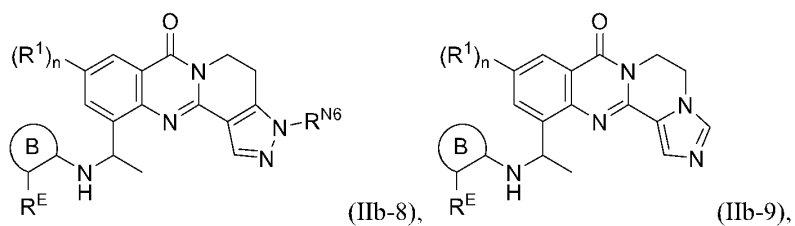
(IIb-5),



(IIb-6),



(IIb-7),

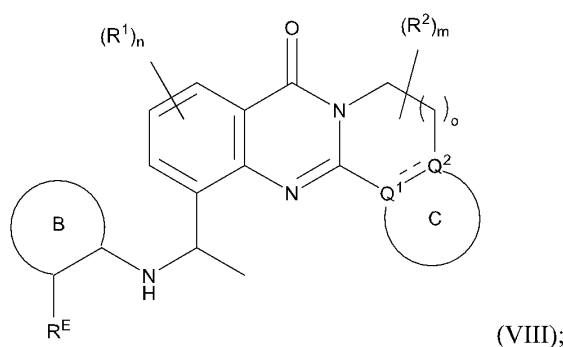


The definitions of the variables therein are provided in the fifth embodiment.

In an alternative of the sixth embodiment, the compound is of Formula (IIa-1). In another alternative of the sixth embodiment, the compound is of Formula (IIa-2). In another alternative of the sixth embodiment, the compound is of Formula (IIa-3). In another alternative of the sixth

- embodiment, the compound is of Formula (IIa-4). In another alternative of the sixth embodiment, the compound is of Formula (IIa-5). In another alternative of the sixth embodiment, the compound is of Formula (IIa-6). In another alternative of the sixth embodiment, the compound is of Formula (IIa-7). In another alternative of the sixth embodiment, the compound is of Formula (IIb-1). In another alternative of the sixth embodiment, the compound is of Formula (IIb-2). In another alternative of the sixth embodiment, the compound is of Formula (IIb-3). In another alternative of the sixth embodiment, the compound is of Formula (IIb-4). In another alternative of the sixth embodiment, the compound is of Formula (IIb-5). In another alternative of the sixth embodiment, the compound is of Formula (IIb-6). In another alternative of the sixth embodiment, the compound is of Formula (IIb-7). In another alternative of the sixth embodiment, the compound is of Formula (IIb-8). In another alternative of the sixth embodiment, the compound is of Formula (IIb-9). In another alternative of the sixth embodiment, the compound is of Formula (IIb-10). In another alternative of the sixth embodiment, the compound is of Formula (IIb-11). In another alternative of the sixth embodiment, the compound is of Formula (IIc-1). In another alternative of the sixth embodiment, the compound is of Formula (IIIa-1). In another alternative of the sixth embodiment, the compound is of Formula (IIIc-1). In another alternative of the sixth embodiment, the compound is of Formula (IVc-1). In another alternative of the sixth embodiment, the compound is of Formula (Va-1). In another alternative of the sixth embodiment, the compound is of Formula (Va-2). In another alternative of the sixth embodiment, the compound is of Formula (Va-3). In another alternative of the sixth embodiment, the compound is of Formula (Vc-1).

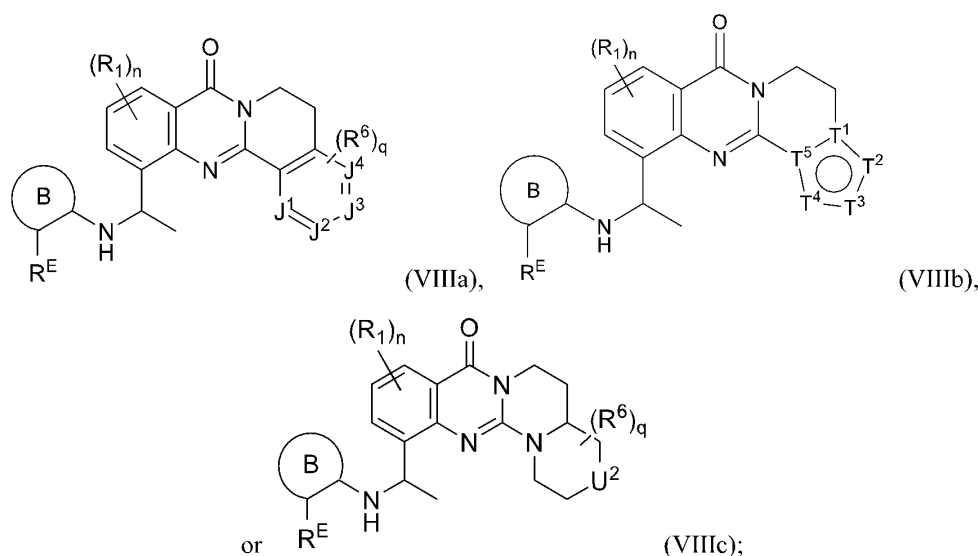
In a seventh embodiment, the present disclosure provides a compound according to the first embodiment, a pharmaceutically acceptable salt thereof, wherein the compound is represented by Formula (VIII):



- or a pharmaceutically acceptable salt thereof, wherein:
- n is 0, 1, or 2;
 - m is 0, 1, or 2;
 - o is 0 or 1;
 - each R¹ is, independently, halo, cyano, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl,
 - NR^{N1a}R^{N1b}, -C(O)R^{1a}, -C(O)OR^{O1a}, -C(O)NR^{N1a}R^{N1b}, OR^{O1a}, C₃₋₆cycloalkyl, phenyl, or

- 5-to 6-membered monocyclic heteroaryl, wherein the C₃₋₆cycloalkyl, phenyl, and 5-to 6-membered monocyclic heteroaryl represented by R¹ are each optionally substituted by one to three halo, C₁₋₃alkyl, C₁₋₃haloalkyl, OH, C₁₋₃alkoxy, C₁₋₃haloalkoxy, -C(O)R^{1a}, -C(O)OR^{O1a}, or -C(O)NR^{N1a}R^{N1b}; each R² is independently halo, oxo, cyano, C₁₋₆alkyl, C₁₋₆haloalkyl, -NR^{N2a}R^{N2b}, -C(O)R^{2a}, -C(O)OR^{O2a}, -C(O)NR^{N2a}R^{N2b}, OR^{O2a}, C₃₋₆cycloalkyl, phenyl, or 5-to 6-membered monocyclic heteroaryl, wherein the C₃₋₆cycloalkyl, phenyl, and 5-to 6-membered monocyclic heteroaryl represented by R² are each optionally substituted by one to three halo, C₁₋₃alkyl, C₁₋₃haloalkyl, OH, C₁₋₃alkoxy, C₁₋₃haloalkoxy, -C(O)R^{2a}, -C(O)OR^{O2a}, or -C(O)NR^{N2a}R^{N2b}; R^{2a}, R^{O2a}, R^{N2a}, and R^{N2b} are each independently H, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, or 4-6 membered heterocyclyl;
- Ring B is phenyl or 5- to 6-membered monocyclic heteroaryl, each of which is substituted with R^E ortho to the NH substituent, and one to three R³; each R³ is independently halo, cyano, C₁₋₆alkyl, C₁₋₆haloalkyl, -NR^{N3a}R^{N3b}, -C(O)R^{3a}, -C(O)OR^{O3a}, -C(O)NR^{N3a}R^{N3b}, OR^{O3a}, C₃₋₆cycloalkyl, phenyl, or 5-to 6-membered monocyclic heteroaryl, wherein the C₃₋₆cycloalkyl, phenyl, and 5-to 6-membered monocyclic heteroaryl represented by R³ are each optionally substituted by one to three halo, C₃₋₃alkyl, C₃₋₃haloalkyl, OH, C₁₋₃alkoxy, C₁₋₃haloalkoxy, -C(O)R^{3a}, -C(O)OR^{O3a}, or -C(O)NR^{N3a}R^{N3b}; R^{3a}, R^{O3a}, R^{N3a}, and R^{N3b} are each independently H, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, or 4-6 membered heterocyclyl;
- Ring C is 6-membered monocyclic heterocyclyl, phenyl, or 5- to 6-membered monocyclic heteroaryl, each of which is optionally substituted with one to three R⁶; Q¹ and Q² are each, independently, C, CH, or N, provided that at least one of Q¹ or Q² is C or CH; each R⁶ is, independently, halo, oxo, cyano, C₁₋₆alkyl, C₁₋₆haloalkyl, -NR^{N6a}R^{N6b}, -C(O)R^{6a}, -C(O)OR^{O6a}, -C(O)NR^{N6a}R^{N6b}, OR^{O6a}, C₁₋₆cycloalkyl, phenyl, or 5-to 6-membered monocyclic heteroaryl, wherein the C₁₋₆cycloalkyl, phenyl, and 5-to 6-membered monocyclic heteroaryl represented by R⁶ are each independently substituted by one to three halo, OH, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, -C(O)R^{6a}, -C(O)OR^{O6a}, or -C(O)NR^{N6a}R^{N6b}; R^{6a}, R^{O6a}, R^{N6a}, and R^{N6b} are each independently H, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆cycloalkyl, or 4-6 membered heterocyclyl. The definitions of the remaining variables are provided in the first embodiment.

In an eighth embodiment, the present disclosure provides a compound according to the seventh embodiment, a pharmaceutically acceptable salt thereof, wherein the compound is represented by Formula (VIIIa), (VIIIb), or (VIIIc):



wherein:

n is 0 or 1;

5 q is 0, 1, or 2;

U^2 is NR^{N6} , CH_2 , or O ;

J^1, J^2, J^3 , and J^4 , are each, independently, N or CH , wherein at least one of J^1, J^2, J^3 , and J^4 is CH ;

T^1 and T^5 , are each, independently, N or C ;

10 T^2, T^3 , and T^4 , are each, independently, N, NR^{N6}, O, S , or CH ;

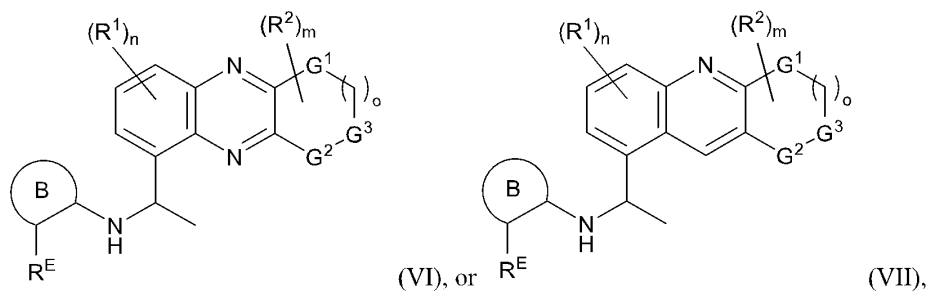
R^{N6} is $H, C_{1-3}alkyl, C_{1-3}haloalkyl, C_{3-6}cycloalkyl, phenyl$, or 5- to 6-membered heteroaryl,

wherein the phenyl and 5- to 6-membered heteroaryl represented by R^{N6} are each optionally substituted by one to three halo, $C_{1-3}alkyl, C_{1-3}haloalkyl, cyano, OH, C_{1-3}alkoxy$, or $C_{1-3}haloalkoxy$.

The definitions of the remaining variables are provided in the seventh embodiment.

15 In an alternative of the eighth embodiment, the compound is of Formula (VIIIa). In another alternative of the eighth embodiment, the compound is of Formula (VIIIb). In another alternative of the eighth embodiment, the compound is of Formula (VIIIc):

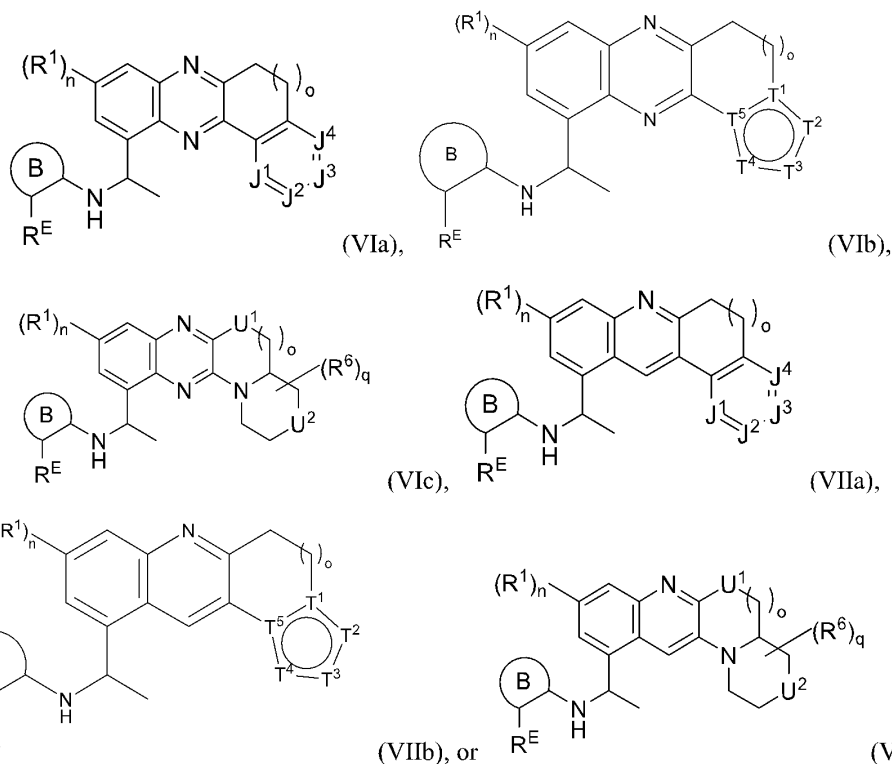
In a ninth embodiment, the present disclosure provides a compound according to the first, second, or third embodiment, a pharmaceutically acceptable salt thereof, wherein the compound is
20 represented by Formula (VI) or (VII):



wherein m and n are each, independently, 0, 1 or 2; and o is 0 or 1. The definitions of the remaining variables are provided in the first, second, or third embodiment.

In an alternative of the ninth embodiment, the compound is of Formula (VI). In another
5 alternative of the ninth embodiment, the compound is of Formula (VII).

In a tenth embodiment, the present disclosure provides a compound according to the ninth embodiment, a pharmaceutically acceptable salt thereof, wherein the compound is represented by Formula (VIa), (VIb), (VIc), (VIIa), (VIIb), or (VIIc):



wherein:

n and o , are each, independently 0 or 1;

q is 0, 1, or 2;

J^1 , J^2 , J^3 , and J^4 , are each, independently, N, CH, or CR^6 ;

T¹ and T⁵, are each, independently, N or C;

T², T³, and T⁴, are each, independently, N, NR^{N6}, O, S, CH, or CR⁶;

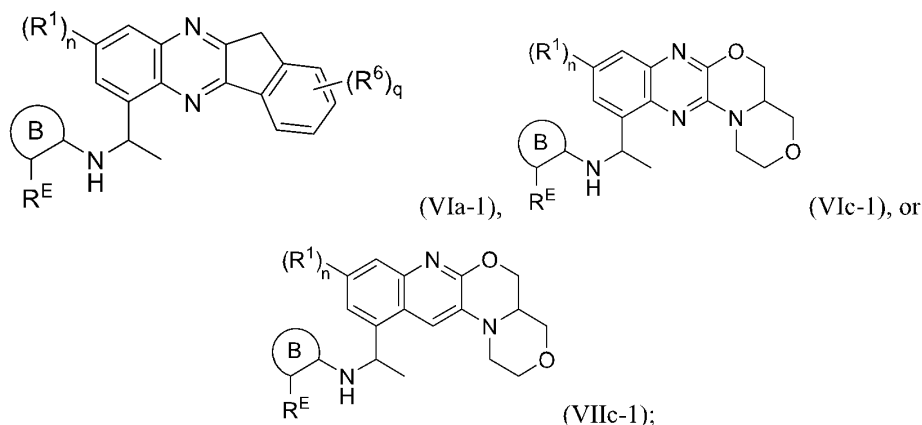
R^{N6} is H, C₁₋₃alkyl, C₁₋₃haloalkyl, C₃₋₆cycloalkyl, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl represented by R^{N6} are each optionally substituted by one to three halo, C₁₋₃alkyl, C₁₋₃haloalkyl, cyano, OH, C₁₋₃alkoxy, or C₁₋₃haloalkoxy;

U¹ is NR^{N2}, CH₂, or O;

U² is NR^{N6}, CH₂, or O. The definitions of the remaining variables are provided in the ninth embodiment.

In an alternative of the tenth embodiment, the compound is of Formula (VIa). In another alternative of the tenth embodiment, the compound is of Formula (VIb). In another alternative of the tenth embodiment, the compound is of Formula (VIc). In another alternative of the tenth embodiment, the compound is of Formula (VIIa). In another alternative of the tenth embodiment, the compound is of Formula (VIIb). In another alternative of the tenth embodiment, the compound is of Formula (VIIc).

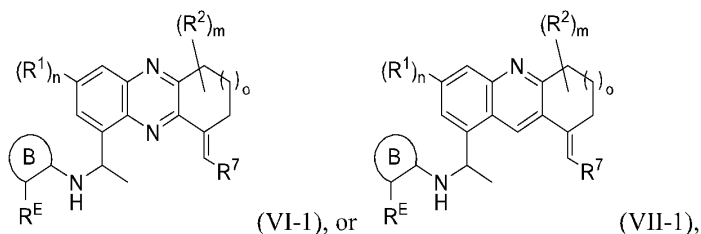
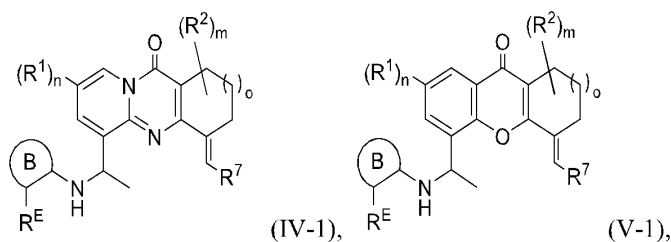
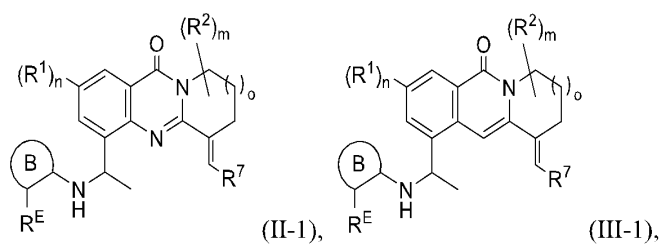
In an eleventh embodiment, the present disclosure provides a compound according to the tenth embodiment, a pharmaceutically acceptable salt thereof, wherein the compound is represented by Formula (VIa-1), (VIc-1), or (VIIc-1):



wherein n is 0 or 1 and q is 0, 1, or 2. The definitions of the remaining variables are provided in the tenth embodiment.

In an alternative of the eleventh embodiment, the compound is of Formula (VIa-1). In another alternative of the eleventh embodiment, the compound is of Formula (VIc-a). In another alternative of the eleventh embodiment, the compound is of Formula (VIIc-1).

In a twelfth embodiment, the present disclosure provides a compound according to the first embodiment, a pharmaceutically acceptable salt thereof, wherein the compound is represented by Formula (II-1), (III-1), (IV-1), (V-1), (VI-1), or (VII-1):



wherein

5 m, n, and o, are each, independently 0 or 1;

R⁷ is 5- or 6-membered heterocyclyl, phenyl, or 5- or 6-membered heteroaryl, each of which is optionally substituted by one to two halo, -OH, -NH₂, cyano, C₁₋₃alkyl, or C₁₋₃haloalkyl.

10 In an alternative of the twelfth embodiment, the compound is of Formula (II-1). In another alternative of the twelfth embodiment, the compound is of Formula (III-1). In another alternative of the twelfth embodiment, the compound is of Formula (IV-1). In another alternative of the twelfth embodiment, the compound is of Formula (V-1). In another alternative of the twelfth embodiment, the compound is of Formula (VI-1). In another alternative of the twelfth embodiment, the compound is of Formula (VII-1).

15 In a thirteenth embodiment, the present disclosure provides a compound according to the twelfth embodiment, a pharmaceutically acceptable salt thereof, wherein R⁷ is phenyl, pyridyl, isoxazolyl, or tetrahydro-2H-pyranyl. The definitions of the remaining variables are provided in the twelfth embodiment.

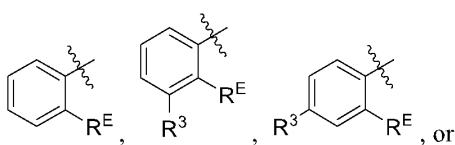
20 In a fourteenth embodiment, the present disclosure provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, or thirteenth embodiment, a pharmaceutically acceptable salt thereof, wherein Ring B is phenyl or 6-membered monocyclic heteroaryl, each of which is substituted with R^E ortho to the NR^{Na} substituent, and further

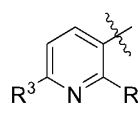
optionally substituted with one or two R^3 . The definitions of the remaining variables are provided in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, or thirteenth embodiment.

In a fifteenth embodiment, the present disclosure provides a compound according to the
 5 fourteenth embodiment, a pharmaceutically acceptable salt thereof, wherein Ring B is phenyl or pyridinyl, each of which is substituted with R^E ortho to the NR^{Na} substituent, and further optionally substituted with one R^3 . The definitions of the remaining variables are provided in the fourteenth embodiment.

In a sixteenth embodiment, the present disclosure provides a compound according to the
 10 fifteenth embodiment, a pharmaceutically acceptable salt thereof, wherein Ring B and R^E , together

with optionally substituted R^3 , are represented by:



 . The definitions of the remaining variables are provided in the fifteenth embodiment.

In a seventeenth embodiment, the present disclosure provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth,
 15 fourteenth, fifteenth, or sixteenth embodiment, a pharmaceutically acceptable salt thereof, wherein R^E is $-C(O)OR^{O3a}$ or $-C(O)NR^{N3a}R^{N3b}$; R^{O3a} is H or C_{1-3} alkyl; and R^{N3a} and R^{N3b} are each independently H, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, -OH, or cyclopropyl. The definitions of the remaining variables are provided in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, or sixteenth embodiment.

In an eighteenth embodiment, the present disclosure provides a compound according to the
 20 seventeenth embodiment, a pharmaceutically acceptable salt thereof, wherein R^E is $-C(O)OH$. The definitions of the remaining variables are provided in the seventeenth embodiment.

In a nineteenth embodiment, the present disclosure provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth,
 25 fifteenth, sixteenth, seventeenth, or eighteenth embodiment, a pharmaceutically acceptable salt thereof, wherein each R^3 is, independently, halo, C_{1-3} alkyl, or C_{1-3} haloalkyl. The definitions of the remaining variables are provided in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, or eighteenth embodiment.

In a twentieth embodiment, the present disclosure provides a compound according to the
 30 nineteenth embodiment, a pharmaceutically acceptable salt thereof, wherein each R^3 is, independently, -Cl, -F, or -CF₃. The definitions of the remaining variables are provided in the nineteenth embodiment.

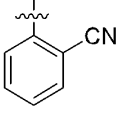
In a twenty-first embodiment, the present disclosure provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, or twentieth embodiment, a pharmaceutically acceptable salt thereof, wherein each R^1 is, independently, CN, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxylalkyl, or halo. The definitions of the remaining variables are provided in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, or twentieth embodiment.

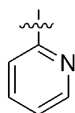
In a twenty-second embodiment, the present disclosure provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, twentieth, or twenty-first embodiment, a pharmaceutically acceptable salt thereof, wherein each R^1 is, independently, C_{1-3} alkyl, C_{1-3} haloalkyl, or halo. The definitions of the remaining variables are provided in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, twentieth, or twenty-first embodiment.

In a twenty-third embodiment, the present disclosure provides a compound according to the twenty-second embodiment, a pharmaceutically acceptable salt thereof, wherein each R^1 is, independently, $-CH_3$ or $-F$. The definitions of the remaining variables are provided in the twenty-second embodiment.

In a twenty-fourth embodiment, the present disclosure provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, or twenty-third embodiment, a pharmaceutically acceptable salt thereof, wherein each R^6 is, independently, halo, cyano, $-OH$, C_{1-3} alkyl, C_{1-3} alkoxy, or $-NH_2$; and R^{N6} is H, C_{1-3} alkyl, phenyl, or pyridinyl, wherein the phenyl is optionally substituted with $-CN$. The definitions of the remaining variables are provided in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, or twenty-third embodiment.

In a twenty-fifth embodiment, the present disclosure provides a compound according to the twenty-fourth embodiment, a pharmaceutically acceptable salt thereof, wherein each R^6 is,

independently, $-Cl$, $-F$, $-OH$, $-OCH_3$, $-OCH(CH_3)_3$, CN, or $-NH_2$; and R^{N6} is H, $-CH_3$, , or



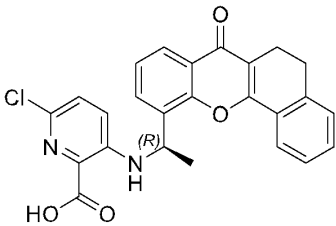
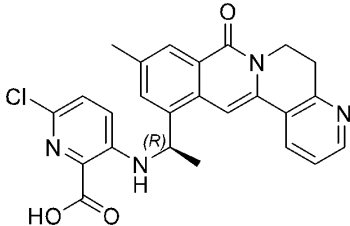
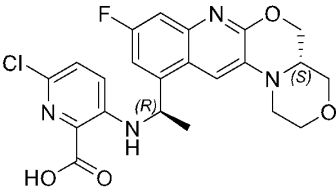
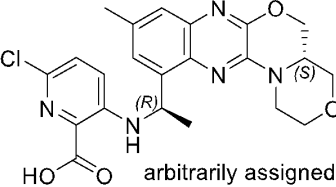
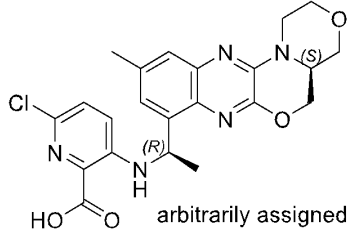
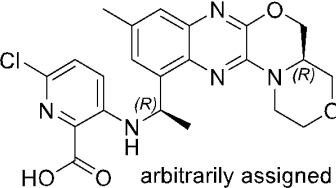
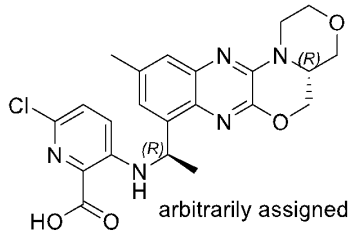
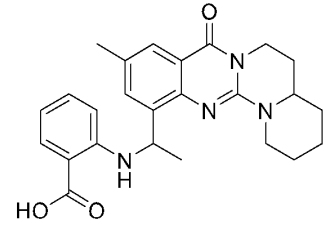
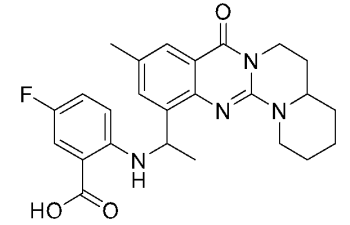
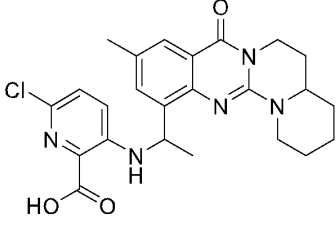
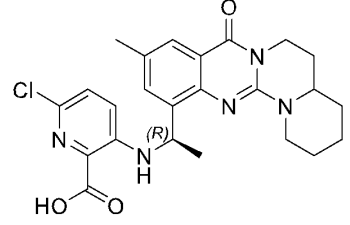
. The definitions of the remaining variables are provided in the twenty-fourth embodiment.

In one aspect or embodiment, the present disclosure provides a compound selected from the compounds disclosed in examples and Table 1, a pharmaceutically acceptable salt or a stereoisomer thereof.

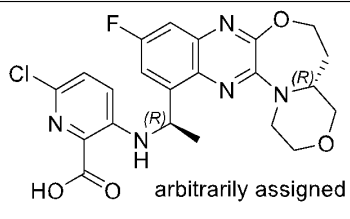
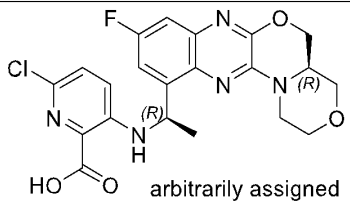
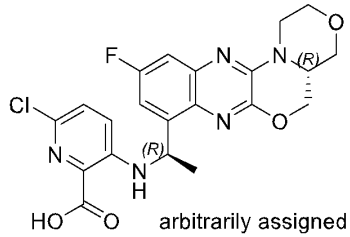
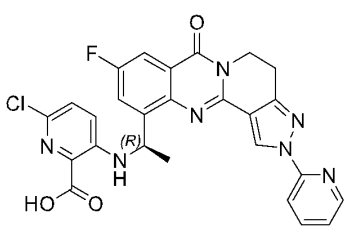
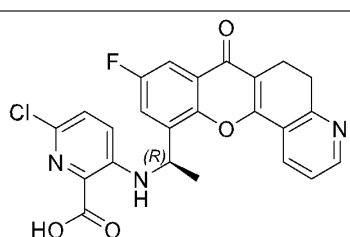
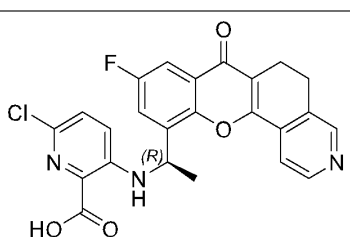
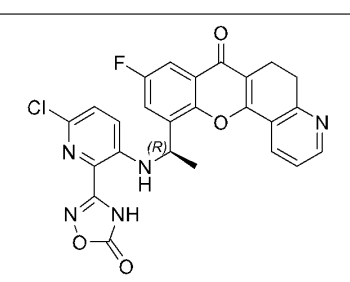
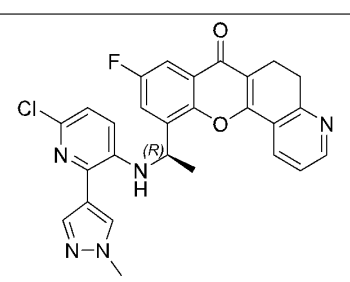
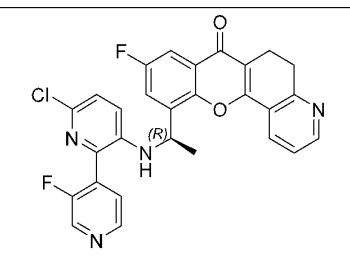
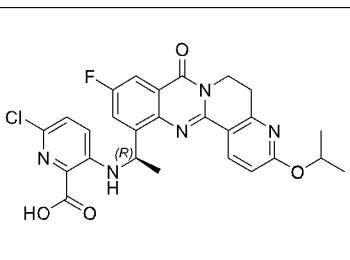
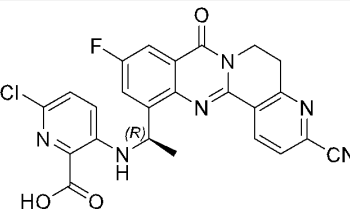
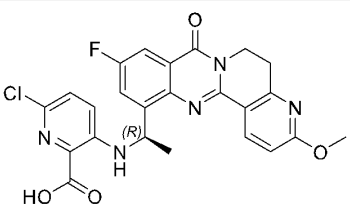
Table 1

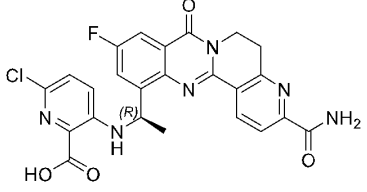
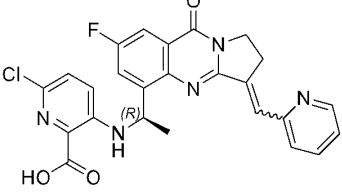
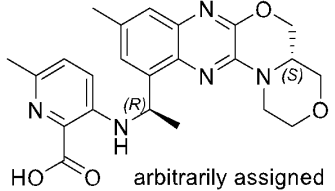
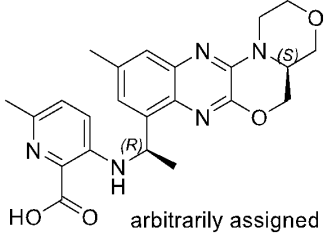
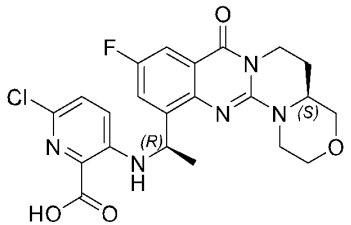
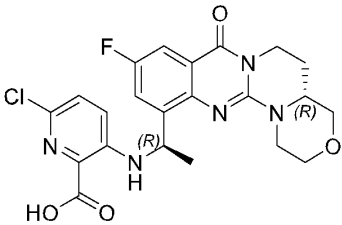
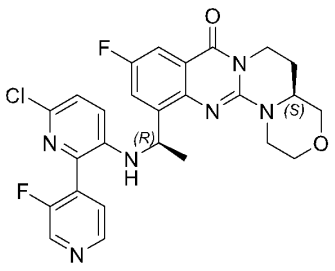
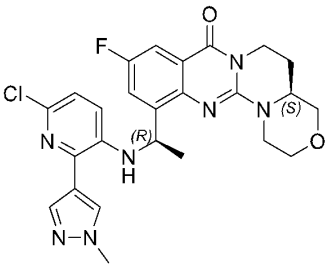
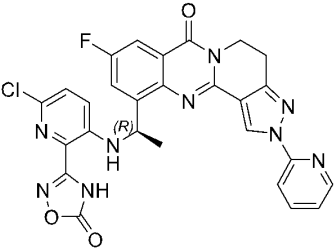
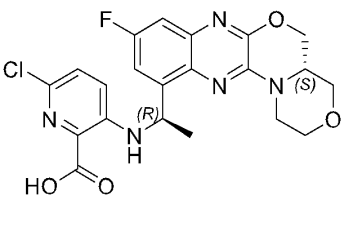
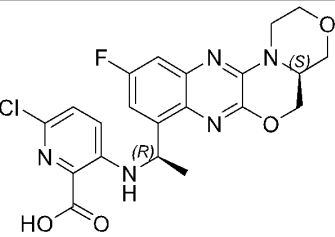
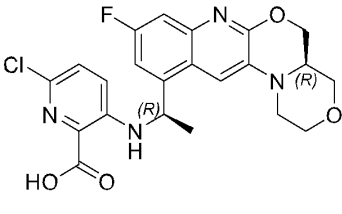
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Example 5		Example 6	
Example 7		Example 8	Intentionally left blank
Example 9		Example 10	

Example 11		Example 12	
Example 13		Example 14	
Example 15		Example 16	
Example 17		Example 18	
Example 19		Example 20	 mixture of the two

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Example 25		Example 26	
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Example 29		Example 30	
Example 31		Example 32	

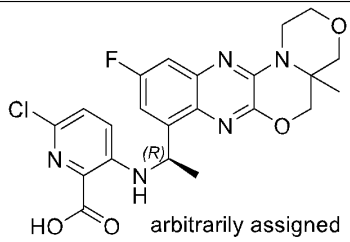
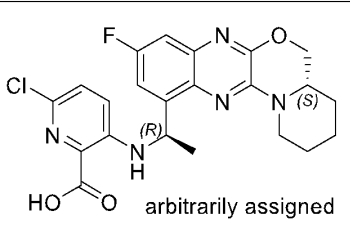
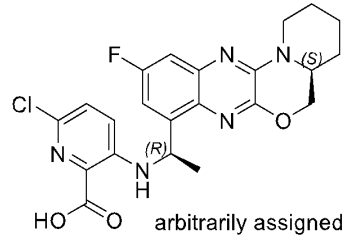
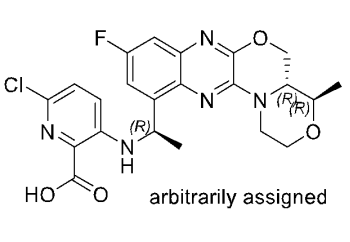
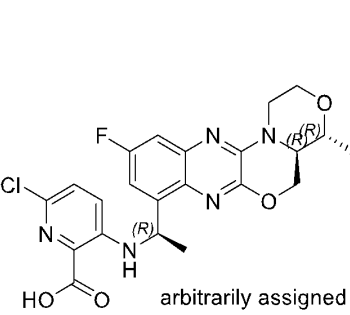
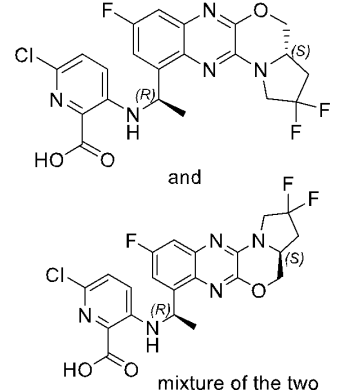
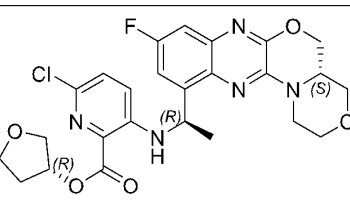
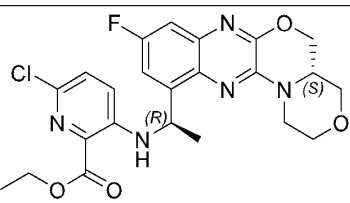
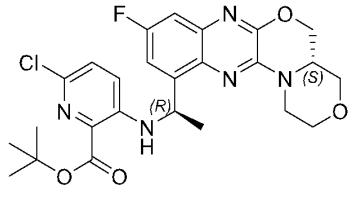
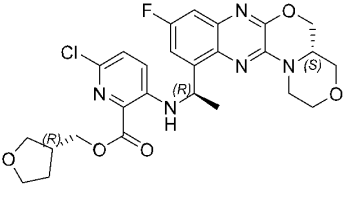
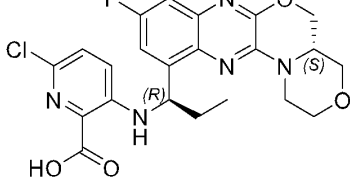
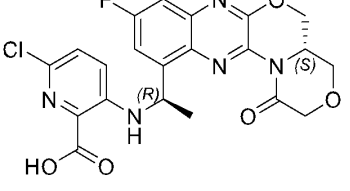
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Example 37		Example 38	
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Example 41		Example 42	
Example 43		Example 44	

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Example 51		Example 52	
Example 53		Example 54	
Example 55		Example 56	

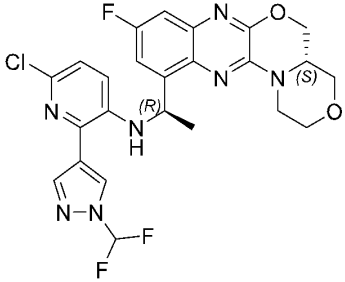
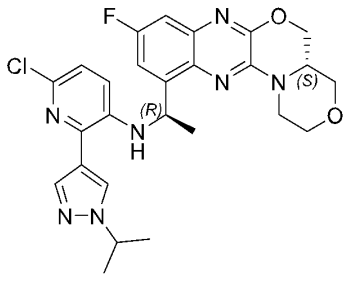
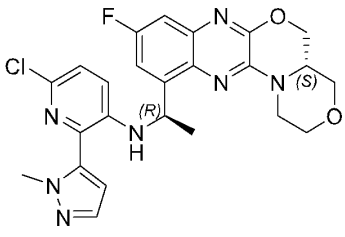
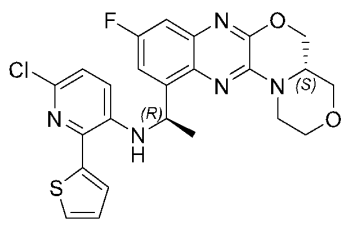
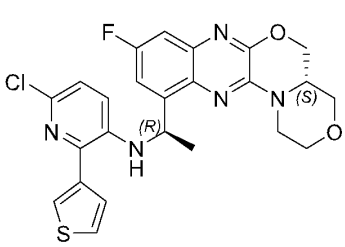
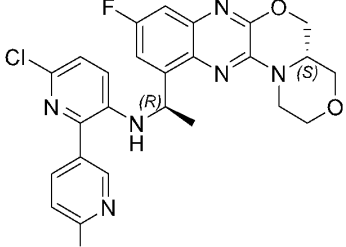
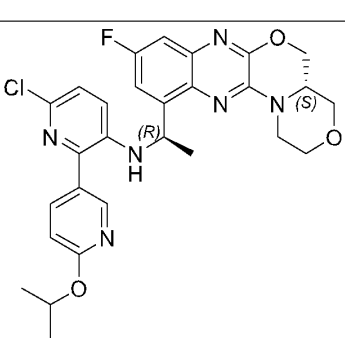
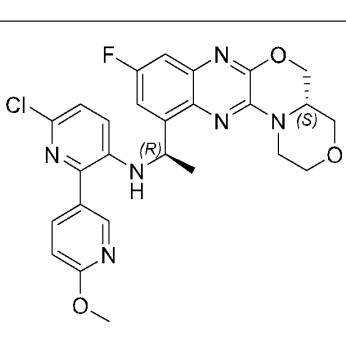
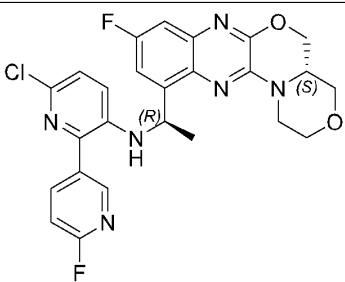
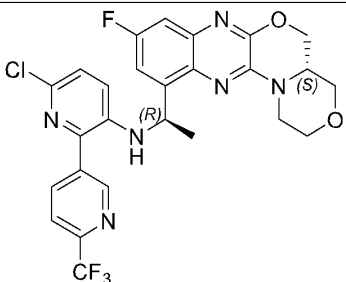
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Example 67		Example 68	

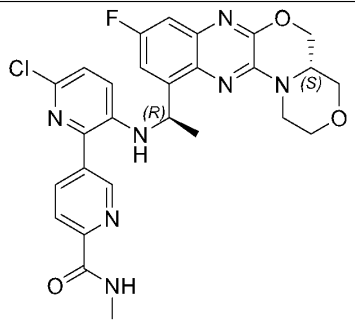
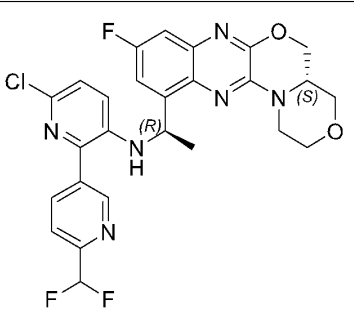
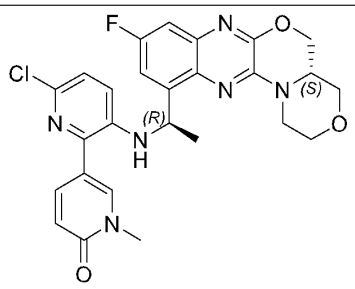
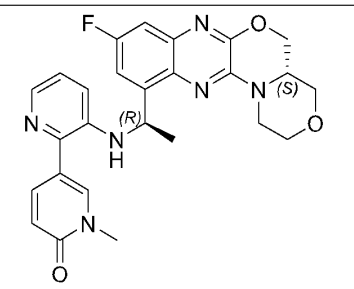
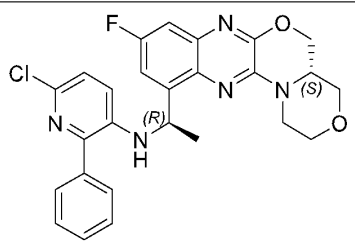
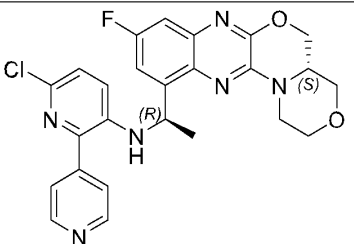
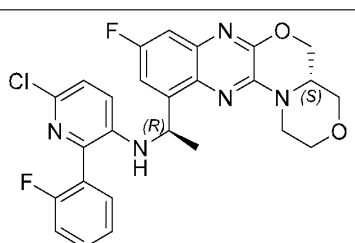
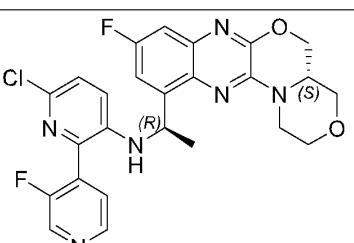
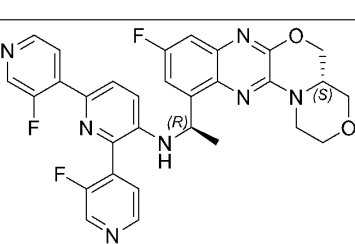
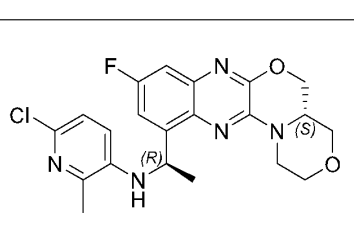
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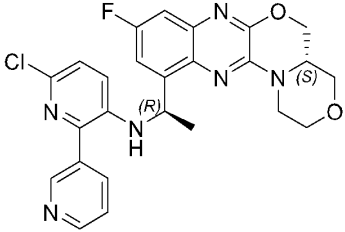
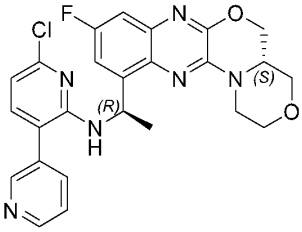
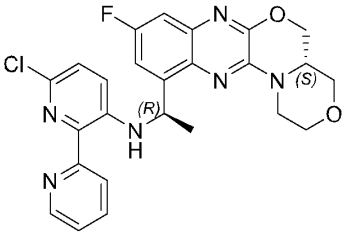
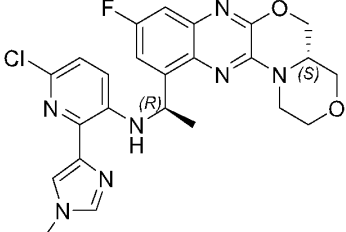
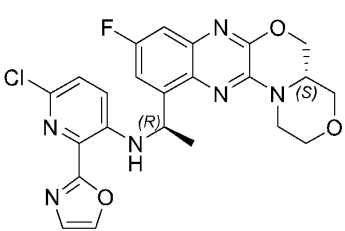
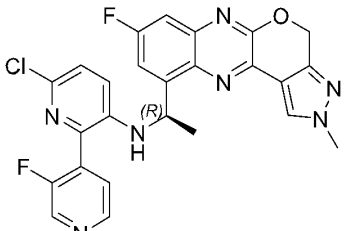
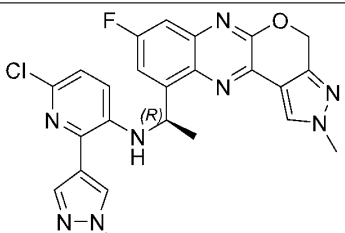
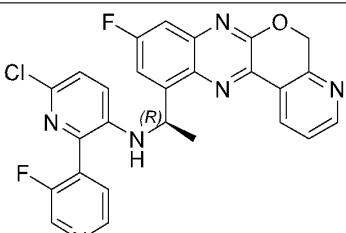
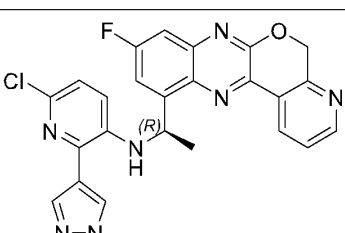
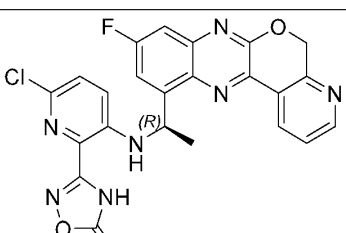
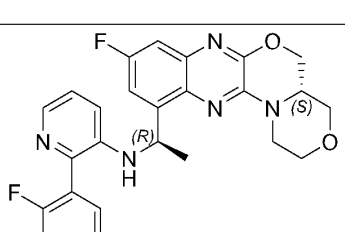
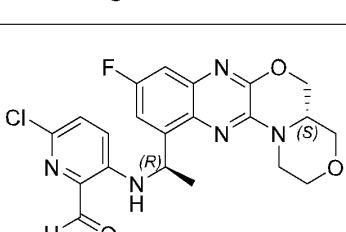
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Example 91		Example 92	
Example 93		Example 94	

Example 95	 arbitrarily assigned	Example 96	 arbitrarily assigned
Example 97	 arbitrarily assigned	Example 98	 arbitrarily assigned
Example 99	 arbitrarily assigned	Example 100	 mixture of the two
Example 101	 arbitrarily assigned	Example 102	 arbitrarily assigned
Example 103	 arbitrarily assigned	Example 104	 arbitrarily assigned
Example 105	 arbitrarily assigned	Example 106	 arbitrarily assigned

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Example 109		Example 110	
Example 111		Example 112	
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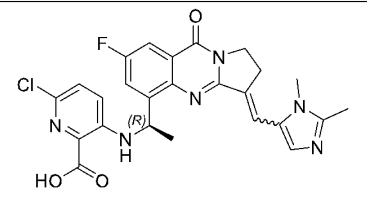
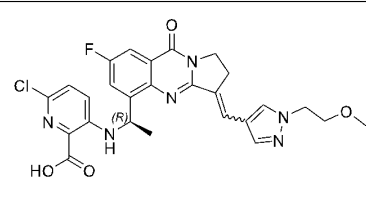
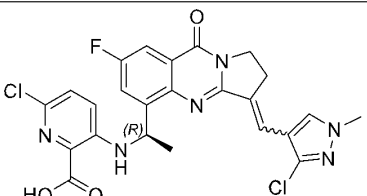
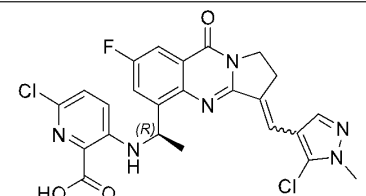
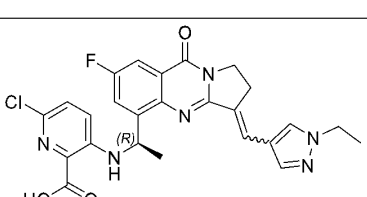
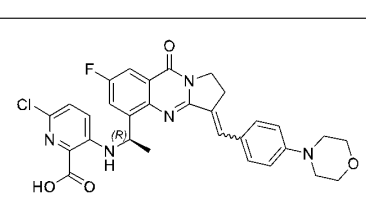
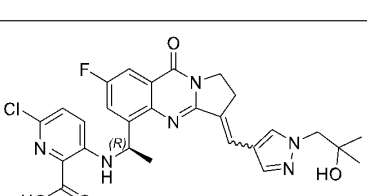
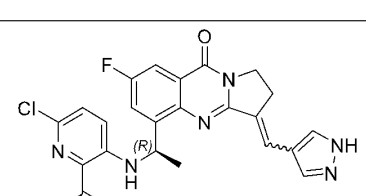
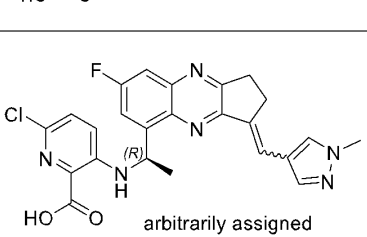
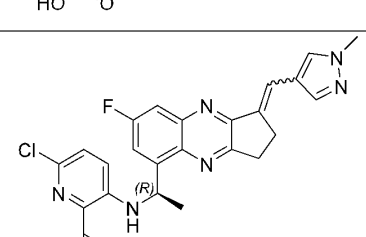
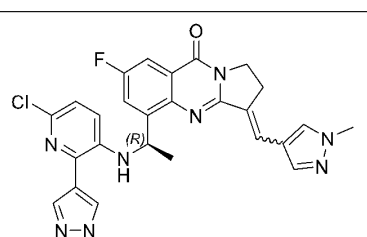
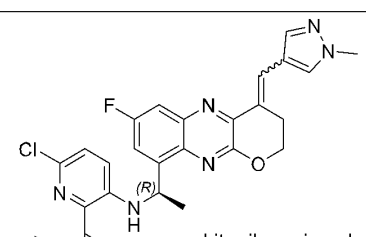
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Example 125		Example 126	

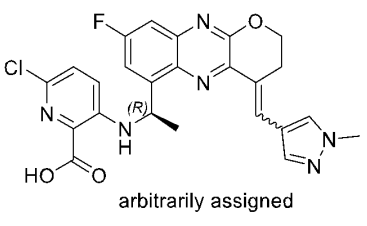
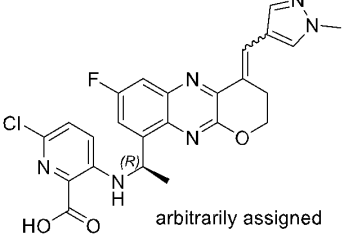
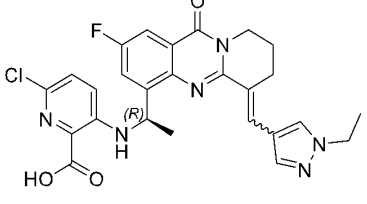
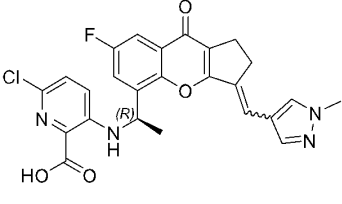
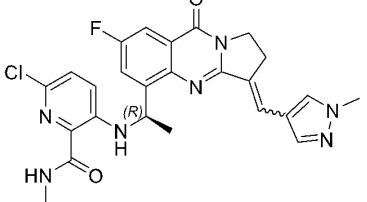
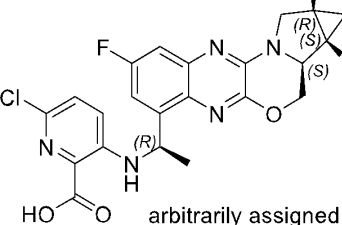
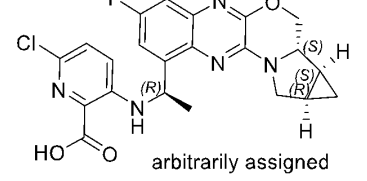
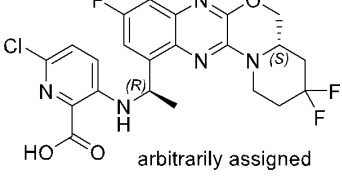
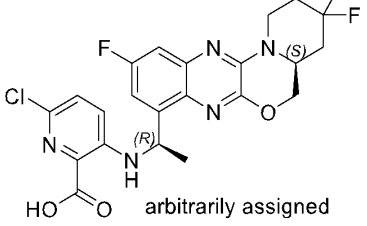
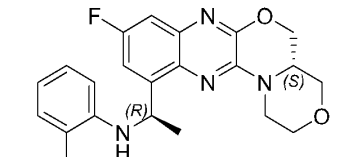
Example 127		Example 128	
Example 129		Example 130	
Example 131		Example 132	
Example 133		Example 134	
Example 135		Example 136	

Example 137		Example 138	
Example 139		Example 140	
Example 141		Example 142	
Example 143		Example 144	
Example 145		Example 146	
Example 147		Example 148	

Example 149		Example 150	
Example 151		Example 152	
Example 153		Example 154	
Example 155		Example 156	
Example 157		Example 158	
Example 159		Example 160	

Example 161		Example 162	
Example 163		Example 164	
Example 165		Example 166	
Example 167		Example 168	
Example 169		Example 170	
Example 171		Example 172	

Example 173		Example 174	
Example 175		Example 176	
Example 177		Example 178	
Example 179		Example 180	
Example 181	 arbitrarily assigned	Example 182	 arbitrarily assigned
Example 183		Example 184	 arbitrarily assigned

Example 185	 arbitrarily assigned	Example 186	 arbitrarily assigned
Example 187	 arbitrarily assigned	Example 188	 arbitrarily assigned
Example 189	 arbitrarily assigned	Example 190	 arbitrarily assigned
Example 191	 arbitrarily assigned	Example 192	 arbitrarily assigned
Example 193	 arbitrarily assigned	Example 194	 arbitrarily assigned

2. Definitions

The term “halo” or “halogen,” as used herein, refers to fluoride, chloride, bromide, or iodide.

- The term “alkyl” used alone or as part of a larger moiety, such as “alkoxy” or “haloalkyl” and the like, means saturated aliphatic straight-chain or branched monovalent hydrocarbon radical of formula $-C_nH_{(2n+1)}$. Unless otherwise specified, an alkyl group typically has 1-6 carbon atoms, *i.e.* C_{1-6} alkyl. As used herein, a “ C_{1-6} alkyl” group means a radical having from 1 to 6 carbon atoms in a linear or branched arrangement. Examples include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-

butyl, *tert*-butyl, n-pentyl, isopentyl, hexyl, and the like.

The terms “haloalkyl” means alkyl, as the case may be, substituted with one or more halogen atoms. In one embodiment, the alkyl can be substituted by one to three halogens. Examples of haloalkyl, include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl and the like.

The term “hydroxyalkyl” means alkyl, as the case may be, substituted with one or more hydroxyl groups. In one embodiment, the alkyl can be substituted by one to three hydroxyl groups.

The term “alkoxy” means an alkyl radical attached through an oxygen linking atom, represented by –O alkyl. For example, “C₁₋₄alkoxy” includes methoxy, ethoxy, propoxy, and butoxy.

The term “haloalkoxy” means alkoxy, as the case may be, substituted with one or more halogen atoms. In one embodiment, the alkoxy can be substituted by one to three halogens.

The term “hydroxyalkoxy” means alkoxy, as the case may be, substituted with one or more hydroxyl groups. In one embodiment, the alkoxy can be substituted by one to three hydroxyl groups. In one embodiment, the alkoxy is substituted by one hydroxyl group.

The term “alkoxyalkyl” means an alkyl group substituted with one or more alkoxy groups (*e.g.*, C₁₋₄alkoxy). In one embodiment, the alkyl can be substituted by one to three alkoxy groups. In one embodiment, the alkyl is substituted by one alkoxy group.

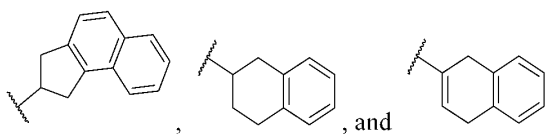
The term “alkenyl” means an alkyl group in which one or more carbon/carbon single bond is replaced by a double bond.

The term “alkynyl” means an alkyl group in which one or more carbon/carbon single bond is replaced by a triple bond.

The term “carbocyclyl” refers to a 3-12 membered non-aromatic hydrocarbon ring system and may exist as a monocyclic ring or a polycyclic ring (*e.g.*, a bicyclic ring including fused, spiro or bridged carbocyclic rings, or a tricyclic ring). In one embodiment, carbocyclyl is 3-, 4-, 5-, 6-, 7-, or 8-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic or tricyclic hydrocarbon ring, any of which may be saturated, partially unsaturated. Any substitutable ring atom can be substituted (*e.g.*, by one or more substituents). Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, and cyclooctadienyl.

In one embodiment, carbocyclyl is intended to include, bridged, fused, and spirocyclic rings. In a spirocyclic carbocyclyl, one atom is common to two different rings. An example of a spirocyclic carbocyclyl is spiro[3.3]heptanyl. In a bridged carbocyclyl, the rings share at least two common non-adjacent atoms. Examples of bridged carbocyclyls include bicyclo[2.2.1]heptanyl, bicyclo[2.2.1]hept-2-enyl, and adamantanyl. In a fused-ring carbocyclyl system, two or more rings may be fused together, such that two rings share one common bond. Examples of two- or three-fused ring carbocyclyls include naphthalenyl, tetrahydronaphthalenyl (tetralinyl), indenyl, indanyl (dihydroindenyl), anthracenyl, phenanthrenyl, and decalyl. The term “carbocyclyl” as used herein,

includes groups in which a carbocyclyl ring is fused to one or more aryl, where the radical or point of attachment is on the carbocyclyl ring. Nonlimiting examples of such fused ring systems include:



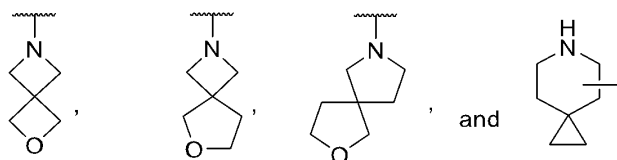
In some embodiments, carbocyclyl refers to a 3-12 membered cycloalkyl.

- 5 The term “cycloalkyl” refers to a cyclic, bicyclic, tricyclic, or polycyclic saturated hydrocarbon groups having 3 to 12 ring carbons. In one embodiment, cycloalkyl may have 3 to 7 ring carbons. Any substitutable ring atom can be substituted (*e.g.*, by one or more substituents). Examples of cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Cycloalkyl may include multiple fused and/or bridged rings. Non-
- 10 limiting examples of fused/bridged cycloalkyl include: bicyclo[1.1.0]butane, bicyclo[2.1.0]pentane, bicyclo[1.1.0]pentane, bicyclo[3.1.0]hexane, bicyclo[2.1.1]hexane, bicyclo[3.2.0]heptane, bicyclo[4.1.0]heptane, bicyclo[2.2.1]heptane, bicyclo[3.1.1]heptane, bicyclo[4.2.0]octane, bicyclo[3.2.1]octane, bicyclo[2.2.2]octane, and the like. Cycloalkyl also includes spirocyclic rings (*e.g.*, spirocyclic bicycle wherein two rings are connected through just one atom). Non-limiting
- 15 examples of spirocyclic cycloalkyls include spiro[2.2]pentane, spiro[2.5]octane, spiro[3.5]nonane, spiro[3.5]nonane, spiro[3.5]nonane, spiro[4.4]nonane, spiro[2.6]nonane, spiro[4.5]decane, spiro[3.6]decane, spiro[5.5]undecane, and the like.

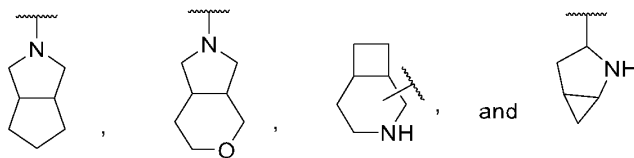
- The term “heterocyclyl” or “heterocyclic” refers to a radical of a 4- to 12-membered non-aromatic, fully saturated or partially unsaturated, ring system having ring carbon atoms and 1 to 4
- 20 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, quaternary nitrogen, oxidized nitrogen (*e.g.*, NO), oxygen, and sulfur, including sulfoxide and sulfone (“4-12 membered heterocyclyl”). In some embodiments, a heterocyclyl group is a 3-7 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“3-7 membered heterocyclyl”). In some
- 25 embodiments, a heterocyclyl group comprises 1-3 heteroatoms selected from oxygen, nitrogen, and sulfur. An oxygen-containing only heterocyclyl refers to a heterocyclyl group comprises 1 or 2 heteroatoms selected from oxygen only. In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic (“monocyclic heterocyclyl”) or polycyclic (*e.g.*, a bicyclic system
- 30 (“bicyclic heterocyclyl”) or tricyclic system (“tricyclic heterocyclyl”); polycyclic ring systems include fused, bridged, or spiro ring systems). Heterocyclyl polycyclic ring systems can include heteroatoms in one or more rings in the polycyclic ring system—including polycyclic ring systems having a non-aromatic ring fused to a phenyl or heteroaryl ring. When a heterocyclyl group is a polycyclic ring system, said ring system includes at least one non-aromatic ring. Exemplary monocyclic heterocyclyl

groups include azetidiny, oxetanyl, thietanyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, tetrahydropyranyl, piperazinyl, morpholinyl, azepanyl, oxepanyl, thiepanyl, tetrahydropyridinyl, and the like. Heterocyclyl polycyclic ring systems can include heteroatoms in one or more rings in the polycyclic ring system. Substituents may be present on one or more rings in the polycyclic ring system.

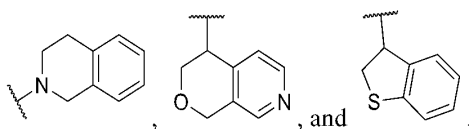
Spiro heterocyclyl refers to 5 to 12 membered polycyclic heterocyclyl with rings connected through one common carbon atom (called as spiro atom), wherein said rings have one or more heteroatoms selected from the group consisting of nitrogen, quaternary nitrogen, oxidized nitrogen (e.g., NO), oxygen, and sulfur, including sulfoxide and sulfone, the remaining ring atoms being C, wherein one or more rings may contain one or more double bonds, but none of the rings has a completely conjugated π -electron system. Representative examples of spiro heterocyclyl include, but are not limited to the following groups:



Fused heterocyclyl refers to a 5 to 12 membered polycyclic heterocyclyl group, wherein each ring in the group shares an adjacent pair of carbon atoms with another ring in the group, wherein one or more rings can contain one or more double bonds, and wherein said rings have one or more heteroatoms selected from the group consisting of nitrogen, quaternary nitrogen, oxidized nitrogen (e.g., NO), oxygen, and sulfur, including sulfoxide and sulfone, the remaining ring atoms being C. Representative examples of fused heterocyclyl include, but are not limited to the following groups:

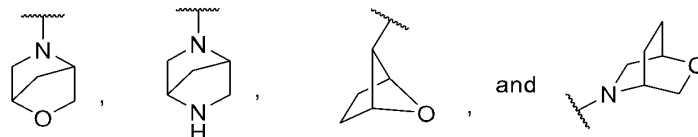


In some embodiments, a fused heterocyclyl include groups in which a non-aromatic heterocyclyl ring is fused to one or more aryl or heteroaryl. Nonlimiting examples of such fused heterocyclyl ring systems include:



Bridged heterocyclyl refers to a 5 to 12 membered polycyclic heterocyclyl group, wherein any two rings in the group share two disconnected atoms, the rings can have one or more double bonds but have no completely conjugated π -electron system, and the rings have one or more heteroatoms selected from the group consisting of nitrogen, quaternary nitrogen, oxidized nitrogen

(*e.g.*, NO), oxygen, and sulfur, including sulfoxide and sulfone as ring atoms, the remaining ring atoms being C. Representative examples of bridged heterocyclyl include, but are not limited to the following groups:



- 5 Generally, the carbocyclyl, the cycloalkyl, or the heterocyclyl may be unsubstituted, or be substituted with one or more substituents as valency allows, wherein the substituents can be independently selected from a number of groups such as oxo, -CN, halogen, alkyl and alkoxy, optionally, the alkyl substitution may be further substituted.

- 10 The term “aryl” refers to a 6 to 10 membered all-carbon monocyclic ring or a polycyclic fused ring (a “fused” ring system means that each ring in the system shares an adjacent pair of carbon atoms with other ring in the system) group, and has a completely conjugated π -electron system. The term “aryl” may be used interchangeably with the terms “aryl ring” “carbocyclic aromatic ring”, “aryl group” and “carbocyclic aromatic group”. Representative examples of aryl are phenyl and naphthyl.

- 15 The term “heteroaryl,” as used herein, refers to a monocyclic or multicyclic aromatic hydrocarbon in which at least one of the ring carbon atoms has been replaced with a heteroatom independently selected from oxygen, nitrogen and sulfur. Preferably, the heteroaryl is based on a C_{5-10} aryl with one or more of its ring carbon atoms replaced by the heteroatom. In some embodiments, heteroaryl comprises 1-4 heteroatoms selected from oxygen, nitrogen, and sulfur. A heteroaryl group may be attached through a ring carbon atom or, where valency permits, through a
20 ring nitrogen atom. Generally, the heteroaryl may be unsubstituted, or be substituted with one or more substituents as valency allows with the substituents being independently selected from halogen, OH, alkyl, alkoxy, and amino (*e.g.*, NH_2 , $NHalkyl$, $N(alkyl)_2$), optionally, the alkyl may be further substituted.

- Examples of monocyclic 5-6 membered heteroaryl groups include furanyl (*e.g.*, 2-furanyl, 25 3-furanyl), imidazolyl (*e.g.*, N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), isoxazolyl (*e.g.*, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), oxadiazolyl (*e.g.*, 2-oxadiazolyl, 5-oxadiazolyl), oxazolyl (*e.g.*, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), pyrazolyl (*e.g.*, 3-pyrazolyl, 4-pyrazolyl), pyrrolyl (*e.g.*, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), pyridyl (*e.g.*, 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (*e.g.*, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl), pyridazinyl (*e.g.*, 3-pyridazinyl), thiazolyl
30 (*e.g.*, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), triazolyl (*e.g.*, 2-triazolyl, 5-triazolyl), tetrazolyl (*e.g.*, tetrazolyl), thienyl (*e.g.*, 2-thienyl, 3-thienyl), pyrimidinyl, pyridinyl and pyridazinyl. Examples of polycyclic aromatic heteroaryl groups include carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinoliny, benzotriazolyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, isoquinoliny, indolyl, isoindolyl, acridinyl, or benzisoxazolyl. A “substituted heteroaryl group” is

substituted at any one or more substitutable ring atom, which is a ring carbon or ring nitrogen atom bonded to a hydrogen.

As used herein, many moieties (*e.g.*, alkyl, alkylene, cycloalkyl, aryl, heteroaryl, or heterocyclyl) are referred to as being either “substituted” or “optionally substituted”. When a moiety is modified by one of these terms, unless otherwise noted, it denotes that any portion of the moiety that is known to one skilled in the art as being available for substitution can be substituted, which includes one or more substituents. Where if more than one substituent is present, then each substituent may be independently selected. Such means for substitution are well-known in the art and/or taught by the instant disclosure. The optional substituents can be any substituents that are suitable to attach to the moiety.

Where suitable substituents are not specifically enumerated, exemplary substituents include, but are not limited to: C₁₋₅alkyl, C₁₋₅hydroxyalkyl, C₁₋₅haloalkyl, C₁₋₅alkoxy, C₁₋₅ haloalkoxy, halogen, hydroxyl, cyano, amino, -CN, -NO₂, -OR^{cl}, -NR^{al}R^{bl}, -S(O)_iR^{al}, -NR^{al}S(O)_iR^{bl}, -S(O)_iNR^{al}R^{bl}, -C(=O)OR^{al}, -OC(=O)OR^{al}, -C(=S)OR^{al}, -O(C=S)R^{al}, -C(=O)NR^{al}R^{bl}, -NR^{al}C(=O)R^{bl}, -C(=S)NR^{al}R^{bl}, -C(=O)R^{al}, -C(=S)R^{al}, NR^{al}C(=S)R^{bl}, -O(C=O)NR^{al}R^{bl}, -NR^{al}(C=S)OR^{bl}, -O(C=S)NR^{al}R^{bl}, -NR^{al}(C=O)NR^{al}R^{bl}, -NR^{al}(C=S)NR^{al}R^{bl}, phenyl, or 5-6 membered heteroaryl. Each R^{al} and each R^{bl} are independently selected from -H and C₁₋₅alkyl, optionally substituted with hydroxyl or C₁₋₃alkoxy; R^{cl} is H, C₁₋₅haloalkyl or C₁₋₅alkyl, wherein the C₁₋₅alkyl is optionally substituted with hydroxyl or C₁₋₃alkoxy.

Unless otherwise defined, the terms used herein have their standard meaning in the art (*e.g.* “hydroxy” or “hydroxyl” is -OH).

Pharmaceutically Acceptable Salts

The term “pharmaceutically acceptable salt” refers to a pharmaceutical salt that is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, and allergic response, and is commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge *et al.* describes pharmacologically acceptable salts in J. Pharm. Sci., 1977, 66, 1-19.

Pharmaceutically acceptable salts of the compounds of any one of the formulae described above include acid addition and base salts.

Included in the present teachings are pharmaceutically acceptable salts of the compounds disclosed herein. Compounds having basic groups can form pharmaceutically acceptable salts with pharmaceutically acceptable acid(s). Suitable pharmaceutically acceptable acid addition salts of the compounds described herein include salts of inorganic acids (such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric, and sulfuric acids) and of organic acids (such as acetic, benzenesulfonic, benzoic, ethanesulfonic, methanesulfonic, and succinic acids). Compounds of the

present teachings with acidic groups such as carboxylic acids can form pharmaceutically acceptable salts with pharmaceutically acceptable base(s). Suitable pharmaceutically acceptable basic salts include ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts).

5 Pharmaceutically acceptable salts of compounds of any one of the formulae described above may be prepared by one or more of three methods:

(i) by reacting the compound of any one of the formulae described above with the desired acid or base;

(ii) by removing an acid- or base-labile protecting group from a suitable precursor of the
10 compound of any one of the formulae described above or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or

(iii) by converting one salt of the compound of any one of the formulae described above to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

All three reactions are typically carried out in solution. The resulting salt may precipitate out
15 and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

The compounds of any one of the formulae described above, and pharmaceutically acceptable salts thereof, may exist in unsolvated and solvated forms.

20 ***Stereoisomers and Other Variations***

The compounds of any one of the formulae described above may exhibit one or more kinds of isomerism (*e.g.* optical, geometric or tautomeric isomerism). Such variation is implicit to the compounds of any one of the formulae described above defined as they are by reference to their structural features and therefore within the scope of the present disclosure.

25 Compounds having one or more chiral centers can exist in various stereoisomeric forms, *i.e.*, each chiral center can have an *R* or *S* configuration, or can be a mixture of both. Stereoisomers are compounds that differ only in their spatial arrangement. Stereoisomers include all diastereomeric and enantiomeric forms of a compound. Enantiomers are stereoisomers that are mirror images of each other. Diastereomers are stereoisomers having two or more chiral centers that are not identical and
30 are not mirror images of each other.

When a compound is designated by its chemical name (*e.g.*, where the configuration is indicated in the chemical name by “*R*” or “*S*”) or its structure (*e.g.*, the configuration is indicated by “wedge” bonds) that indicates a single enantiomer, unless indicated otherwise, the compound is at least 60%, 70%, 80%, 90%, 99% or 99.9% optically pure (also referred to as “enantiomerically
35 pure”). Optical purity is the weight in the mixture of the named or depicted enantiomer divided by the total weight in the mixture of both enantiomers.

When the stereochemistry of a disclosed compound is named or depicted by structure, and the

named or depicted structure encompasses more than one stereoisomer (*e.g.*, as in a diastereomeric pair), it is to be understood that one of the encompassed stereoisomers or any mixture of the encompassed stereoisomers is included. It is to be further understood that the stereoisomeric purity of the named or depicted stereoisomers at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight. The stereoisomeric purity in this case is determined by dividing the total weight in the mixture of the stereoisomers encompassed by the name or structure by the total weight in the mixture of all of the stereoisomers.

When two stereoisomers are depicted by their chemical names or structures, and the chemical names or structures are connected by an “and”, a mixture of the two stereoisomers is intended.

When two stereoisomers are depicted by their chemical names or structures, and the names or structures are connected by an “or”, one or the other of the two stereoisomers is intended, but not both.

When a disclosed compound having a chiral center is depicted by a structure without showing a configuration at that chiral center, the structure is meant to encompass the compound with the *S* configuration at that chiral center, the compound with the *R* configuration at that chiral center, or the compound with a mixture of the *R* and *S* configuration at that chiral center. When a disclosed compound having a chiral center is depicted by its chemical name without indicating a configuration at that chiral center with “*S*” or “*R*”, the name is meant to encompass the compound with the *S* configuration at that chiral center, the compound with the *R* configuration at that chiral center or the compound with a mixture of the *R* and *S* configuration at that chiral center.

Racemic mixture means 50% of one enantiomer and 50% of the corresponding enantiomer. When a compound with one chiral center is named or depicted without indicating the stereochemistry of the chiral center, it is understood that the name or structure encompasses both possible enantiomeric forms (*e.g.*, both enantiomerically-pure, enantiomerically-enriched or racemic) of the compound. When a compound with two or more chiral centers is named or depicted without indicating the stereochemistry of the chiral centers, it is understood that the name or structure encompasses all possible diastereomeric forms (*e.g.*, diastereomerically pure, diastereomerically enriched and equimolar mixtures of one or more diastereomers (*e.g.*, racemic mixtures) of the compound.

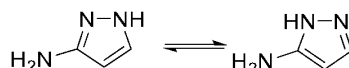
The term “geometric isomer” means isomers that differ in the orientation of substituent atoms in relationship to a carbon-carbon double bond, to a carbocyclic ring, or to a bridged bicyclic system. Substituent atoms (other than hydrogen) on each side of a carbon-carbon double bond may be in an *E* or *Z* configuration according to the Cahn-Ingold-Prelog priority rules. In the “*E*” configuration, the substituents having the highest priorities are on opposite sides in relationship to the carbon-carbon double bond. In the “*Z*” configuration, the substituents having the highest priorities are oriented on the same side in relationship to the carbon-carbon double bond.

Substituents around a carbon-carbon double bond can also be referred to as “*cis*” or “*trans*,”

where “cis” represents substituents on the same side of the double bond and “trans” represents substituents on opposite sides of the double bond. The arrangement of substituents around a carbocyclic ring can also be designated as “cis” or “trans.” The term “cis” represents substituents on the same side of the plane of the ring, and the term “trans” represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated “cis/trans.”

Where structural isomers are interconvertible via a low energy barrier, tautomeric isomerism (“tautomerism”) can occur. This can take the form of proton tautomerism in compounds of any one of the formulae described above containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds which contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

In certain instances tautomeric forms of the disclosed compounds exist, such as the tautomeric structures shown below:



When a geometric isomer is depicted by name or structure, it is to be understood that the named or depicted isomer exists to a greater degree than another isomer, that is that the geometric isomeric purity of the named or depicted geometric isomer is greater than 50%, such as at least 60%, 70%, 80%, 90%, 99%, or 99.9% pure by weight. Geometric isomeric purity is determined by dividing the weight of the named or depicted geometric isomer in the mixture by the total weight of all of the geometric isomers in the mixture.

Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation.

Conventional techniques for the preparation/isolation of individual enantiomers/diastereomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of any one of the formulae described above contains an acidic or basic moiety, a base or acid such as 1-phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person. Chiral compounds of any one of the formulae described above (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2% to 20%, and from 0 to 5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture. Chiral

chromatography using sub-and supercritical fluids may be employed. Methods for chiral chromatography useful in some embodiments of the present disclosure are known in the art (see, for example, Smith, Roger M., Loughborough University, Loughborough, UK; Chromatographic Science Series (1998), 75 (Supercritical Fluid Chromatography with Packed Columns), pp. 223-249 and
5 references cited therein). Columns can be obtained from Chiral Technologies, Inc, West Chester, Pa., USA, a subsidiary of Daicel[®] Chemical Industries, Ltd., Tokyo, Japan.

It must be emphasized that the compounds of any one of the formulae described above have been drawn herein in a single tautomeric form, all possible tautomeric forms are included within the scope of the present disclosure.

10

3. Administration and Dosing

Typically, a compound of the present disclosure is administered in an amount effective to treat a condition as described herein. The compounds of the present disclosure can be administered as compound *per se*, or alternatively, as a pharmaceutically acceptable salt. For administration and
15 dosing purposes, the compound *per se* or pharmaceutically acceptable salt thereof will simply be referred to as the compounds of the present disclosure.

The compounds of the present disclosure are administered by any suitable route in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds of the present disclosure may be administered orally, rectally, vaginally,
20 parenterally, or topically.

The compounds of the present disclosure may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the bloodstream directly from the mouth.

25

In another embodiment, the compounds of the present disclosure may also be administered directly into the bloodstream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion
30 techniques.

In another embodiment, the compounds of the present disclosure may also be administered topically to the skin or mucosa, that is, dermally or transdermally. In another embodiment, the compounds of the present disclosure can also be administered intranasally or by inhalation. In another embodiment, the compounds of the present disclosure may be administered rectally or vaginally. In
35 another embodiment, the compounds of the present disclosure may also be administered directly to the eye or ear.

The dosage regimen for the compounds of the present disclosure and/or compositions

containing said compounds is based on a variety of factors, including the type, age, weight, sex and medical condition of the patient; the severity of the condition; the route of administration; and the activity of the particular compound employed. Thus the dosage regimen may vary widely.

Suitable subjects according to the present disclosure include mammalian subjects, including
5 non-human mammal such as primates, rodents (mice, rats, hamsters, rabbits *etc*). In one embodiment, humans are suitable subjects. Human subjects may be of either gender and at any stage of development.

4. *Pharmaceutical Compositions*

10 In another embodiment, the present disclosure comprises pharmaceutical compositions. Such pharmaceutical compositions comprise a compound of the present disclosure presented, a pharmaceutically acceptable salt, or a stereoisomer thereof with a pharmaceutically acceptable carrier or excipient. Other pharmacologically active substances can also be present.

As used herein, “pharmaceutically acceptable carrier or excipient” includes any and all
15 solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Examples of pharmaceutically acceptable carriers include one or more of water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof, and may include isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol, or sorbitol in the composition.
20 Pharmaceutically acceptable substances such as wetting agents or minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the antibody or antibody portion.

The compositions of present disclosure may be in a variety of forms. These include, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions (*e.g.*, injectable and
25 infusible solutions), dispersions or suspensions, tablets, pills, powders, liposomes and suppositories. The form depends on the intended mode of administration and therapeutic application.

Typical compositions are in the form of injectable or infusible solutions, such as compositions similar to those used for passive immunization of humans with antibodies in general. One mode of administration is parenteral (*e.g.* intravenous, subcutaneous, intraperitoneal, intramuscular). In another
30 embodiment, the antibody is administered by intravenous infusion or injection. In yet another embodiment, the antibody is administered by intramuscular or subcutaneous injection.

Oral administration of a solid dose form may be, for example, presented in discrete units, such as hard or soft capsules, pills, cachets, lozenges, or tablets, each containing a predetermined amount of at least one compound of the present disclosure. In another embodiment, the oral
35 administration may be in a powder or granule form. In another embodiment, the oral dose form is sub-lingual, such as, for example, a lozenge. In such solid dosage forms, the compounds of any one of the formulae described above are ordinarily combined with one or more adjuvants. Such capsules or

tablets may contain a controlled release formulation. In the case of capsules, tablets, and pills, the dosage forms also may comprise buffering agents or may be prepared with enteric coatings.

In another embodiment, oral administration may be in a liquid dose form. Liquid dosage forms for oral administration include, for example, pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art (*e.g.*, water). Such compositions also may comprise adjuvants, such as wetting, emulsifying, suspending, flavoring (*e.g.*, sweetening), and/or perfuming agents.

In another embodiment, the present disclosure comprises a parenteral dose form.

“Parenteral administration” includes, for example, subcutaneous injections, intravenous injections, intraperitoneally, intramuscular injections, intrasternal injections, and infusion. Injectable preparations (*i.e.*, sterile injectable aqueous or oleaginous suspensions) may be formulated according to the known art using suitable dispersing, wetting agents, and/or suspending agents.

In another embodiment, the present disclosure comprises a topical dose form.

“Topical administration” includes, for example, transdermal administration, such as via transdermal patches or iontophoresis devices, intraocular administration, or intranasal or inhalation administration. Compositions for topical administration also include, for example, topical gels, sprays, ointments, and creams. A topical formulation may include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. When the compounds of present disclosure are administered by a transdermal device, administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, Finnin and Morgan, *J. Pharm. Sci.*, 88:955-958, 1999.

Formulations suitable for topical administration to the eye include, for example, eye drops wherein the compound of present disclosure is dissolved or suspended in a suitable carrier. A typical formulation suitable for ocular or aural administration may be in the form of drops of a micronized suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (*i.e.*, absorbable gel sponges, collagen) and non-biodegradable (*i.e.*, silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed linked polyacrylic acid, polyvinyl alcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methylcellulose, or a heteropolysaccharide polymer, for example, gelatin, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

For intranasal administration or administration by inhalation, the compounds of the present disclosure are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant. Formulations suitable for intranasal administration are typically administered in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurized container, pump, spray, atomizer (preferably an atomizer using electrohydrodynamics to produce a fine mist), or nebulizer, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

In another embodiment, the present disclosure comprises a rectal dose form. Such rectal dose form may be in the form of, for example, a suppository. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Other carrier materials and modes of administration known in the pharmaceutical art may also be used. Pharmaceutical compositions of the present disclosure may be prepared by any of the well-known techniques of pharmacy, such as effective formulation and administration procedures.

The above considerations in regard to effective formulations and administration procedures are well known in the art and are described in standard textbooks. Formulation of drugs is discussed in, for example, Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pa., 1975; Liberman *et al.*, Eds., *Pharmaceutical Dosage Forms*, Marcel Dekker, New York, N.Y., 1980; and Kibbe *et al.*, Eds., *Handbook of Pharmaceutical Excipients* (3rd Ed.), American Pharmaceutical Association, Washington, 1999.

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5. Method of Treatment

The terms "individual" or "patient," used interchangeably, refer to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

The terms "treatment," "treat," and "treating" refer to reversing, alleviating, or inhibiting the progress of a disease described herein. In some embodiments, treatment may be administered after one or more signs or symptoms of the disease have developed or have been observed (*i.e.*, therapeutic treatment). In other embodiments, treatment may be administered in the absence of signs or symptoms of the disease. For example, treatment may be administered to a susceptible subject prior to the onset of symptoms (*i.e.*, prophylactic treatment) (*e.g.*, in light of a history of symptoms and/or in light of exposure to a pathogen). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

The terms “condition,” “disease,” and “disorder” are used interchangeably.

The term “administer,” “administering,” or “administration” refers to methods introducing a compound disclosed herein, or a composition thereof, in or on a patient. These methods include, but are not limited to, intraarticular (in the joints), intravenous, intramuscular, intratumoral, intradermal, intraperitoneal, subcutaneous, orally, topically, intrathecally, inhalationally, transdermally, rectally, and the like. Administration techniques that can be employed with the agents and methods described herein are found in *e.g.*, Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, current ed.; Pergamon; and Remington’s, *Pharmaceutical Sciences* (current edition), Mack Publishing Co., Easton, Pa.

Generally, an effective amount of a compound taught herein varies depending upon various factors, such as the given drug or compound, the pharmaceutical formulation, the route of administration, the type of disease or disorder, the identity of the subject or host being treated, and the like, but can nevertheless be routinely determined by one skilled in the art. An effective amount of a compound of the present teachings may be readily determined by one of ordinary skill by routine methods known in the art.

The term “therapeutically effective amount” means an amount when administered to the subject which results in beneficial or desired results, including clinical results, *e.g.*, inhibits, suppresses or reduces the symptoms of the condition being treated in the subject as compared to a control. For example, a therapeutically effective amount can be an amount effective for detectable killing or inhibition of the growth or spread of cancer cells; the size or number of tumors; or other measure of the level, stage, progression or severity of the cancer. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the disease, the particular anticancer agent, its mode of administration, combination treatment with other therapies, and the like.

Compounds of the present disclosure can inhibit PI3K α and therefore are useful for treating diseases wherein the underlying pathology is, wholly or partially, mediated by PI3K α (*e.g.*, PI3K α mutation). Such diseases include cancer and CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome).

In some embodiments, the present disclosure provides a method of modulating PI3K (*e.g.*, PI3K α) activity (*e.g.*, *in vitro* or *in vivo*), comprising contacting a cell with a therapeutically effective amount of a compound of Formula (I) or (I’), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof.

In some embodiments, the present disclosure provides a method of modulating mutated PI3K α activity (*e.g.*, *in vitro* or *in vivo*), comprising contacting a cell with a therapeutically effective amount of a compound of Formula (I) or (I’), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof.

In some embodiments, the present disclosure provides a method of treating or preventing a

disease or disorder disclosed herein in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutical composition of the present disclosure.

5 In some embodiments, the present disclosure provides a method of treating a disease or disorder disclosed herein in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutical composition of the present disclosure.

In some embodiments, the disease or disorder is associated with an implicated PI3K (*e.g.*,
10 PI3K α) activity. In some embodiments, the disease or disorder is a disease or disorder in which PI3K (*e.g.*, PI3K α) activity is implicated.

In some embodiments, the disease or disorder is associated with an implicated mutated PI3K α activity. In some embodiments, the disease or disorder is a disease or disorder in which mutated PI3K α activity is implicated.

15 In some embodiments, the disease or disorder is a cancer.

In some embodiments, the cancer is selected from acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), adrenocortical carcinoma, aids-related cancers, aids-related lymphoma, anal cancer, astrocytoma, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, osteosarcoma, malignant fibrous histiocytoma, brain tumors, breast cancer, bronchial tumors, Burkitt
20 lymphoma, carcinoid tumor, cancer of unknown primary, cardiac (heart) tumors, atypical teratoid/rhabdoid tumor, primary CNS lymphoma, cervical cancer, cholangiocarcinoma, chordoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), colorectal cancer, craniopharyngioma, cutaneous t-cell lymphoma, mycosis fungoides, Sezary syndrome, ductal carcinoma in situ (DCIS), embryonal tumors, medulloblastoma, endometrial cancer, ependymoma,
25 esophageal cancer, esthesioneuroblastoma, Ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, fallopian tube cancer, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor, malignant gastrointestinal stromal tumors (GIST), germ cell tumors, gestational trophoblastic disease, hairy cell leukemia, head and neck cancer, hepatocellular cancer, Langerhans cell histiocytosis, Hodgkin lymphoma, islet cell tumors, pancreatic neuroendocrine
30 tumors, Kaposi sarcoma, kidney cancer, laryngeal cancer, leukemia, liver cancer, lung cancer, lymphoma, male breast cancer, intraocular melanoma, Merkel cell carcinoma, malignant mesothelioma, metastatic cancer, metastatic squamous neck cancer, midline tract carcinoma with nut gene changes, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma/plasma cell neoplasms, myelodysplastic syndromes, myelodysplastic neoplasms, myeloproliferative neoplasms,
35 chronic myeloproliferative neoplasm, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer, oral cancer, lip and oral cavity cancer, oropharyngeal cancer, malignant fibrous histiocytoma of bone, ovarian cancer, pancreatic

cancer, pancreatic neuroendocrine tumors (islet cell tumors), papillomatosis, paraganglioma, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromocytoma, pituitary tumor, plasma cell neoplasm, multiple myeloma, pleuropulmonary blastoma, primary central nervous system (CNS) lymphoma, primary peritoneal cancer, prostate cancer, rectal cancer, recurrent cancer, renal cell (kidney) cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma, childhood vascular tumors, skin cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma of the skin, testicular cancer, oropharyngeal cancer, hypopharyngeal cancer, thymoma, thymic carcinoma, thyroid cancer, tracheobronchial tumors, transitional cell cancer of the renal pelvis and ureter, urethral cancer, uterine sarcoma, vaginal cancer, vascular tumors, vulvar cancer, and Wilms tumor.

In some embodiments, the cancer is Endometrial cancer, Breast cancer, Oesophageal squamous-cell cancer, Cervical squamous-cell carcinoma, Cervical adenocarcinoma, Colorectal adenocarcinoma, Bladder Urothelial Carcinoma, Glioblastoma, Ovarian cancer, Non-small-cell Lung cancer, Esophagogastric cancer, Nerve-sheath tumor, Head and neck squamous-cell carcinoma, Melanoma, Esophagogastric adenocarcinoma, Soft-tissue sarcoma, Prostate cancer, Fibrolamellar carcinoma, Hepatocellular carcinoma, Diffuse glioma, Colorectal cancer, Pancreatic cancer, Cholangiocarcinoma, B-cell lymphoma, Mesothelioma, Adrenocortical carcinoma, Renal non-clear-cell carcinoma, Renal clear-cell carcinoma, Germ-cell carcinoma, Thymic tumor, Pheochromocytoma, Miscellaneous neuroepithelial tumor, thyroid cancer, leukemia, or encapsulated glioma.

In some embodiments, the cancer is a breast cancer, a prostate cancer, or a brain cancer.

In some embodiments, the cancer is a breast cancer. In some embodiments, the cancer is a prostate cancer. In some embodiments, the cancer is a brain cancer.

In some embodiments, the breast cancer is metastatic breast cancer. In some embodiments, the breast cancer is ductal carcinoma in situ (DCIS). In some embodiments, the breast cancer is invasive ductal carcinoma. In some embodiments, the breast cancer is triple negative breast cancer. In some embodiments, the breast cancer is medullary carcinoma. In some embodiments, the breast cancer is tubular carcinoma. In some embodiments, the breast cancer is mucinous carcinoma. In some embodiments, the breast cancer is Paget disease of the breast or nipple. In some embodiments, the breast cancer is inflammatory breast cancer (IBC).

In some embodiments, the prostate cancer is an adenocarcinoma. In some embodiments, the prostate cancer is a small cell carcinoma. In some embodiments, the prostate cancer is a neuroendocrine tumor. In some embodiments, the prostate cancer is a transitional cell carcinoma. In some embodiments, the prostate cancer is a sarcoma.

In some embodiments, the brain cancer is an acoustic neuroma. In some embodiments, the brain cancer is an astrocytoma. In some embodiments, the brain cancer is a brain metastasis. In some embodiments, the brain cancer is choroid plexus carcinoma. In some embodiments, the brain cancer is

craniopharyngioma. In some embodiments, the brain cancer is an embryonal tumor. In some embodiments, the brain cancer is an ependymoma. In some embodiments, the brain cancer is a glioblastoma. In some embodiments, the brain cancer is a glioma. In some embodiments, the brain cancer is a medulloblastoma. In some embodiments, the brain cancer is a meningioma. In some
 5 embodiments, the brain cancer is an oligodendroglioma. In some embodiments, the brain cancer is a pediatric brain tumor. In some embodiments, the brain cancer is a pineoblastoma. In some embodiments, the brain cancer is a pituitary tumor.

 In some embodiments, the cancer is breast cancer (such as hormone receptor positive, HER2 negative breast cancer, HER2 positive breast cancer and triple negative breast cancer), endometrial
 10 cancer, uterine cancer, gastric cancer, leukemia, lymphoma, sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, head and neck cancer, brain cancer, or prostate cancer

 In some embodiments, the disease or disorder associated with PI3K α (*e.g.*, PI3K α mutation) includes, but is not limited to, CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome), PIK3CA-related overgrowth
 15 syndrome (PROS), breast cancer, brain cancer, prostate cancer, endometrial cancer, gastric cancer, leukemia, lymphoma, sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, or head and neck cancer.

 In some embodiments, the diseases or disorder associated with PI3K α (*e.g.*, PI3K α mutation) is CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome).
 20

 In some embodiments, the disease or disorder associated with PI3K α (*e.g.*, PI3K α mutation) is PIK3CA-related overgrowth syndrome (PROS).

 In some embodiments, the disease or disorder associated with PI3K α (*e.g.*, PI3K α mutation) is breast cancer, brain cancer, prostate cancer, endometrial cancer, gastric cancer, leukemia, lymphoma, sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, or head and neck
 25 cancer.

 In some embodiments, the disease or disorder associated with PI3K α (*e.g.*, PI3K α mutation) is breast cancer, brain cancer, prostate cancer, endometrial cancer, gastric cancer, colorectal cancer, lung cancer, ovarian cancer, skin cancer, or head and neck cancer.

30 In some embodiments, the disease or disorder associated with PI3K α (*e.g.*, PI3K α mutation) is leukemia, lymphoma, or sarcoma.

 In some embodiments, the cancer is endometrial cancer, head and neck cancer, or a sarcoma.

 In some embodiments, the cancer is endometrial cancer. In some embodiments the cancer is head and neck cancer. In some embodiments, the cancer is a sarcoma.

35 In some embodiments, the sarcoma is soft tissue sarcoma, osteosarcoma, chondrosarcoma, Ewing sarcoma, hemangioendothelioma, angiosarcoma, fibrosarcoma, myofibrosarcoma, chordoma, adamantinoma, liposarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumor,

rhabdomyosarcoma, synovial sarcoma, or malignant solitary fibrous tumor.

In some embodiments, the sarcoma is soft tissue sarcoma. In some embodiments the soft tissue sarcoma is liposarcoma, atypical lipomatous tumor, dermatofibrosarcoma protuberans, malignant solitary fibrous tumor, inflammatory myofibroblastic tumor, low-grade myofibroblastic sarcoma, fibrosarcoma, myxofibrosarcoma, low-grade fibromyxoid sarcoma, giant cell tumor of soft tissues, leiomyosarcoma, malignant glomus tumor, rhabdomyosarcoma, hemangioendothelioma, angiosarcoma of soft tissue, extraskeletal osteosarcoma, gastrointestinal stromal tumor, malignant gastrointestinal stromal tumor (GIST), malignant peripheral nerve sheath tumor, malignant Triton tumor, malignant granular cell tumor, malignant ossifying fibromyxoid tumor, stromal sarcoma, myoepithelial carcinoma, malignant phosphaturic mesenchymal tumor, synovial sarcoma, epithelioid sarcoma, alveolar soft part sarcoma, clear cell sarcoma of soft tissue, extraskeletal myxoid chondrosarcoma, extraskeletal Ewing sarcoma, desmoplastic small round cell tumor, extrarenal rhabdoid tumor, perivascular epithelioid cell tumor, intimal sarcoma, undifferentiated spindle cell sarcoma, undifferentiated pleomorphic sarcoma, undifferentiated round cell sarcoma, undifferentiated epithelioid sarcoma, or undifferentiated sarcoma, not otherwise specified.

In some embodiments, the present disclosure provides a method of treating or preventing a cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutical composition of the present disclosure.

In some embodiments, the present disclosure provides a method of treating a cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutical composition of the present disclosure.

In some embodiments, the present disclosure provides a method of treating or preventing a breast cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutical composition of the present disclosure.

In some embodiments, the present disclosure provides a method of treating a breast cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutical composition of the present disclosure.

In some embodiments, the present disclosure provides a method of treating or preventing a prostate cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutical composition of the present disclosure.

In some embodiments, the present disclosure provides a method of treating a prostate cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount

of a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutical composition of the present disclosure.

In some embodiments, the present disclosure provides a method of treating or preventing a brain cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutical composition of the present disclosure.

In some embodiments, the present disclosure provides a method of treating a brain cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutical composition of the present disclosure.

In some embodiments, the present disclosure provides a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof for use in modulating PI3K (*e.g.*, PI3K α) activity (*e.g.*, *in vitro* or *in vivo*).

In some embodiments, the present disclosure provides a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof for use in modulating mutated PI3K α activity (*e.g.*, *in vitro* or *in vivo*).

In some embodiments, the present disclosure provides a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof for use in treating or preventing a disease or disorder disclosed herein.

In some embodiments, the present disclosure provides a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof for use in treating a disease or disorder disclosed herein.

In some embodiments, the present disclosure provides a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof for use in treating or preventing a cancer in a subject in need thereof.

In some embodiments, the present disclosure provides a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof for use in treating a cancer in a subject in need thereof.

In some embodiments, the present disclosure provides a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof for use in treating or preventing a breast cancer in a subject in need thereof.

In some embodiments, the present disclosure provides a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof for use in treating a breast cancer in a subject in need thereof.

In some embodiments, the present disclosure provides a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof for use in treating or preventing a prostate cancer in a subject in need thereof.

In some embodiments, the present disclosure provides a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof for use in treating a prostate cancer in a subject in need thereof.

5 In some embodiments, the present disclosure provides a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof for use in treating or preventing a brain cancer in a subject in need thereof.

In some embodiments, the present disclosure provides a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof for use in treating a brain cancer in a subject in need thereof.

10 In some embodiments, the present disclosure provides use of a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof in the manufacture of a medicament for modulating PI3K (*e.g.*, PI3K α) activity (*e.g.*, *in vitro* or *in vivo*).

In some embodiments, the present disclosure provides use of a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof in the manufacture of a
15 medicament for modulating mutated PI3K α activity (*e.g.*, *in vitro* or *in vivo*).

In some embodiments, the present disclosure provides use of a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof in the manufacture of a medicament for treating or preventing a disease or disorder disclosed herein.

In some embodiments, the present disclosure provides use of a compound of Formula (I) or
20 (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof in the manufacture of a medicament for treating a disease or disorder disclosed herein.

In some embodiments, the present disclosure provides use of a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof in the manufacture of a medicament for treating or preventing a cancer in a subject in need thereof.

25 In some embodiments, the present disclosure provides use of a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof in the manufacture of a medicament for treating a cancer in a subject in need thereof.

In some embodiments, the present disclosure provides use of a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof in the manufacture of a
30 medicament for treating or preventing a breast cancer in a subject in need thereof.

In some embodiments, the present disclosure provides use of a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof in the manufacture of a medicament for treating a breast cancer in a subject in need thereof.

In some embodiments, the present disclosure provides use of a compound of Formula (I) or
35 (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof in the manufacture of a medicament for treating or preventing a prostate cancer in a subject in need thereof.

In some embodiments, the present disclosure provides use of a compound of Formula (I) or

(I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof in the manufacture of a medicament for treating a prostate cancer in a subject in need thereof.

In some embodiments, the present disclosure provides use of a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof in the manufacture of a medicament for treating or preventing a brain cancer in a subject in need thereof.

In some embodiments, the present disclosure provides use of a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof in the manufacture of a medicament for treating a brain cancer in a subject in need thereof.

The present disclosure provides compounds that function as modulators (*i.e.* inhibitors) of PI3K activity. The present disclosure therefore provides a method of modulating PI3K activity *in vitro* or *in vivo*, said method comprising contacting a cell with a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, as defined herein.

In some embodiments, PI3K α modulation is inhibition of PI3K α .

In some embodiments, the PI3K α inhibitor is a compound of Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof. In some embodiments, the PI3K α inhibitor is a mutated PI3K α inhibitor. In some embodiments, the PI3K α inhibitor is a PI3K α H1047R mutant inhibitor. In some embodiments, the PI3K α inhibitor is a PI3K α H1047L mutant inhibitor.

Effectiveness of compounds of the disclosure can be determined by industry-accepted assays/disease models according to standard practices of elucidating the same as described in the art and are found in the current general knowledge.

The present disclosure also provides a method of treating a disease or disorder in which PI3K α activity is implicated in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a compound Formula (I) or (I'), a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

The disclosure provides a method of modulating the activity of the PI3K α allosteric active site, wherein the modulation is induced through peripheral site targeting. In some embodiments, the peripheral site is targeted with an agent selected from a small molecule, a peptide, a peptidomimetic, a protein, a protein mimetic, a nucleic acid, an antibody, an antibody-drug conjugate, a nucleoprotein complex, an immunotherapy, or a combination thereof.

6. Treatment Kits

One aspect of the present disclosure relates to a kit for conveniently and effectively carrying out the methods or uses in accordance with the present disclosure. In general, the pharmaceutical pack or kit comprises one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the disclosure. Such kits are especially suited for the delivery of solid oral forms such as tablets or capsules. Such a kit preferably includes a number of unit dosages, and

may also include a card having the dosages oriented in the order of their intended use. If desired, a memory aid can be provided, for example in the form of numbers, letters, or other markings or with a calendar insert, designating the days in the treatment schedule in which the dosages can be administered. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceutical products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

The following representative examples contain important additional information, exemplification and guidance which can be adapted to the practice of this disclosure in its various embodiments and the equivalents thereof. These examples are intended to help illustrate the invention, and are not intended to, nor should they be construed to, limit its scope. Indeed, various modifications of the present disclosure, and many further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art upon review of this document, including the examples which follow and the references to the scientific and patent literature cited herein.

The contents of the cited references are incorporated herein by reference to help illustrate the state of the art.

In addition, for purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in "Organic Chemistry," Thomas Sorrell, University Science Books, Sausalito: 1999, and "Organic Chemistry," Morrison & Boyd (3d Ed), the entire contents of both of which are incorporated herein by reference.

7. Preparation

The compounds of any one of the formulae described above, may be prepared by the general and specific methods described below, using the common general knowledge of one skilled in the art of synthetic organic chemistry. Such common general knowledge can be found in standard reference books such as *Comprehensive Organic Chemistry*, Ed. Barton and Ollis, Elsevier; *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, Larock, John Wiley and Sons; and *Compendium of Organic Synthetic Methods*, Vol. I-XII (published by Wiley-Interscience). The starting materials used herein are commercially available or may be prepared by routine methods known in the art.

In the preparation of the compounds of any one of the formulae described above, it is noted that some of the preparation methods described herein may require protection of remote functionality (e.g., primary amine, secondary amine, carboxyl in any one of the formulae described above precursors). The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. The need for such protection is readily

determined by one skilled in the art. The use of such protection/deprotection methods is also within the skill in the art. For a general description of protecting groups and their use, see Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, 1991.

For example, certain compounds contain primary amines or carboxylic acid functionalities which may interfere with reactions at other sites of the molecule if left unprotected. Accordingly, such functionalities may be protected by an appropriate protecting group which may be removed in a subsequent step. Suitable protecting groups for amine and carboxylic acid protection include those protecting groups commonly used in peptide synthesis (such as N-t-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), and 9-fluorenylmethyloxycarbonyl (Fmoc) for amines, and lower alkyl or benzyl esters for carboxylic acids) which are generally not chemically reactive under the reaction conditions described and can typically be removed without chemically altering other functionality in the any one of the formulae described above compounds.

The Schemes/Examples described below are intended to provide a general description of the methodology employed in the preparation of the compounds of the present disclosure. Some of the compounds of the present present disclosure may contain single or multiple chiral centers with the stereochemical designation (*R*) or (*S*). It will be apparent to one skilled in the art that all of the synthetic transformations can be conducted in a similar manner whether the materials are enantioenriched or racemic. Moreover, the resolution to the desired optically active material may take place at any desired point in the sequence using well known methods such as described herein and in the chemistry literature.

EXAMPLES

Abbreviations

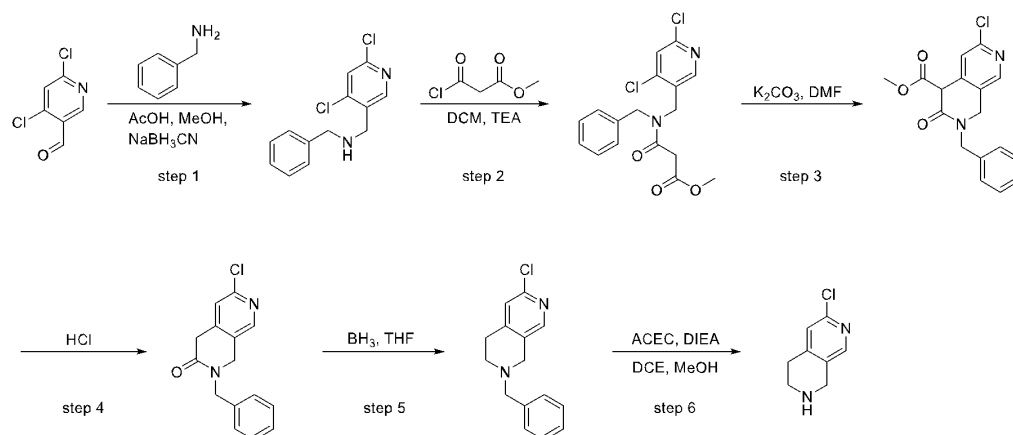
rt	Room temperature
N ₂	Nitrogen
DCM	Dichloromethane
DCE	1,2-Dichloroethane
DMF	N, N-dimethylformamide
DMSO	Dimethyl sulfoxide
Et ₂ O	Diethyl ether
EtOH	Ethyl alcohol
DME	1,2-Dimethoxyethane
EtOAc	Ethyl acetate
THF	Tetrahydrofuran
CHCl ₃	Chloroform

TEA	Triethylamine
H ₂ O ₂	Hydrogen peroxide
DIPEA	N, N-Diisopropylethylamine
HATU	2-(7-Azabenzotriazol-1-yl)-N, N, N', N'-tetramethyluronium hexafluorophosphate
BOP	1H-Benzotriazol-1-yloxytris(dimethylamino)phosphonium Hexafluorophosphate
PyBOP	benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate
PPh ₃	Triphenylphosphine
DIAD	Diisopropyl azodicarboxylate
Pd(PPh ₃) ₂ Cl ₂	Bis(triphenylphosphine)palladium(II) chloride
Pd(PPh ₃) ₄	Tetrakis(triphenylphosphine)palladium
X-phos	2-(Dicyclohexylphosphino)-2',4',6'-tri-i-propyl-1,1'-biphenyl
Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)dipalladium
Pd(dppf)Cl ₂	[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
DIBAL-H	Diisobutylaluminium hydride
(NH ₄) ₂ S ₂ O ₈	Ammonium persulfate
KF	Potassium fluoride
NaBH ₄	Sodium borohydride
LiOH·H ₂ O	Lithium hydroxide monohydrate
LiHMDS	Lithium bis(trimethylsilyl)amide
Ti(OEt) ₄	Titanium ethoxide
TiCl ₄	Titanium tetrachloride
HCl	Hydrochloric acid
AcOH	Acetic acid
POCl ₃	Phosphorus oxychloride
CeCl ₃	Cerium (III) chloride
Na ₂ SO ₄	Sodium sulfate
NaHCO ₃	Sodium bicarbonate
Na ₂ S ₂ O ₃	Sodium thiosulfate
Cs ₂ CO ₃	Cesium carbonate
KOAc	Potassium acetate
Na ₂ CO ₃	Sodium carbonate
NH ₄ Cl	Ammonium chloride
LC-MS	Liquid chromatography mass spectrometry
Prep-HPLC	Preparative-scale high performance liquid chromatography
K ₂ CO ₃	Potassium carbonate

	m-CPBA	3-Chloroperoxybenzoic acid
	MeOH	Methanol
	ACN	Acetonitrile
	CDI	1,1'-Carbonyldiimidazole
5	DBU	1,8-Diazabicyclo[5.4.0]undecane-7-ene
	MTBE	tert-Butyl methyl ether
	NaCl	Sodium chloride
	BINAP	1,1'-Binaphthyl-2,2'-diphenyl phosphine
	CH ₃ ONa	Sodium methoxide
10	AlCl ₃	Aluminum chloride
	TFAA	Trifluoroacetic anhydride
	NaNO ₂	Sodium nitrite
	KI	Potassium iodide
	NaH	Sodium hydride
15	NaClO	Sodium hypochlorite
	CuI	Cuprous iodide
	BBr ₃	Boron tribromide
	IBX	2-Iodoxybenzoic acid
	POBr ₃	Phosphorus oxybromide
20	Xant-phos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
	t-BuOK	Potassium tert-butoxide
	TMSCl	Chlorotrimethylsilane
	(Boc) ₂ O	Di-tert-butyl decarbonate
	CuBr ₂	Cupric bromide
25	Fe	Iron
	CAN	Ceric ammonium nitrate
	PyCLOP	Chlorotripyrrolidinophosphonium hexafluorophosphate

Section 1. Synthetic Processes to Prepare Intermediates

Intermediate 1



Step 1:

- 5 To a stirred solution of 4,6-dichloronicotinaldehyde (3 g, 17.1 mmol) in methanol (20 mL) was added acetic acid (511 mg, 8.5 mmol) and phenylmethanamine (2 g, 18.7 mmol) at 0 °C. The mixture was stirred at 25 °C under N₂ for 1 hour. Then sodium cyanoborohydride (1.6 g, 25.5 mmol) was added and the mixture was stirred at 25 °C for 1 hour. The mixture was diluted with water (50 mL) and extracted with DCM (100 mL). The organic layer was washed with brine (100 mL), dried over
- 10 Na₂SO₄, filtered and concentrated *in vacuo* to give crude product, which was purified by silica gel chromatography to give N-benzyl-1-(4,6-dichloropyridin-3-yl)methanamine (3.8 g, crude) as a yellow solid, which was used to the next step without further purification. LC-MS: m/z 267.0 [M+H]⁺.

Step 2:

- To a stirred solution of N-benzyl-1-(4,6-dichloropyridin-3-yl)methanamine (5 g, 18.7 mmol) and triethylamine (9.4 g, 93.5 mmol) in DCM (80 mL) was added methyl 3-chloro-3-oxopropanoate (5.1 g, 36.4 mmol) at 0 °C. The mixture was stirred at 25 °C under N₂ atmosphere for 1 hour. The mixture was diluted with water (100 mL) and extracted with DCM (100 mL). The organic layer was washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give crude product, which was purified by silica gel chromatography to give methyl 3-(benzyl((4,6-dichloropyridin-3-yl)methyl)amino)-3-oxopropanoate (5 g, 72% yield) as a yellow solid. LC-MS: m/z 367.0 [M+H]⁺.

Step 3:

- To a stirred solution of methyl 3-(benzyl((4,6-dichloropyridin-3-yl)methyl)amino)-3-oxopropanoate (1.5 g, 4.1 mmol) in DMF (20 mL) was added potassium carbonate (1.7 g, 12.3 mmol) at 20 °C. The resulting mixture was stirred at 120 °C under N₂ atmosphere for 5 hours. The mixture was diluted with water (100 mL), and extracted with DCM (100 mL). The organic layer was washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give crude product, which was

purified by silica gel chromatography to give methyl 2-benzyl-6-chloro-3-oxo-1,2,3,4-tetrahydro-2,7-naphthyridine-4-carboxylate (1.2 g, 88% yield) as a yellow solid. LC-MS: m/z 331.1 $[M+H]^+$.

Step 4:

A solution of methyl 2-benzyl-6-chloro-3-oxo-1,2,3,4-tetrahydro-2,7-naphthyridine-4-carboxylate (1 g, 3 mmol) in concentrated HCl (15 mL) was stirred at 100 °C under N₂ for 1 hour. The pH of the mixture was adjusted to 8 with sat. aqueous NaHCO₃. The mixture was diluted with water (50 mL) and extracted with DCM (100 mL). The organic layer was washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give 2-benzyl-6-chloro-1,4-dihydro-2,7-naphthyridin-3(2H)-one (600 mg, 73% yield) as a yellow oil. LC-MS: m/z 273.1 $[M+H]^+$.

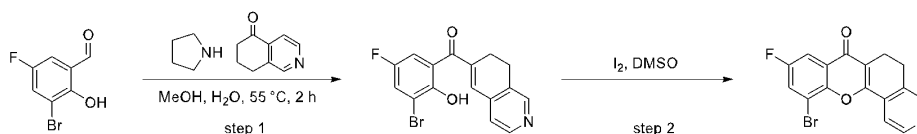
Step 5:

A solution of 2-benzyl-6-chloro-1,4-dihydro-2,7-naphthyridin-3(2H)-one (700 mg, 2.5 mmol) in borane (1 M in THF, 25 mmol, 25 mL) was stirred at 70 °C under N₂ for 1 hour. The mixture was quenched with MeOH (10 mL), then 2 N HCl (10 mL) was added and stirring was continued for 1 hour. The mixture was diluted with water (100 mL) and extracted with DCM (100 mL). The organic layer was washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give 2-benzyl-6-chloro-1,2,3,4-tetrahydro-2,7-naphthyridine (500 mg, 75% yield) as a yellow solid. LC-MS: m/z 259.1 $[M+H]^+$.

Step 6:

To a stirred solution of 2-benzyl-6-chloro-1,2,3,4-tetrahydro-2,7-naphthyridine (500 mg, 1.9 mmol) and DIPEA (750 mg, 5.8 mmol) in DCE (10 mL) was added 1-chloroethyl carbonochloridate (1.1 g, 7.7 mmol) at 0 °C. The mixture was stirred at 70 °C under N₂ atmosphere for 2 hours. The mixture was concentrated *in vacuo*, and then methanol (10 mL) was added. The mixture was stirred at 70 °C for 2 hours. Then the mixture was concentrated *in vacuo* to give 6-chloro-1,2,3,4-tetrahydro-2,7-naphthyridine (500 mg, crude) as a yellow oil, which was used to the next step without further purification.

Intermediate 2



Step 1:

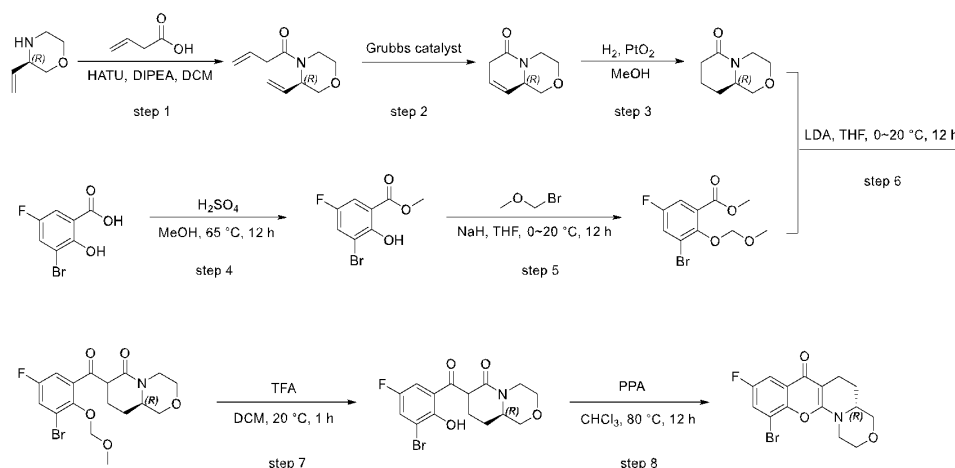
To a solution of 7,8-dihydro-6H-isoquinolin-5-one (1 g, 6.9 mmol) in methanol (20 mL) was added pyrrolidine (194.8 mg, 2.7 mmol), 3-bromo-5-fluoro-2-hydroxybenzaldehyde (1.5 g, 6.9 mmol) and H₂O (10 mL). The mixture was stirred at 60 °C for 12 hours. The resulting mixture was quenched by addition of saturated NH₄Cl aqueous solution (5 mL) and extracted with EtOAc (20 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and

concentrated under reduced pressure. The residue was purified by flash chromatography to give (3-bromo-5-fluoro-2-hydroxy-phenyl)-(7,8-dihydroisoquinolin-6-yl)methanone (700 mg, 29% yield) as a yellow solid. LC-MS: m/z 348.0 $[M+H]^+$.

Step 2:

- 5 To a solution of (3-bromo-5-fluoro-2-hydroxy-phenyl)-(7,8-dihydroisoquinolin-6-yl)methanone (450 mg, 1.3 mmol) in DMSO (2 mL) was added I_2 (500 mg, 2 mmol). The mixture was stirred at 100 °C for 8 hours. The resulting mixture was quenched by addition of saturated Na_2SO_3 aqueous solution (20 mL) and extracted with EtOAc (50 mL $\times$ 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure.
- 10 The residue was purified by flash chromatography to give 11-bromo-9-fluoro-5,6-dihydrochromeno[2,3-f]isoquinolin-7-one (170 mg, 38% yield) as a white solid. LC-MS: m/z 346.0 $[M+H]^+$.

Intermediate 3



15

Step 1:

- To a solution of (3R)-3-vinylmorpholine hydrochloride (500 mg, 3.3 mmol) in DCM (10 mL) was added HATU (1.3 g, 3.3 mmol), DIPEA (1.7 g, 13.4 mmol) and but-3-enoic acid (431.5 mg, 5 mmol). The mixture was stirred at 20 °C for 12 hours. The resulting mixture was quenched by addition of saturated NH_4Cl aqueous solution (5 mL) and extracted with EtOAc (30 mL $\times$ 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to give 1-[(3R)-3-vinylmorpholin-4-yl]but-3-en-1-one (480 mg, 79% yield) as colorless oil. LC-MS: m/z 182.1 $[M+H]^+$.
- 20

Step 2:

- 25 To a solution of 1-[(3R)-3-vinylmorpholin-4-yl]but-3-en-1-one (480 mg, 2.7 mmol) in DCM (10 mL) was added 1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium (112.4 mg, 0.1

mmol). The mixture was degassed and backfilled with N₂ for 3 times and stirred at 20 °C for 36 hours. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography to give (9aR)-3,4,7,9a-tetrahydro-1H-pyrido[2,1-c][1,4]oxazin-6-one (350 mg, 86% yield) as yellow oil. LC-MS: m/z 154.0 [M+H]⁺.

5 **Step 3:**

To a round flask were added (9aR)-3,4,7,9a-tetrahydro-1H-pyrido[2,1-c][1,4]oxazin-6-one (350 mg, 2.3 mmol), PtO₂ (20 mg, 0.1 mmol) and methanol (2 mL). The mixture was backfilled with H₂ for three times and stirred at 20 °C for 6 hours. The resulting mixture was filtered and concentrated under reduced pressure to give (9aR)-3,4,7,8,9,9a-hexahydro-1H-pyrido[2,1-c][1,4]oxazin-6-one (350 mg, 98% yield) as black oil. LC-MS: m/z 156.0 [M+H]⁺.

10 **Step 4:**

To a solution of 3-bromo-5-fluoro-2-hydroxy-benzoic acid (1.6 g, 6.8 mmol) in MeOH (10 mL) was added H₂SO₄ (668 mg, 6.8 mmol). The mixture was stirred at 60 °C for 12 hours. The resulting mixture was added to water and filtered. The filter cake was washed with water, dried under reduced pressure to give methyl 3-bromo-5-fluoro-2-hydroxy-benzoate (1.6 g, 94% yield) as a brown solid.

15 **Step 5:**

To a solution of methyl 3-bromo-5-fluoro-2-hydroxy-benzoate (1.4 g, 5.6 mmol) in THF (10 mL) was added NaH (60% dispersion in oil, 449.7 mg, 11.2 mmol, 60% purity). The mixture was stirred at 0 °C for 1 hour. Then bromo(methoxy)methane (1.4 g, 11.2 mmol) was added to the mixture and stirred at 20 °C for 12 hours. The resulting mixture was quenched by addition of saturated NH₄Cl aqueous solution (5 mL) and extracted with EtOAc (30 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give methyl 3-bromo-5-fluoro-2-(methoxymethoxy)benzoate (2.1 g, crude) as yellow oil.

20 **Step 6:**

25 To a round flask was added (9aR)-3,4,7,8,9,9a-hexahydro-1H-pyrido[2,1-c][1,4]oxazin-6-one (300 mg, 1.9 mmol) and THF (20 mL). The solution was degassed and backfilled with N₂ for 3 times. Then (diisopropylamino)lithium (2.0 M, 2 mL) was added to the solution at 0 °C and stirred for 0.5 hour. Then methyl 3-bromo-5-fluoro-2-(methoxymethoxy)benzoate (700 mg, 2.4 mmol) was added to the mixture at 0 °C. The mixture was allowed to warm to 20 °C and stirred at 20 °C for 12 hours. The resulting mixture was quenched by addition of saturated NH₄Cl aqueous solution (20 mL) and extracted with EtOAc (50 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to give (9aR)-7-[3-bromo-5-fluoro-2-(methoxymethoxy)benzoyl]-3,4,7,8,9,9a-hexahydro-1H-pyrido[2,1-c][1,4]oxazin-6-one (400 mg, 50% yield) as a yellow solid.

30 LC-MS: m/z 415.8 [M+H]⁺.

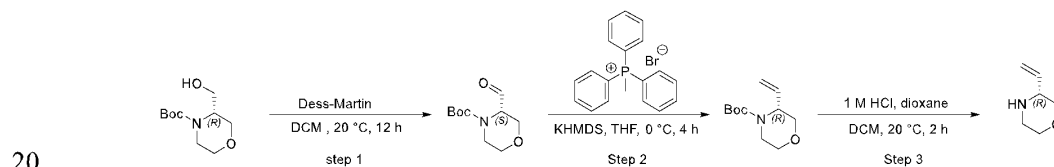
35 **Step 7:**

To a solution of (9aR)-7-[3-bromo-5-fluoro-2-(methoxymethoxy)benzoyl]-3,4,7,8,9,9a-hexahydro-1H-pyrido[2,1-c][1,4]oxazin-6-one (400 mg, 1 mmol) in DCM (5 mL) was added TFA (1.5 g, 13.1 mmol). The mixture was stirred at 20 °C for 1 hour. The resulting mixture was quenched by addition of saturated NaHCO₃ aqueous solution (5 mL) and extracted with EtOAc (30 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give (9aR)-7-(3-bromo-5-fluoro-2-hydroxy-benzoyl)-3,4,7,8,9,9a-hexahydro-1H-pyrido[2,1-c][1,4]oxazin-6-one (350 mg, 97% yield) as brown oil. LC-MS: m/z 372.0 [M+H]⁺.

Step 8:

To a solution of (9aR)-7-(3-bromo-5-fluoro-2-hydroxy-benzoyl)-3,4,7,8,9,9a-hexahydro-1H-pyrido[2,1-c][1,4]oxazin-6-one (300 mg, 0.8 mmol) in CHCl₃ (20 mL) was added PPA (8.4 g, 5 mL). The mixture was stirred at 80 °C for 12 hours. The resulting mixture was added to water and extracted with EtOAc (20 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to give (7R)-16-bromo-14-fluoro-5,18-dioxo-2-azatetracyclo[8.8.0.0.0^{2,7}.0^{12,17}]octadeca-1(10),12(17),13,15-tetraen-11-one (120 mg, 42% yield) as a yellow solid. LC-MS: m/z 354.0 [M+H]⁺.

Intermediate 4



Step 1:

To a solution of tert-butyl (3R)-3-(hydroxymethyl)morpholine-4-carboxylate (5 g, 23 mmol) in DCM (20 mL) was added (1,1-diacetoxy-3-oxo-1,2-benziodoxol-1-yl) acetate (11.7 g, 27.6 mmol). The mixture was stirred at 20 °C for 12 hours. The resulting mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to give tert-butyl (3S)-3-formylmorpholine-4-carboxylate (4.5 g, 90% yield) as green oil.

Step 2:

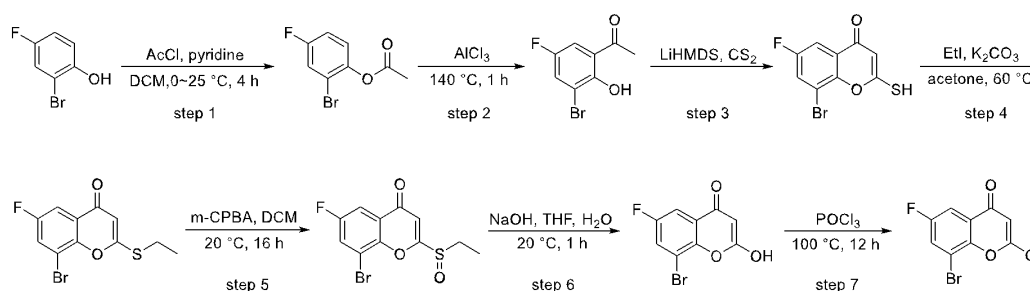
To a solution of methyl(triphenyl)phosphonium;bromide (8.2 g, 23 mmol) in THF (50 mL) was added potassium;bis(trimethylsilyl)azanide (1 M, 23 mL) at 0 °C dropwise. Then tert-butyl (3S)-3-formylmorpholine-4-carboxylate (4.5 g, 20.9 mmol) was added to the mixture at 0 °C. The mixture was allowed to warm to 20 °C and stirred for 12 hours. The resulting mixture was quenched by addition of saturated NH₄Cl aqueous solution (50 mL) and extracted with EtOAc (200 mL × 3). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and

concentrated under reduced pressure. The residue was purified by flash chromatography to give tert-butyl (3R)-3-vinylmorpholine-4-carboxylate (900 mg, 20% yield) as yellow oil.

Step 3:

To a solution of tert-butyl (3R)-3-vinylmorpholine-4-carboxylate (900 mg, 4.2 mmol) in DCM (5 mL) was added a solution of 4 M HCl in dioxane (1 mL). The mixture was stirred at 20 °C for 12 hours. The resulting mixture was concentrated under reduced pressure to give (3R)-3-vinylmorpholine hydrochloride (450 mg, 71% yield) as a yellow solid which was used to the next step without further purification.

Intermediate 5



Step 1:

To a stirred solution of 2-bromo-4-fluorophenol (10 g, 52.4 mmol) and pyridine (5 g, 62.8 mmol) in DCM (100 mL) was added acetyl chloride (4.9 g, 62.8 mmol) dropwise at 0 °C. The mixture was stirred at 25 °C for 4 hours and quenched with water (300 mL), acidized with 1 N HCl to pH~5, extracted with DCM (250 mL × 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo to give 2-bromo-4-fluorophenyl acetate (12.2 g, crude) as colorless oil which was used to the next step directly without further purification.

Step 2:

A mixture of 2-bromo-4-fluorophenyl acetate (12.2 g, 52.4 mmol) and AlCl₃ (20.9 g, 157 mmol) was degassed and purged with N₂ three times and stirred at 140 °C for 1 hour. The reaction was cooled, diluted with DCM (200 mL) and poured into ice water (400 mL). The mixture was filtered, and the aqueous phase was extracted with DCM (300 mL × 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*, the residue was purified by flash column chromatography on silica gel to give 1-(3-bromo-5-fluoro-2-hydroxyphenyl)ethanone (11 g, 90% yield) as a white solid.

Step 3:

To a stirred solution of 1-(3-bromo-5-fluoro-2-hydroxyphenyl)ethanone (11 g, 47.2 mmol) in THF (150 mL) was added LiHMDS (7.9 g, 47.2 mmol) dropwise at -70 °C. The mixture was allowed to warm to -5~0 °C and stirred for 0.5 hour. The reaction was cooled to -20 °C and methanedithione (10.8 g, 141.6 mmol) in THF (50 mL) was added dropwise at -20 °C. The mixture was then stirred at

25 °C for 16 hours and quenched with water (500 mL). The mixture was acidized with 1 N HCl to pH~5, extracted with EtOAc (400 mL × 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 8-bromo-6-fluoro-2-mercapto-4H-chromen-4-one (12 g, crude) as a yellow solid which was used to the next step directly without further purification. LC-MS: m/z 274.9 [M+H]⁺.

Step 4:

To a mixture of 8-bromo-6-fluoro-2-sulfanyl-chromen-4-one (12 g, 43.6 mmol) and K₂CO₃ (7.2 g, 52.4 mmol) in acetone (150 mL) was added iodoethane (27.2 g, 174.5 mmol). The mixture was stirred at 60 °C for 4 hours. The mixture was poured into water (600 mL) and extracted with DCM (400 mL × 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*, the residue was purified by flash column chromatography on silica gel to give 8-bromo-2-(ethylthio)-6-fluoro-4H-chromen-4-one (12 g, 90.8% yield) as a yellow solid. LC-MS: m/z 302.9 [M+H]⁺.

Step 5:

To a stirred mixture of 8-bromo-2-ethylsulfanyl-6-fluoro-chromen-4-one (2 g, 6.6 mmol) in DCM (10 mL) was added m-CPBA (1.1 g, 6.6 mmol) under N₂. The mixture was stirred at 20 °C for 16 hours. The mixture was dissolved in water (150 mL) and extracted with EtOAc (150 mL × 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*, the residue was purified by flash column chromatography on silica gel to give 8-bromo-2-ethylsulfinyl-6-fluoro-chromen-4-one (2 g, 95% yield) as a red solid.

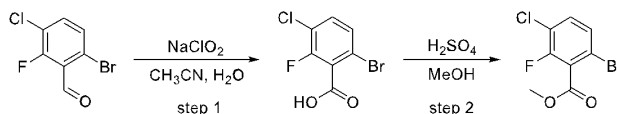
Step 6:

To a solution of 8-bromo-2-ethylsulfinyl-6-fluoro-chromen-4-one (2 g, 6.3 mmol) in THF (5 mL) were added NaOH (800 mg, 20 mmol) and water (1 mL). The mixture was stirred at 20 °C for 2 hours. The reaction was quenched by addition of saturated NH₄Cl aqueous solution (5 mL) and extracted with EtOAc (30 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give 8-bromo-6-fluoro-2-hydroxy-chromen-4-one (1.2 g, 73.9% yield) as a yellow solid. LC-MS: m/z 258.9 [M+H]⁺.

Step 7:

A solution of 8-bromo-6-fluoro-2-hydroxy-chromen-4-one (1.6 g, 6.3 mmol) in phosphoryl trichloride (16.5 g, 107.3 mmol) was stirred at 100 °C for 12 hours. The resulting mixture was added to water (20 mL) slowly and extracted with EtOAc (50 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to give 8-bromo-2-chloro-6-fluoro-chromen-4-one (230 mg, 13.2% yield) as a yellow solid. LC-MS: m/z 276.9 [M+H]⁺.

Intermediate 6



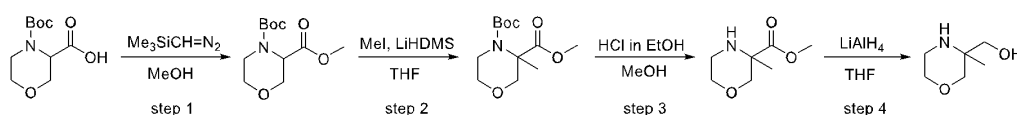
Step 1:

To a stirred solution of 6-bromo-3-chloro-2-fluoro-benzaldehyde (800 mg, 3.4 mmol) in CH₃CN (10 mL) was added a solution of NaClO₂ (457 mg, 5.1 mmol) in H₂O (5 mL) at 0 °C. The mixture was stirred at rt for 2 hours. The mixture was poured into saturated Na₂SO₃ (aq. 20 mL) and stirred at rt for 30 minutes. The mixture was diluted with water (50 mL), adjusted pH to 2 with 1 N HCl, extracted with DCM (300 mL × 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*, the residue was purified by flash column chromatography on silica gel (eluting with DCM/MeOH from 0 to 20%) to afford 6-bromo-3-chloro-2-fluoro-benzoic acid (600 mg, 70% yield) as yellow oil. LC-MS: m/z 253.1 [M+H]⁺.

Step 2:

To a stirred solution of 6-bromo-3-chloro-2-fluoro-benzoic acid (200 mg, 789.1 μmol) in MeOH (5 mL) was added H_2SO_4 (774 mg, 7.9 mmol) at rt. The mixture was stirred at 75 $^\circ\text{C}$ for 15 hours. The mixture was cooled to rt, diluted with water (50 mL), basified with saturated Na_2CO_3 aqueous to pH~9, extracted with DCM (200 mL $\times$ 2). The combined organic layer was dried over Na_2SO_4 , filtered and concentrated in vacuo, the residue was purified by flash column chromatography on silica gel (eluting with DCM/MeOH from 0 to 10%) to afford methyl 6-bromo-3-chloro-2-fluoro-benzoate (200 mg, 94% yield) as a yellow solid. LC-MS: m/z 267.1 $[\text{M}+\text{H}]^+$.

Intermediate 7



Step 1:

25 To a stirred solution of 4-tert-butoxycarbonylmorpholine-3-carboxylic acid (1 g, 4.3 mmol) in DCM (10 mL) and MeOH (10 mL) was added diazomethyl(trimethyl)silane (494 mg, 4.3 mmol) in batches. The mixture was stirred at rt for 1 hour, and the mixture was directly concentrated to give 4-(tert-butyl) 3-methyl morpholine-3,4-dicarboxylate (1 g, crude).

Step 2:

To a stirred solution of 4-(tert-butyl) 3-methyl morpholine-3,4-dicarboxylate (1 g, 4.1 mmol) in THF (10 mL) was added a solution of lithium;bis(trimethylsilyl)azanide (682 mg, 4.1 mmol) in THF dropwise at 0 °C under N₂. Then iodomethane (579 mg, 4.1 mmol) was added to the above mixture at 0 °C. The mixture was stirred at rt for 3 hours and methanol was added dropwise to quench the reaction. The mixture was poured into water, extracted with ethyl acetate, the combined organic phase

was dried over anhydrous Na_2SO_4 , filtered, and the filtrate was concentrated and purified by column chromatography to give 4-(tert-butyl) 3-methyl 3-methylmorpholine-3,4-dicarboxylate (600 mg, 56% yield).

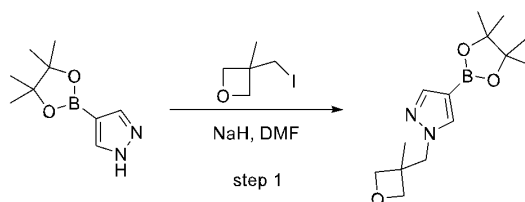
Step 3:

- 5 To a stirred solution of 4-(tert-butyl) 3-methyl 3-methylmorpholine-3,4-dicarboxylate (600 mg, 2.3 mmol) in DCM (10 mL) was added a solution of HCl in EtOH (4 M, 0.5 mL) under N_2 . The mixture was stirred at rt for 1 hour, and the mixture was concentrated to give methyl 3-methylmorpholine-3-carboxylate (400 mg, crude). LC-MS: m/z 160.1 $[\text{M}+\text{H}]^+$.

Step 4:

- 10 To a stirred solution of methyl 3-methylmorpholine-3-carboxylate (400 mg, 2.5 mmol) in THF (10 mL) was added lithium;alumanuide (143 mg, 3.8 mmol) in batches at 0 °C and the mixture was stirred at rt for 30 minutes. The reaction was quenched with EtOAc, stirred at rt for 0.5 hour, dried over anhydrous Na_2SO_4 , filtered, and concentrated to give crude product which was purified by column chromatography to give (3-methylmorpholin-3-yl)methanol (300 mg, 91% yield). LC-MS: m/z 132.1
- 15 $[\text{M}+\text{H}]^+$.

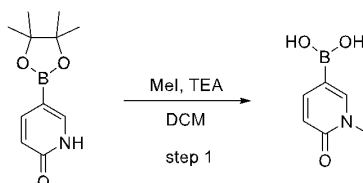
Intermediate 8



Step 1:

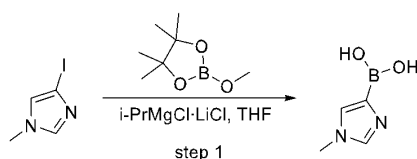
- 20 To a stirred solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (200 mg, 1 mmol) in DMF (5 mL) was added 3-(iodomethyl)-3-methyl-oxetane (219 mg, 1 mmol), NaH (49 mg, 1.2 mmol, 60% dispersion in oil) at 20 °C. The mixture was stirred at 80 °C for 1 hour. The mixture was diluted with water (50 mL) and extracted with DCM (50 mL $\times$ 2), the organic layer was washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue
- 25 was purified by silica gel chromatography to give 1-((3-methyloxetan-3-yl)methyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (100 mg, 35% yield) as a yellow solid.

Intermediate 9

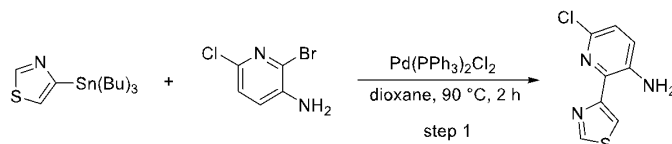


Step 1:

To a stirred solution of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyridin-2-one (100 mg, 452.4 μ mol) and TEA (230 mg, 2.3 mmol) in DCM (5 mL) was added iodomethane (128 mg, 904.7 μ mol). The mixture was stirred at 50 °C for 25 hours under N₂ before it was cooled to rt. The mixture was concentrated. The residue was purified by prep-HPLC to give (1-methyl-6-oxo-3-pyridyl)boronic acid (30 mg, 43.4% yield) as a white solid. LC-MS: m/z 154.1 [M+H]⁺.

Intermediate 10**Step 1:**

To a solution of 4-iodo-1-methyl-imidazole (200 mg, 961.5 μ mol) in THF (6 mL) was added lithium;chloro(isopropyl)magnesium;chloride (209.4 mg, 1.4 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 hour. Then 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (227.8 mg, 1.4 mmol) was added and the mixture was stirred at 0 °C for 1 hour. The mixture was quenched with aq.NH₄Cl (1 mL) and diluted with water (25 mL). The water phase was purified by reverse phase chromatography (A: 0.05% FA in water, B: CH₃CN, Gradient: 0 ~ 10% of B) to afford (1-methylimidazol-4-yl)boronic acid (40 mg, 33% yield) as a light-yellow solid.

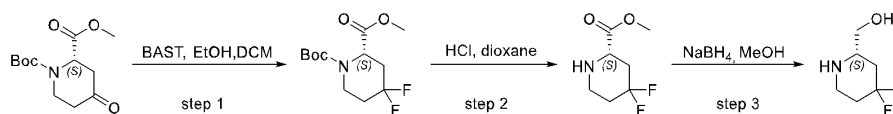
Intermediate 11

20

Step 1:

To a sealed tube was added 2-bromo-6-chloro-pyridin-3-amine (100 mg, 482 μ mol), tributyl(thiazol-4-yl)stannane (180.4 mg, 0.5 mmol), dichloropalladium;triphenylphosphane (67.7 mg, 0.1 mmol) and dioxane (2 mL). The mixture was backfilled with N₂ and stirred at 100 °C for 2 hours. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography to afford 6-chloro-2-thiazol-4-yl-pyridin-3-amine (60 mg, 58.8% yield) as yellow oil. LC-MS: m/z 211.9 [M+H]⁺.

25

Intermediate 12**Step 1:**

- 5 To a stirred solution of 1-(tert-butyl) 2-methyl (S)-4-oxopiperidine-1,2-dicarboxylate (2 g, 7.8 mmol) in DCM (20 mL) was added 2-methoxy-N-(2-methoxyethyl)-N-(trifluoro-sulfonyl)ethanamine (3.4 g, 15.6 mmol) at 0 °C, then ethanol (18 mg, 389 μmol) in DCM (5 mL) was added dropwise, the mixture was stirred at 20 °C under N₂ for 12 hours. The mixture was diluted with water (50 mL) and extracted with DCM (100 mL × 2). The combined organic layer was washed with brine (100 mL), dried over
- 10 Na₂SO₄, filtered and concentrated under reduced pressure. The mixture was purified by silica gel chromatography to give 1-(tert-butyl) 2-methyl (S)-4,4-difluoropiperidine-1,2-dicarboxylate (1 g, 46% yield) as yellow oil. LC-MS: m/z 280.3 [M+H]⁺.

Step 2:

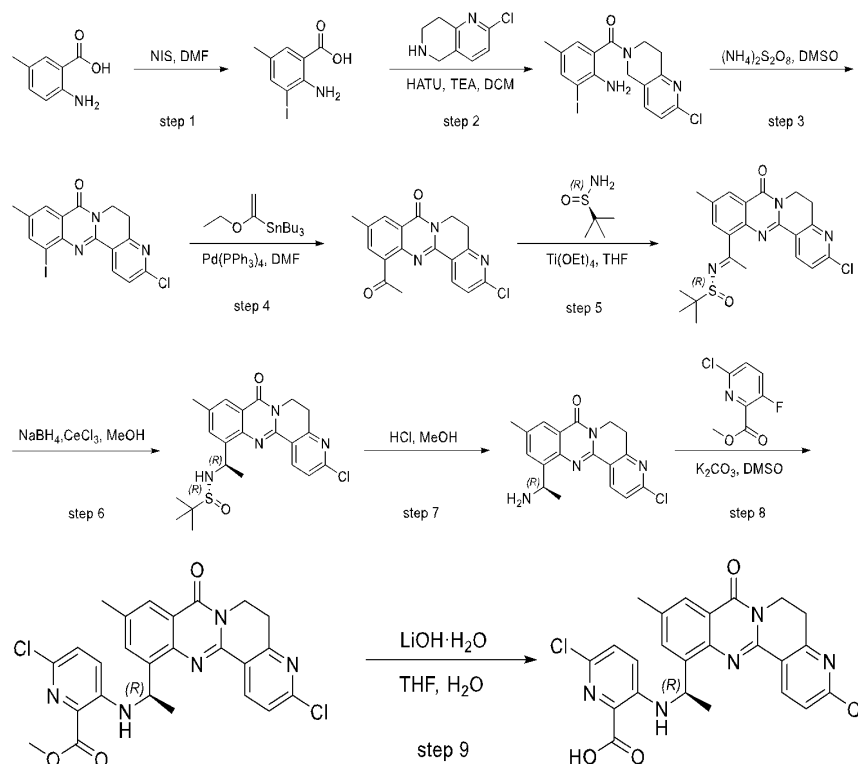
- To a stirred solution of 1-(tert-butyl) 2-methyl (S)-4,4-difluoropiperidine-1,2-dicarboxylate (1.5 g, 5.4
- 15 mmol) in dioxane (10 mL) was added HCl (2 mL, 4.0 M in 1,4-dioxane) at 0 °C. The mixture was stirred at 0 °C for 30 minutes. The pH of the mixture was adjusted to 8 with saturated aqueous NaHCO₃, then diluted with water (50 mL) and extracted with DCM (100 mL × 2), the organic layer was washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give methyl (S)-4,4-difluoropiperidine-2-carboxylate (900 mg, 94% yield) as yellow oil.
- 20 LC-MS: m/z 180.1 [M+H]⁺.

Step 3:

- To a stirred solution of methyl (S)-4,4-difluoropiperidine-2-carboxylate (900 mg, 5.1 mmol) in methanol (10 mL) was added NaBH₄ (380 mg, 10.1 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 minutes. Then 2 N HCl (5 mL) was added and stirred at 20 °C for 30 minutes. The pH of the
- 25 mixture was adjusted to 7 with saturated aqueous NaHCO₃, then concentrated *in vacuo*, the residue was diluted with MeOH and filtered, the filtrate was concentrated under reduced pressure to give (S)-(4,4-difluoropiperidin-2-yl)methanol (700 mg, crude) as yellow oil which was used in the next step without further purification.

Section 2. Synthetic Processes to Prepare Claimed Compounds

Example 1



5 Step 1:

To a stirred solution of 2-amino-5-methylbenzoic acid (10 g, 66.1 mmol) in DMF (100 mL) was added 1-iodopyrrolidine-2,5-dione (16.3 g, 72.7 mmol) at 20 °C, and the mixture was stirred at 70 °C under N₂ atmosphere for 3 hours. The mixture was diluted with water (50 mL) and extracted with DCM (100 mL × 2). The organic layer was washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-5 % MeOH in DCM) to give 2-amino-3-iodo-5-methylbenzoic acid (15 g, 81% yield) as a yellow solid. LC-MS: m/z 278.1 [M+H]⁺.

Step 2:

To a stirred solution of 2-amino-3-iodo-5-methylbenzoic acid (3 g, 10.8 mmol) in DCM was added 2-chloro-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (2.2 g, 10.8 mmol), HATU (4.3 g, 11.3 mmol) and TEA (5.4 g, 54.1 mmol) at 20 °C. The mixture was stirred at 20 °C for 2 hours. Then the mixture was diluted with water (50 mL), extracted with DCM (100 mL × 2). The organic layer was washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The mixture was purified by silica gel chromatography to give (2-amino-3-iodo-5-methylphenyl)-(2-chloro-7,8-dihydro-5H-1,6-naphthyridin-6-yl)methanone (3 g, 64% yield) as a yellow solid. LC-MS: m/z 428.0 [M+H]⁺.

Step 3:

To a stirred solution of (2-amino-3-iodo-5-methyl-phenyl)-(2-chloro-7,8-dihydro-5H-1,6-naphthyridin-6-yl)methanone (2 g, 4.6 mmol) in DMSO was added (NH₄)₂S₂O₈ (4.2 g, 18.7 mmol) at 20 °C. The mixture was stirred at 60 °C under N₂ for 2 hours. The mixture was filtered and the filter cake was dried *in vacuo* to give 3-chloro-12-iodo-10-methyl-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-8-one (1.9 g, 99% yield) as a yellow solid. LC-MS: m/z 424.1 [M+H]⁺.

Step 4:

To a stirred solution of 3-chloro-12-iodo-10-methyl-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-8-one (500 mg, 1.2 mmol) in DMF was added Pd(PPh₃)₄ (273 mg, 236 μmol) and tributyl(1-ethoxyvinyl)stannane (554 mg, 1.5 mmol) at 20 °C. The mixture was stirred at 100 °C under N₂ for 6 hours. The mixture was cooled to rt, diluted with DCM (50 mL), and then quenched with sat. aqueous KF (50 mL). The mixture was stirred at 20 °C under N₂ for 2 hours, then filtered. The filtrate was separated, and the organic layer was concentrated *in vacuo*. The residue was redissolved in acetone (30 mL) and 2 N HCl (5 mL) was added. The mixture was stirred at 20 °C under N₂ for 1 hour. Then the mixture was diluted with water (100 mL) and extracted with DCM (200 mL). The organic layer was dried with Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give 12-acetyl-3-chloro-10-methyl-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-8-one (400 mg, 99% yield) as a yellow solid. LC-MS: m/z 340.1 [M+H]⁺.

Step 5:

To a stirred solution of 12-acetyl-3-chloro-10-methyl-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-8-one (100 mg, 294 μmol) in THF (10 mL) was added Ti(OEt)₄ (2 g, 8.8 mmol) and (R)-2-methylpropane-2-sulfinamide (71 mg, 588 μmol) at 20 °C. The mixture was stirred at 85 °C for 12 hours. Upon completion, the mixture was diluted with EtOAc (50 mL) and water (50 mL) was added. The mixture was filtered, and the filtrate was extracted with EtOAc (50 mL × 2). The organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography to give (NE,R)-N-[1-(3-chloro-10-methyl-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-12-yl)ethylidene]-2-methyl-propane-2-sulfinamide (120 mg, 92% yield) as a yellow solid. LC-MS: m/z 443.1 [M+H]⁺.

Step 6:

To a stirred solution of (NE,R)-N-[1-(3-chloro-10-methyl-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-12-yl)ethylidene]-2-methyl-propane-2-sulfinamide (100 mg, 225 μmol) in methanol (15 mL) was added CeCl₃ (55 mg, 225 μmol), NaBH₄ (9 mg, 225 μmol) at 25 °C and the mixture was stirred at 25 °C for 10 minutes. The mixture was quenched with water (50 mL), and extracted with DCM (100 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give the crude product, which was purified by silica gel chromatography to give (R)-N-[(1R)-1-(3-chloro-10-methyl-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-12-yl)ethyl]-2-methyl-propane-2-sulfinamide (100 mg, 99% yield) as a yellow solid. LC-MS: m/z 445.1 [M+H]⁺.

Step 7:

To a stirred solution of (R)-N-[(1R)-1-(3-chloro-10-methyl-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-12-yl)ethyl]-2-methyl-propane-2-sulfonamide (20 mg, 44 μmol) in methanol (5 mL) was added HCl (0.5 mL, 4.0 M in ethanol) at 0 °C. The mixture was stirred at 0 °C for 30 minutes. The pH of the mixture was adjusted to 8 with sat. aqueous NaHCO_3 . The mixture was diluted with water (50 mL) and extracted with DCM (100 mL). The organic layer was washed with brine (100 mL), dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to give 12-[(1R)-1-aminoethyl]-3-chloro-10-methyl-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-8-one (10 mg, 65% yield) as a yellow oil. LC-MS: m/z 341.1 $[\text{M}+\text{H}]^+$.

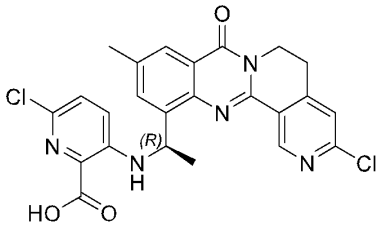
Step 8:

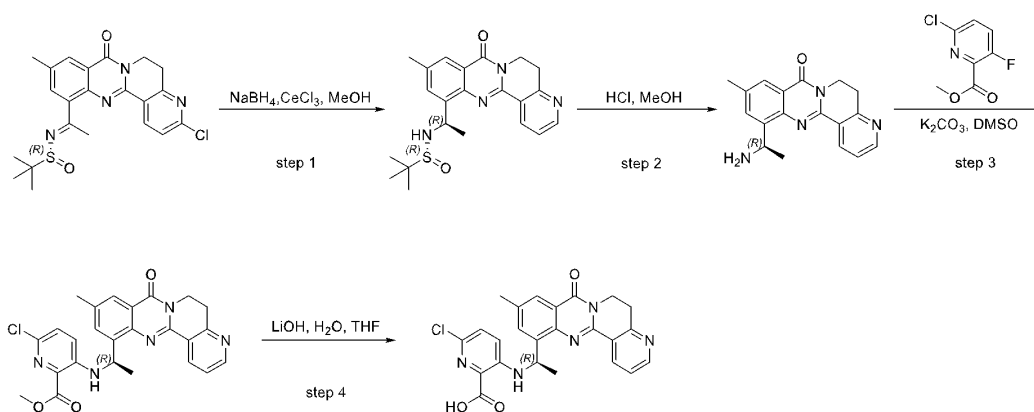
To a stirred solution of 12-[(1R)-1-aminoethyl]-3-chloro-10-methyl-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-8-one (10 mg, 29 μmol) in DMSO (5 mL) was added methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (17 mg, 88 μmol) and potassium carbonate (16 mg, 117 μmol) at 20 °C. The mixture was stirred at 80 °C for 2 hours. The mixture was diluted with water (10 mL) and extracted with EtOAc (50 mL). The organic layer was dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to give the crude product, which was purified by silica gel chromatography to give methyl 6-chloro-3-[(1R)-1-(3-chloro-10-methyl-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-12-yl)ethyl]amino]pyridine-2-carboxylate (10 mg, 66% yield) as a yellow oil. LC-MS: m/z 510.1 $[\text{M}+\text{H}]^+$.

Step 9:

To a methyl 6-chloro-3-[(1R)-1-(3-chloro-10-methyl-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-12-yl)ethyl]amino]pyridine-2-carboxylate (10 mg, 22 μmol) in mixed solvents of water and THF (8 mL, 1:3) was added lithium hydroxide monohydrate (6 mg, 260 μmol) at 20 °C. The mixture was stirred at 20 °C for 2 hours. The pH of the mixture was adjusted to 6 with sat. aqueous NH_4Cl , and then extracted with DCM (50 mL). The organic layer was dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to give the crude product, which was purified by prep-HPLC to give 6-chloro-3-[(1R)-1-(3-chloro-10-methyl-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-12-yl)ethyl]amino]pyridine-2-carboxylic acid (1 mg, 10% yield) as a white solid. LC-MS: m/z 496.1 $[\text{M}+\text{H}]^+$.

The following compound has been prepared in analogy to the representative procedures described for **Example 1**.

ID	Structure	LC-MS: m/z [M+H] ⁺
Example 2		496.1

Example 3**Step 1:**

- 5 To a stirred solution of (NE,R)-N-[1-(3-chloro-10-methyl-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-12-yl)ethylidene]-2-methyl-propane-2-sulfinamide (100 mg, 225 μ mol) in methanol (15 mL) was added CeCl_3 (110 mg, 450 μ mol) and NaBH_4 (85 mg, 2.3 mmol) at 25 $^\circ\text{C}$ and the mixture was stirred at 25 $^\circ\text{C}$ for 5 hours. The mixture was diluted with water (50 mL) and extracted with DCM (100 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give the
- 10 crude product, which was purified by silica gel chromatography to give (R)-2-methyl-N-((R)-1-(10-methyl-8-oxo-5,8-dihydro-6H-[1,6]naphthyridino[5,6-b]quinazolin-12-yl)ethyl)propane-2-sulfinamide (92 mg, 99% yield) as a yellow solid. LC-MS: m/z 411.2 [M+H]⁺.

Step 2:

- 15 To a stirred solution of (R)-2-methyl-N-((R)-1-(10-methyl-8-oxo-5,8-dihydro-6H-[1,6]naphthyridino[5,6-b]quinazolin-12-yl)ethyl)propane-2-sulfinamide (20 mg, 44 μ mol) in methanol (5 mL) was added HCl (0.5 mL, 4 M in ethanol) at 0 $^\circ\text{C}$. The mixture was stirred at 0 $^\circ\text{C}$ for 30 minutes. The pH of the mixture was adjusted to $\sim$ 8 with sat. aqueous NaHCO_3 . The mixture was diluted with water (50 mL) and extracted with DCM (100 mL). The organic layer was washed with brine (100 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give (R)-12-(1-aminoethyl)-
- 20 10-methyl-5,6-dihydro-8H-[1,6]naphthyridino[5,6-b]quinazolin-8-one (10 mg, 72% yield) as a yellow oil. LC-MS: m/z 307.1 [M+H]⁺.

Step 3:

To a stirred solution of (R)-12-(1-aminoethyl)-10-methyl-5,6-dihydro-8H-[1,6]naphthyridino[5,6-b]quinazolin-8-one (10 mg, 33 μ mol) in DMSO (5 mL) was added methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (17 mg, 88 μ mol) and potassium carbonate (16 mg, 117 μ mol) at 20 °C. The mixture was stirred at 80 °C for 2 hours. Then the mixture was diluted with water (10 mL) and extracted with EtOAc (50 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give the crude product, which was purified by silica gel chromatography to give methyl (R)-6-chloro-3-((1-(10-methyl-8-oxo-5,8-dihydro-6H-[1,6]naphthyridino[5,6-b]quinazolin-12-yl)ethyl)amino)picolinate (10 mg, 23% yield) as a yellow oil. LC-MS: m/z 476.1 [M+H]⁺.

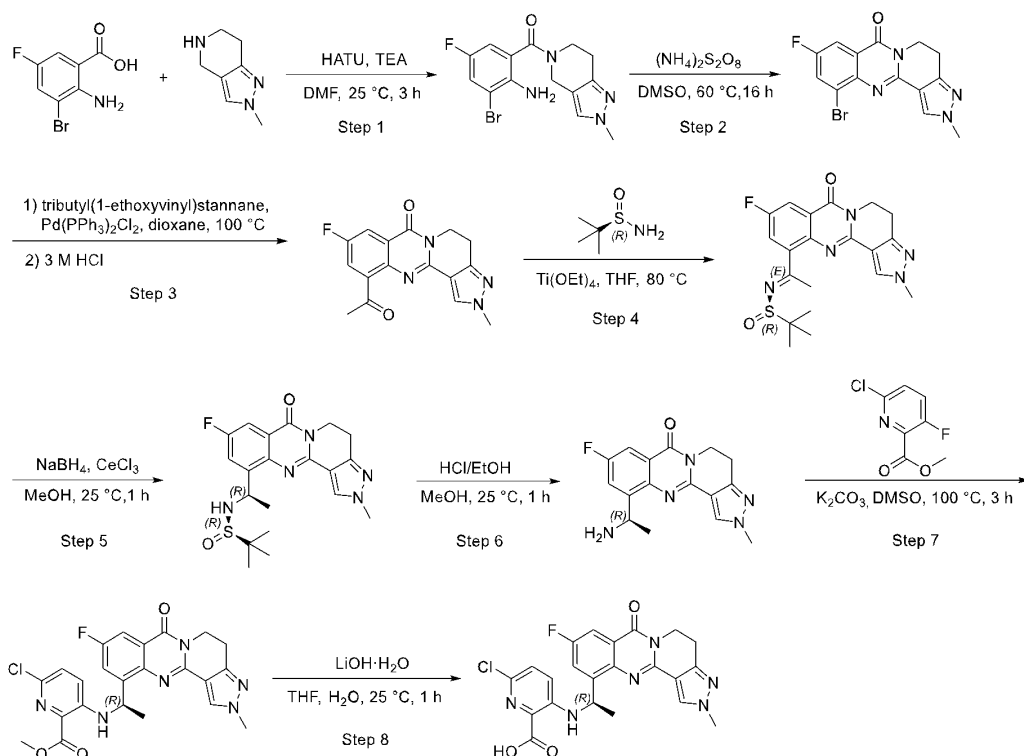
Step 4:

To a methyl (R)-6-chloro-3-((1-(10-methyl-8-oxo-5,8-dihydro-6H-[1,6]naphthyridino[5,6-b]quinazolin-12-yl)ethyl)amino)picolinate (10 mg, 22 μ mol) in mixed solvents of water and THF (8 mL, 1:3) was added lithium hydroxide monohydrate (6 mg, 260 μ mol) at 20 °C and the mixture was stirred at 20 °C for 2 hours. The pH of the mixture was adjusted to ~6 with sat. aqueous NH₄Cl, and then extracted with DCM (50 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give the crude product, which was purified by prep-HPLC to give (R)-6-chloro-3-((1-(10-methyl-8-oxo-5,8-dihydro-6H-[1,6]naphthyridino[5,6-b]quinazolin-12-yl)ethyl)amino)picolinic acid (2.2 mg, 23% yield) as a white solid. LC-MS: m/z 462.1 [M+H]⁺.

The following compound has been prepared in analogy to the representative procedures described for **Example 3**.

ID	Structure	LC-MS: m/z [M+H] ⁺
Example 4		462.1

Example 5



Step 1:

To a stirred solution of 2-amino-3-bromo-5-fluorobenzoic acid (2 g, 8.5 mmol) and HATU (3.9 g, 10.2 mmol) in DMF (20 mL) was added 2-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine (1.7 g, 10.2 mmol) and TEA (4.3 g, 42.6 mmol) at rt. The mixture was stirred at 25 °C for 3 hours. The mixture was diluted with EtOAc (300 mL) and then washed with brine (70 mL × 2). The organic phase was dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford the crude product, which was purified by silica gel chromatography to afford (2-amino-3-bromo-5-fluorophenyl)(2-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl)methanone (2.4 g, 80% yield) as a yellow solid. LC-MS: m/z 353.1, 355 [M+H]⁺.

Step 2:

To a stirred solution of (2-amino-3-bromo-5-fluorophenyl)(2-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl)methanone (1.3 g, 3.7 mmol) in DMSO (50 mL) was added (NH₄)₂S₂O₈ (3.4 g, 14.7 mmol) at rt. The mixture was stirred at 60 °C for 16 hours. The mixture was diluted with EtOAc (300 mL) and then washed with brine (70 mL × 2). The organic phase was dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford the crude product, which was purified by silica gel chromatography to afford 11-bromo-9-fluoro-2-methyl-4,5-dihydropyrazolo[4',3':3,4]pyrido[2,1-b]quinazolin-7(2H)-one (700 mg, 54% yield) as a yellow solid. LC-MS: m/z 349.1, 351 [M+H]⁺.

Step 3:

To a stirred solution of 11-bromo-9-fluoro-2-methyl-4,5-dihydropyrazolo[4',3':3,4]pyrido[2,1-b]quinazolin-7(2H)-one (700 mg, 2 mmol) and Pd(PPh₃)₂Cl₂ (231.7 mg, 200.5 μmol) in dioxane (10 mL) was added tributyl(1-ethoxyvinyl)stannane (1.1 g, 3 mmol). The mixture was degassed with a stream of N₂ for three times and then stirred at 100 °C for 16 hours. The mixture was cooled to rt and quenched with 1 M HCl (aq.) (1 mL). The mixture was diluted with DCM (200 mL), then washed with 10% aq. NaHCO₃ (15 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford crude product. The crude product was purified by silica gel chromatography to afford 11-acetyl-9-fluoro-2-methyl-4,5-dihydropyrazolo[4',3':3,4]pyrido[2,1-b]quinazolin-7(2H)-one (400 mg, 64% yield) as a yellow solid. LC-MS: m/z 313 [M+H]⁺.

Step 4:

To a stirred solution of 11-acetyl-9-fluoro-2-methyl-4,5-dihydropyrazolo[4',3':3,4]pyrido[2,1-b]quinazolin-7(2H)-one (400 mg, 1.3 mmol) in Ti(OEt)₄ (6 mL) was added (R)-2-methylpropane-2-sulfonamide (310.5 mg, 2.6 mmol). The mixture was stirred at 70 °C for 5 hours under N₂ atmosphere. The mixture was diluted with EtOAc (200 mL) and then water (20 mL) was added. The mixture was stirred at 20 °C for 0.5 hour. The mixture was filtered, and the organic layer was washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford crude product. The crude product was purified by silica gel chromatography to afford (R,E)-N-(1-(9-fluoro-2-methyl-7-oxo-2,4,5,7-tetrahydropyrazolo[4',3':3,4]pyrido[2,1-b]quinazolin-11-yl)ethylidene)-2-methylpropane-2-sulfonamide (200 mg, 40 % yield) as a yellow solid. LC-MS: m/z 416.1 [M+H]⁺.

Step 5:

To a stirred solution of (R,E)-N-(1-(9-fluoro-2-methyl-7-oxo-2,4,5,7-tetrahydropyrazolo[4',3':3,4]pyrido[2,1-b]quinazolin-11-yl)ethylidene)-2-methylpropane-2-sulfonamide (200 mg, 498.1 μmol) and CeCl₃ (122.8 mg, 498.2 μmol) in methanol (12 mL) was added NaBH₄ (28.3 mg, 747.3 μmol). The mixture was stirred at 20 °C for 15 minutes. The mixture was diluted with CH₂Cl₂ (100 mL) and then washed with brine (30 mL × 2). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford crude product. The crude product was purified by silica gel chromatography to afford (R)-N-((R)-1-(9-fluoro-2-methyl-7-oxo-2,4,5,7-tetrahydropyrazolo[4',3':3,4]pyrido[2,1-b]quinazolin-11-yl)ethyl)-2-methylpropane-2-sulfonamide (100 mg, 50% yield). LC-MS: m/z 418.1 [M+H]⁺.

Step 6:

To a stirred solution of (R)-N-((R)-1-(9-fluoro-2-methyl-7-oxo-2,4,5,7-tetrahydropyrazolo[4',3':3,4]pyrido[2,1-b]quinazolin-11-yl)ethyl)-2-methylpropane-2-sulfonamide (100 mg, 247.9 μmol) in methanol (10 mL) was added a solution of HCl in EtOH (1.5 mL, 4 N). The mixture was stirred at 20 °C for 10 minutes. The mixture was diluted with CH₂Cl₂ (100 mL) and then was washed with 10% NaHCO₃ (aq., 15 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford (R)-11-(1-aminoethyl)-9-fluoro-2-methyl-4,5-

dihydropyrazolo[4',3':3,4]pyrido[2,1-b]quinazolin-7(2H)-one (50 mg, crude) as a gray solid, which was used to the next step without further purification. LC-MS: m/z 314.1 $[M+H]^+$.

Step 7:

To a stirred solution of (R)-11-(1-aminoethyl)-9-fluoro-2-methyl-4,5-

- 5 dihydropyrazolo[4',3':3,4]pyrido[2,1-b]quinazolin-7(2H)-one (40 mg, 127.7 μmol) in DMSO (2 mL) was added K_2CO_3 (35.3 mg, 255.3 μmol) and methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (36.3 mg, 191.5 μmol). The mixture was stirred at 100 °C for 3 hours. The mixture was diluted with EtOAc (100 mL) and then washed with brine (30 mL $\times$ 3). The organic layer was dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to afford crude product. Then the crude product was purified by silica gel
- 10 chromatography to afford methyl (R)-6-chloro-3-((1-(9-fluoro-2-methyl-7-oxo-2,4,5,7-tetrahydropyrazolo[4',3':3,4]pyrido[2,1-b]quinazolin-11-yl)ethyl)amino)picolinate (20 mg, 32% yield) as a light yellow solid. LC-MS: m/z 483.1 $[M+H]^+$.

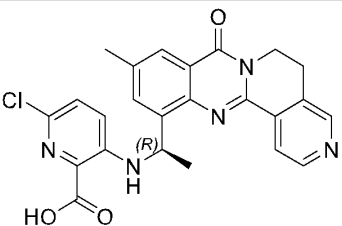
Step 8:

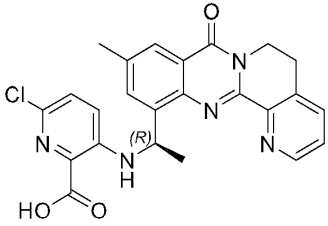
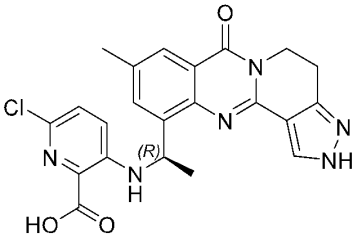
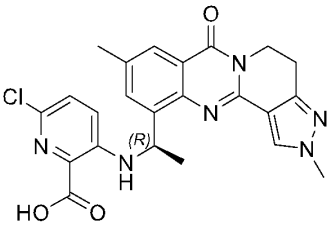
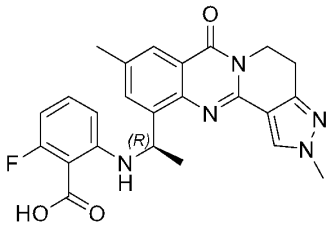
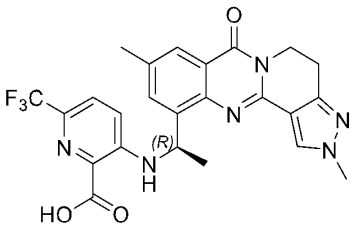
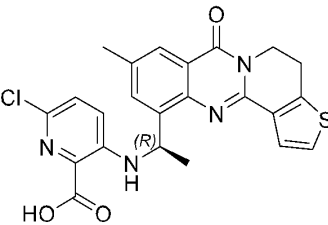
To a stirred solution of (R)-6-chloro-3-((1-(9-fluoro-2-methyl-7-oxo-2,4,5,7-

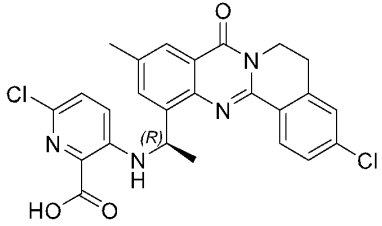
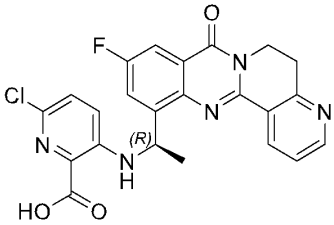
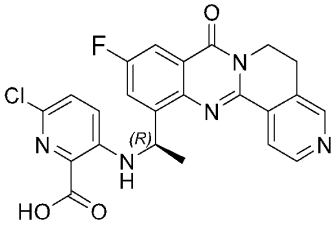
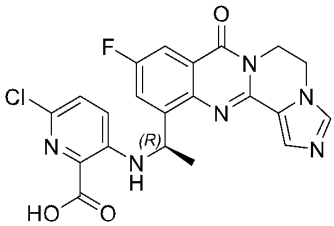
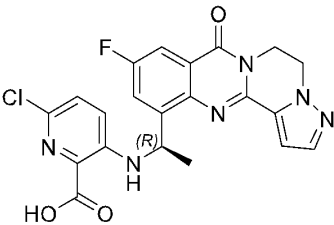
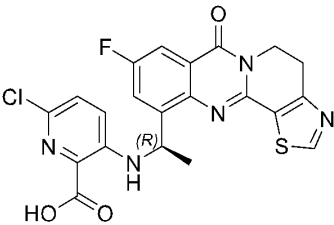
- 15 tetrahydropyrazolo[4',3':3,4]pyrido[2,1-b]quinazolin-11-yl)ethyl)amino)picolinate (20 mg, 41 μmol) in mixed solvents of THF and water (5 mL, 4:1) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (6.8 mg, 284.6 μmol). The mixture was stirred at 20 °C for 1 hour. The mixture was adjusted to pH $\sim$ 6 with 1 N HCl (aq.) and then extracted with CH_2Cl_2 (30 mL $\times$ 3). The organic layer was dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to afford crude product. The crude product was purified by prep-HPLC to
- 20 afford (R)-6-chloro-3-((1-(9-fluoro-2-methyl-7-oxo-2,4,5,7-tetrahydropyrazolo[4',3':3,4]pyrido[2,1-b]quinazolin-11-yl)ethyl)amino)picolinic acid (10 mg, 52% yield) as a white solid. LC-MS: m/z 469.1 $[M+H]^+$.

The following compounds have been prepared in analogy to the representative procedures described for **Example 5**.

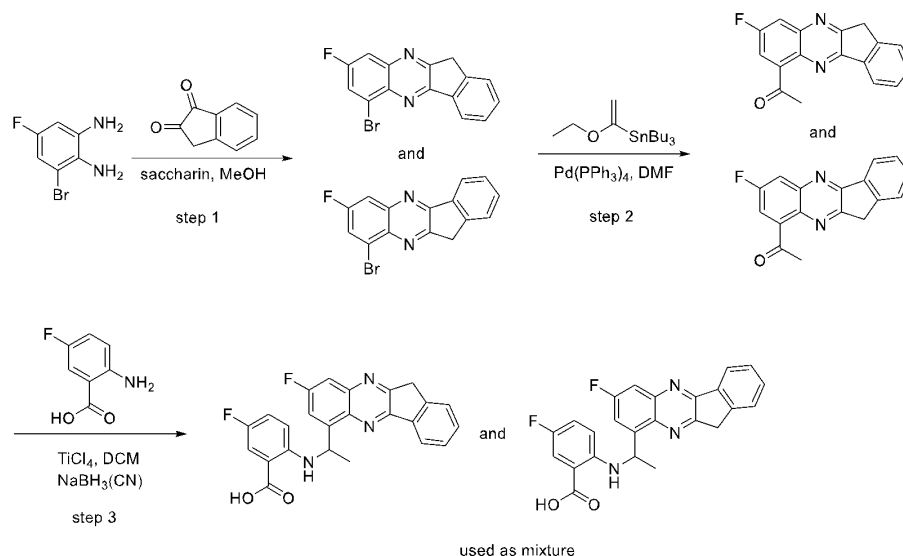
25

ID	Structure	LC-MS: m/z $[M+H]^+$
Example 6		462.1

Example 7		462.1
Example 8	Intentionally left blank	
Example 9		451.1
Example 10		465.1
Example 11		448.2
Example 12		499.1
Example 13		467.1

Example 14		495.1
Example 15		466.0
Example 16		466.1
Example 17		455.1
Example 18		455.1
Example 19		472.0

Example 20



Step 1:

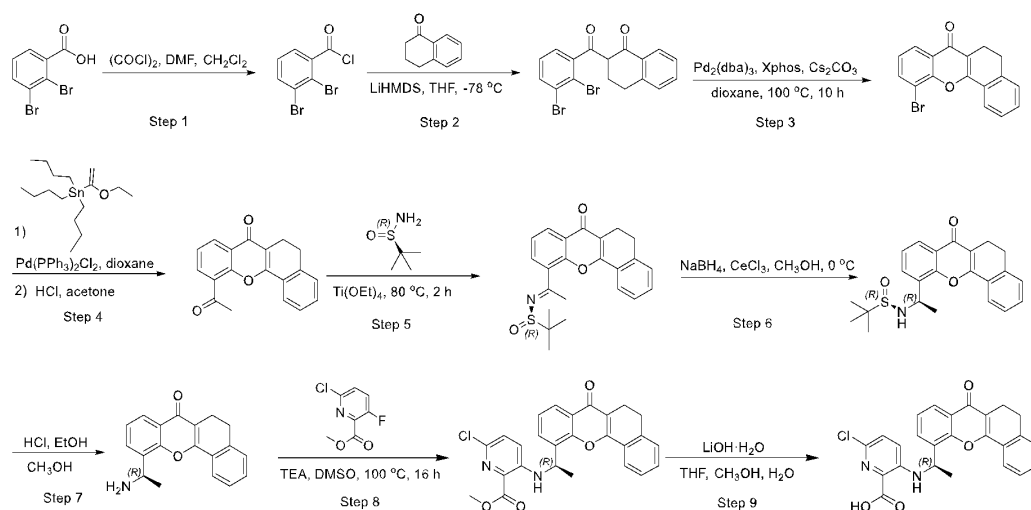
To a stirred solution of indane-1,2-dione (712 mg, 4.8 mmol) in methanol (10 mL) was added
 5 saccharin (89.3 mg, 487 μ mol) and 3-bromo-5-fluoro-benzene-1,2-diamine (1 g, 4.8 mmol) at 25 °C
 and the mixture was stirred at 25 °C under N₂ atmosphere for 1 hour. The mixture was diluted with
 water (50 mL), and extracted with DCM (100 mL $\times$ 2). The organic layer was washed with brine (100
 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 6-bromo-8-fluoro-11H-
 indeno[1,2-b]quinoxaline and 9-bromo-7-fluoro-11H-indeno[1,2-b]quinoxaline (1.5 g, 97% yield) as
 10 a yellow solid. LC-MS: *m/z* 315.2 [M+H]⁺.

Step 2:

A mixture of 6-bromo-8-fluoro-11H-indeno[1,2-b]quinoxaline and 9-bromo-7-fluoro-11H-
 indeno[1,2-b]quinoxaline (1 g, 3.2 mmol) in DMF (20 mL) was added Pd(PPh₃)₄ (733 mg, 634 μ mol)
 and tributyl(1-ethoxyvinyl)stannane (1.2 g, 3.2 mmol) at 20 °C. The mixture was stirred at 100 °C for
 15 4 hours. The mixture was diluted with DCM (50 mL), and then quenched with sat. aqueous KF (50
 mL). The mixture was stirred at rt for 2 hours, then filtered. The filtrate was separated, and the
 organic layer was concentrated *in vacuo*. The residue was redissolved in acetone (30 mL) and 2 N
 HCl (5 mL) was added. The mixture was stirred at 20 °C for 30 minutes. Then the mixture was diluted
 with water (50 mL) and extracted with DCM (100 mL). The organic layer was dried over Na₂SO₄,
 20 filtered, and concentrated *in vacuo* to give the crude product, which was purified by silica gel flash
 column chromatography to give 1-(8-fluoro-11H-indeno[2,1-b]quinoxalin-6-yl)ethanone and 1-(7-
 fluoro-11H-indeno[1,2-b]quinoxalin-9-yl)ethanone (500 mg, 56% yield) as a yellow solid. LC-MS:
m/z 279.1 [M+H]⁺.

Step 3:

To a stirred mixture of 1-(8-fluoro-11H-indeno[2,1-b]quinoxalin-6-yl)ethenone, 1-(7-fluoro-11H-indeno[1,2-b]quinoxalin-9-yl)ethanone (mixture of the two, 50 mg, 179 μ mol) and 2-amino-5-fluorobenzoic acid (62 mg, 400 μ mol) in DCM (2 mL) was added TiCl_4 (340 mg, 1.8 mmol) at 25 $^\circ\text{C}$ and the resulting mixture was stirred at 25 $^\circ\text{C}$ for 1 hour. Then sodium cyanoborohydride (112 mg, 1.8 mmol) was added, and the mixture was stirred at 25 $^\circ\text{C}$ for 2 hours. The mixture was diluted with water (30 mL), and extracted with DCM (50 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give the crude product, which was purified by prep-HPLC to give 5-fluoro-2-[1-(8-fluoro-11H-indeno[2,1-b]quinoxalin-6-yl)ethylamino]benzoic acid and 5-fluoro-2-[1-(7-fluoro-11H-indeno[1,2-b]quinoxalin-9-yl)ethylamino]benzoic acid (2 mg, 3% yield) as a yellow solid. LC-MS: m/z 418.1 $[\text{M}+\text{H}]^+$.

Example 21**Step 1:**

To a stirred solution of 2,3-dibromobenzoic acid (2.5 g, 8.9 mmol) and DMF (65.3 mg, 0.9 mmol) in CH_2Cl_2 (40 mL) was added oxalyl dichloride (1.1 g, 8.9 mmol). The mixture was stirred at 20 $^\circ\text{C}$ for 0.5 hour. The mixture was concentrated *in vacuo* to afford 2,3-dibromobenzoyl chloride (2.6 g, 97% yield) as a light-yellow solid, which was used to the next step without further purification.

Step 2:

To a stirred solution of LiHMDS (1.7 g, 10 mmol) in THF (30 mL) was added a solution of 3,4-dihydronaphthalen-1(2H)-one (1.5 g, 10 mmol) in THF (10 mL) at -78 $^\circ\text{C}$ under N_2 protection. The reaction was stirred at -78 $^\circ\text{C}$ for 1 hour. Then a suspension of 2,3-dibromobenzoyl chloride (2.6 g, 8.7 mmol) in THF (30 mL) was dropwise added to the reaction mixture at -78 $^\circ\text{C}$ and the reaction was stirred at -78 $^\circ\text{C}$ for 1 hour. The mixture was quenched with aq. HCl (1 N, 20 mL), diluted with water (100 mL) and extracted with CH_2Cl_2 (100 mL $\times$ 2). The combined organic layers were dried over

Na₂SO₄, filtered, and concentrated *in vacuo* to afford crude product. The crude product was purified by column chromatography on silica gel to afford 2-(2,3-dibromobenzoyl)-3,4-dihydronaphthalen-1(2H)-one (2.2 g, 62% yield) as a light-yellow solid. LC-MS: m/z 406.9 [M+H]⁺.

Step 3:

- 5 To a stirred solution of 2-(2,3-dibromobenzoyl)-3,4-dihydronaphthalen-1(2H)-one (700 mg, 1.7 mmol), XPhos (163.5 mg, 343 μmol) and Cs₂CO₃ (1.4 g, 4.3 mmol) in dioxane (12 mL) was added Pd₂(dba)₃ (177.5 mg, 171.5 μmol). The mixture was degassed with a stream of N₂ for three times and then stirred at 100 °C for 10 hours. The mixture was diluted with water (50 mL) and extracted with CH₂Cl₂ (100 mL × 2). The combined extracts were washed with brine (50 mL) and dried over
- 10 anhydrous Na₂SO₄. Solvents were evaporated to afford crude product. The crude product was purified by column chromatography on silica gel to afford 11-bromo-5,6-dihydro-7H-benzo[c]xanthen-7-one (210 mg, 37% yield) as a light-yellow solid. LC-MS: m/z 327.0 [M+H]⁺.

Step 4:

- 15 To a stirred solution of 11-bromo-5,6-dihydro-7H-benzo[c]xanthen-7-one (210 mg, 641.8 μmol) in dioxane (10 mL) was added tributyl(1-ethoxyvinyl)stannane (463.6 mg, 1.3 mmol) and Pd(PPh₃)₂Cl₂ (90.1 mg, 128.3 μmol). The mixture was degassed with a stream of N₂ for three times and then stirred at 100 °C for 16 hours. The reaction was quenched with sat. KF solution (50 mL) and the mixture was extracted with CH₂Cl₂ (150 mL × 2). The combined extracts were washed with brine (50 mL) and dried over anhydrous Na₂SO₄. Solvent was evaporated and the crude product was redissolved in
- 20 acetone (20 mL). HCl (5 mL, 2 N) was added to the mixture and the solution was then stirred at 20 °C for 20 minutes. The mixture was diluted with CH₂Cl₂ (150 mL) and washed with 10% NaHCO₃ (aq.) (50 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford crude product. The crude product was purified by column chromatography on silica gel to afford 11-acetyl-5,6-dihydro-7H-benzo[c]xanthen-7-one (110 mg, 59% yield) as a light-yellow solid. LC-MS: m/z 291.1 [M+H]⁺.

Step 5:

- 25 To a stirred solution of 11-acetyl-5,6-dihydro-7H-benzo[c]xanthen-7-one (110 mg, 378.9 μmol) in Ti(OEt)₄ (4 mL) was added (R)-2-methylpropane-2-sulfinamide (137.7 mg, 1.1 mmol). The mixture was stirred at 80 °C for 2 hours under N₂ protection. The mixture was diluted with EtOAc (200 mL) and then water (50 mL) was added. The mixture was stirred at 20 °C for 0.5 hour. The mixture was
- 30 filtered, and the organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford crude product. The crude product was purified by column chromatography on silica gel to afford (R,E)-2-methyl-N-(1-(7-oxo-5,7-dihydro-6H-benzo[c]xanthen-11-yl)ethylidene)propane-2-sulfinamide (160 mg, crude) as a light yellow oil. LC-MS: m/z 394.1 [M+H]⁺.

Step 6:

- 35 To a stirred solution of (R,E)-2-methyl-N-(1-(7-oxo-5,7-dihydro-6H-benzo[c]xanthen-11-yl)ethylidene)propane-2-sulfinamide (140 mg, 355.7 μmol) and CeCl₃ (35.1 mg, 142.3 μmol) in

methanol (10 mL) was added NaBH₄ (29.6 mg, 782.7 μmol). The mixture was stirred at 0 °C for 5 minutes. The mixture was diluted with CH₂Cl₂ (70 mL) and then washed with brine (30 mL × 2). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford crude product. The crude product was purified by column chromatography on silica gel to afford (R)-2-methyl-N-((R)-1-(7-oxo-5,7-dihydro-6H-benzo[c]xanthen-11-yl)ethyl)propane-2-sulfinamide (130 mg, 92.3% yield) as a light-yellow solid. LC-MS: m/z 396.1 [M+H]⁺.

Step 7:

To a stirred solution of (R)-2-methyl-N-((R)-1-(7-oxo-5,7-dihydro-6H-benzo[c]xanthen-11-yl)ethyl)propane-2-sulfinamide (35 mg, 88.5 μmol) in methanol (10 mL) was added a solution of HCl in EtOH (1.5 mL, 4 N). The mixture was stirred at 20 °C for 5 minutes. The mixture was diluted with CH₂Cl₂ (100 mL) and then was washed with 10% aq. NaHCO₃ (15 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford (R)-11-(1-aminoethyl)-5,6-dihydro-7H-benzo[c]xanthen-7-one (35 mg, crude) as a white solid, which was used to the next step without further purification. LC-MS: m/z 292.1 [M+H]⁺.

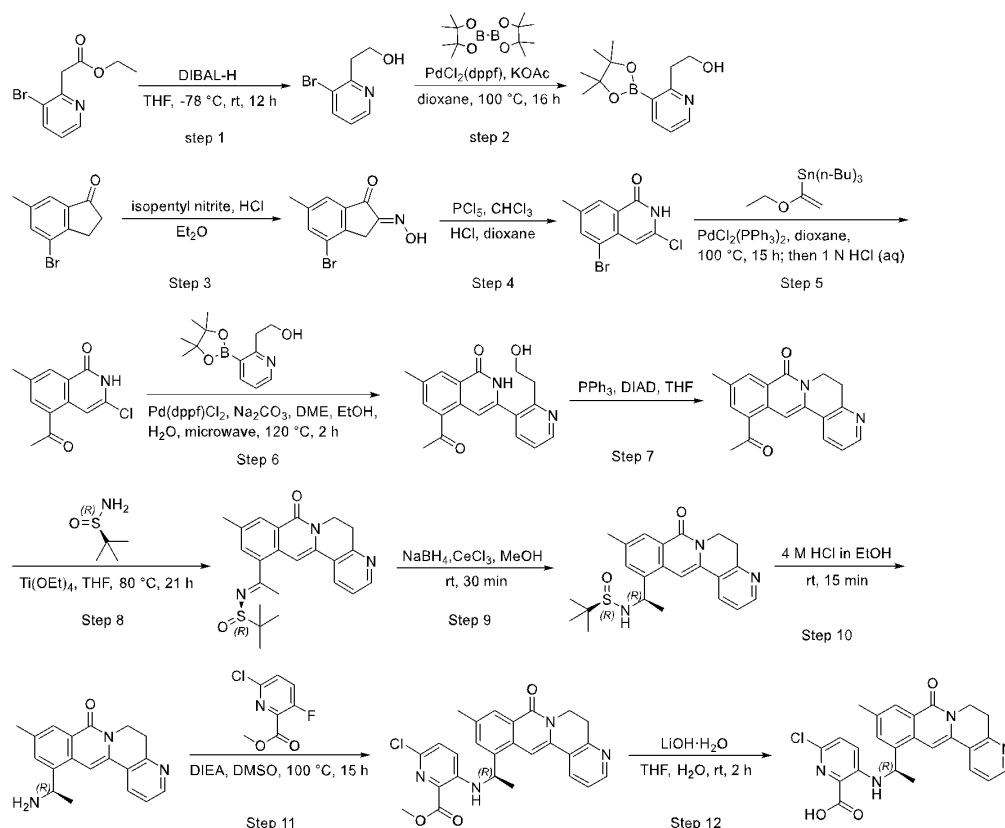
Step 8:

To a stirred solution of (R)-11-(1-aminoethyl)-5,6-dihydro-7H-benzo[c]xanthen-7-one (35 mg, 120.1 μmol) and triethylamine (48.6 mg, 480.5 μmol) in DMSO (3 mL) was added methyl 6-chloro-3-fluoropicolinate (34.2 mg, 180.2 μmol). The mixture was stirred at 100 °C for 16 hours. The mixture was diluted with EtOAc (100 mL) and then was washed with brine (30 mL × 3). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford crude product. The crude product was purified by column chromatography on silica gel to afford methyl (R)-6-chloro-3-((1-(7-oxo-5,7-dihydro-6H-benzo[c]xanthen-11-yl)ethyl)amino)picolinate (13 mg, 23.5% yield) as a white solid. LC-MS: m/z 461.1 [M+H]⁺.

Step 9:

To a stirred solution of methyl (R)-6-chloro-3-((1-(7-oxo-5,7-dihydro-6H-benzo[c]xanthen-11-yl)ethyl)amino)picolinate (13 mg, 28.2 μmol) in mixed solvents of THF, methanol (1 mL) and water (6 mL, 4:1:1) was added LiOH·H₂O (5.9 mg, 141.0 μmol). The mixture was stirred at 20 °C for 20 minutes. The mixture was adjusted to PH ~ 5 with aq. HCl (1 N), then diluted with brine (20 mL) and extracted with CH₂Cl₂ (60 mL × 2). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford crude product. The crude product was purified by Prep-HPLC (A: 0.05% formic acid in water, B: CH₃CN, Gradient: 10 ~ 75% of B) to afford (R)-6-chloro-3-((1-(7-oxo-5,7-dihydro-6H-benzo[c]xanthen-11-yl)ethyl)amino)picolinic acid (8 mg, 63.5% yield) as a white solid. LC-MS: m/z 447.1 [M+H]⁺.

Example 22



Step 1:

To a stirred solution of ethyl 2-(3-bromopyridin-2-yl)acetate (2 g, 8.2 mmol) in anhydrous THF (30 mL) was added DIBAL-H (1 M in hexane) (16.4 mL, 16.4 mmol) dropwise at -78 °C. The resulting red solution was stirred for 12 hours at room temperature. Reaction was quenched with sat. potassium sodium tartrate solution (30 mL) at 0 °C and stirred for 1 hour at room temperature. The resulting mixture was extracted with ethyl acetate (50 mL × 3). The combined organic phases were washed with brine (60 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel to obtain 2-(3-bromopyridin-2-yl)ethan-1-ol (0.9 g, 54% yield) as a brown oil. LC-MS: m/z 202.0 [M+H]⁺.

Step 2:

To a flask containing 2-(3-bromopyridin-2-yl)ethan-1-ol (900 mg, 4.5 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.2 g, 4.9 mmol) in dioxane (20 mL) was added KOAc (874 mg, 8.9 mmol) and Pd(dppf)Cl₂ (323.2 mg, 445.4 μmol). The solution was degassed by N₂ gas balloon. The mixture was then heated to 100 °C for 16 hours. The mixture was cooled to room temperature, filtered through a pad of Celite. The filter cake was washed with ethyl acetate (20 mL × 2). The combined solution was concentrated *in vacuo* to obtain 2-(3-(4,4,5,5-tetramethyl-1,3,2-

dioxaborolan-2-yl)pyridin-2-yl)ethan-1-ol (2.2 g, crude) as a black oil, which was used to next step without further purification. LC-MS: m/z 250.2 $[M+H]^+$.

Step 3:

To a suspension of 4-bromo-6-methyl-2,3-dihydro-1H-inden-1-one (2 g, 8.9 mmol) in Et₂O (20 mL) and concentrated HCl (20 mL) was added isopentyl nitrite (5.2 g, 44.4 mmol) dropwise at 25 °C and the mixture was stirred at 25 °C for 5 hours. The solid was collected by filtration and washed with Et₂O to give (E)-4-bromo-2-(hydroxyimino)-6-methyl-2,3-dihydro-1H-inden-1-one (1.8 g, 80% yield) as a white solid. LC-MS: m/z 253.9 $[M+H]^+$.

Step 4:

To a suspension of (E)-4-bromo-2-(hydroxyimino)-6-methyl-2,3-dihydro-1H-inden-1-one (1.8 g, 7.1 mmol) in CHCl₃ (36 mL) was added PCl₅ (2.2 g, 10.6 mmol) slowly at 25 °C and the mixture was stirred at 25 °C for 16 hours. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in a solution of 4 M HCl in dioxane (25 mL). The reaction mixture was stirred at 25 °C for 16 hours. The reaction mixture was concentrated *in vacuo*. The residue was diluted with CH₂Cl₂ (50 mL) and washed with water (60 mL) and sat. NaHCO₃ (30 mL). Then the suspension was filtered, and the aqueous layer was extracted with CH₂Cl₂:MeOH=10:1 (V:V) (80 mL × 2). The combined organic phase was washed with brine (100 mL) and dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*, and the combined crude product was washed with Et₂O to give 5-bromo-3-chloro-7-methylisoquinolin-1(2H)-one (1.9 g, 98% yield) as an off-white solid. LC-MS: m/z 271.9 $[M+H]^+$.

Step 5:

To a mixture of 5-bromo-3-chloro-7-methylisoquinolin-1(2H)-one (1.9 g, 7 mmol) and tributyl(1-ethoxyvinyl)stannane (3 g, 8.4 mmol) in dioxane (40 mL) was added Pd(PPh₃)₂Cl₂ (489.4 mg, 697.2 μmol) and the resulting mixture was purged with nitrogen for three times. The reaction mixture is stirred at 100 °C under nitrogen for 16 hours. The reaction mixture was cooled to room temperature, poured into 1 N HCl (aq.) (40 mL), and stirred for 1 hour. The mixture is neutralized to approximately pH ~ 8 using 10% Na₂CO₃ (aq.). The mixture was diluted by CH₂Cl₂: MeOH =10:1 (100 mL, V: V) and the phases were separated. The aqueous layer was extracted with mixed solvents of CH₂Cl₂ and MeOH (100 mL × 3, V: V = 10:1). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel to afford 5-acetyl-3-chloro-7-methylisoquinolin-1(2H)-one (1.3 g, 79% yield) as an earthy yellow solid. LC-MS: m/z 236.0 $[M+H]^+$.

Step 6:

To a microwave tube containing 5-acetyl-3-chloro-7-methylisoquinolin-1(2H)-one (150 mg, 636.5 μmol), 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)ethan-1-ol (1.4 g, 5.7 mmol) in mixed solvents of DME, EtOH and water (10 mL, 3:1:1) was added sodium carbonate (134.9 mg, 1.3 mmol), and Pd(dppf)Cl₂ (46.2 mg, 63.7 μmol). The mixture was degassed by N₂ gas balloon. The tube was then sealed and heated to 120 °C for 2 hours with microwave irradiation. The

mixture was cooled to room temperature, filtered through a pad of Celite, which was washed with ethyl acetate (20 mL $\times$ 3). The combined solution was concentrated *in vacuo* to obtain crude product, which was purified by flash column chromatography on silica gel to afford a black solid, which was purified by prep-HPLC to give 5-acetyl-3-(2-(2-hydroxyethyl)pyridin-3-yl)-7-methylisoquinolin-1(2H)-one (40 mg, 19.5% yield) as an off-white solid. LC-MS: *m/z* 323.1 [M+H]⁺.

Step 7:

To a stirred solution of 5-acetyl-3-(2-(2-hydroxyethyl)pyridin-3-yl)-7-methylisoquinolin-1(2H)-one (40 mg, 124.1 μ mol) and PPh₃ (48.8 mg, 186.1 μ mol) in anhydrous THF (8 mL) under an atmosphere of N₂ was added a solution of DIAD (37.6 mg, 186.1 μ mol) in THF (0.5 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 20 hours. The reaction mixture was heated to 60 °C for 2 hours, cooled to room temperature, and then a solution of PPh₃ (97.6 mg, 372.3 μ mol), DIAD (75.3 mg, 372.3 μ mol) in THF (5 mL) was added. The reaction mixture was then stirred for 3 hours. The mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel to obtain 12-acetyl-10-methyl-5,6-dihydro-8H-isoquinolino[3,2-f][1,6]naphthyridin-8-one (200 mg, crude) as a pale yellow solid. LC-MS: *m/z* 305.1 [M+H]⁺.

Step 8:

To a stirred solution of 12-acetyl-10-methyl-5,6-dihydro-8H-isoquinolino[3,2-f][1,6]naphthyridin-8-one (200 mg, 657.2 μ mol) in THF (6 mL) was added (R)-2-methylpropane-2-sulfinamide (199.1 mg, 1.6 mmol) followed by Ti(OEt)₄ (1.5 g, 6.6 mmol). The mixture was stirred at 80 °C for 21 hours. Upon completion, the reaction mixture was cooled to 5 °C, quenched with ice water (20 mL) and diluted with ethyl acetate (30 mL). The reaction mixture was stirred vigorously for 0.5 hour, filtered through a pad of Celite, and the filter cake was washed with ethyl acetate (30 mL). The filtrate was separated and the aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layers were washed with water (50 mL $\times$ 2) and sat. aqueous sodium chloride (50 mL), dried over sodium sulfate and concentrated *in vacuo* to afford (R,E)-2-methyl-N-(1-(10-methyl-8-oxo-5,8-dihydro-6H-isoquinolino[3,2-f][1,6]naphthyridin-12-yl)ethylidene)propane-2-sulfinamide (210 mg, 78.4% yield) as an off-white solid. LC-MS: *m/z* 408.2 [M+H]⁺.

Step 9:

To a stirred solution of (R,E)-2-methyl-N-(1-(10-methyl-8-oxo-5,8-dihydro-6H-isoquinolino[3,2-f][1,6]naphthyridin-12-yl)ethylidene)propane-2-sulfinamide (210 mg, 515.3 μ mol) and CeCl₃ (76.2 mg, 309.2 μ mol) in MeOH (8 mL) at room temperature was added NaBH₄ (21.4 mg, 566.8 μ mol). The reaction mixture was stirred at room temperature for 30 minutes. Upon completion, the mixture was quenched with NH₄Cl(aq.) (30 mL) and filtered. The filter cake was washed with ethyl acetate (20 mL $\times$ 2), and the aqueous layer was extracted with ethyl acetate (40 mL $\times$ 2). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel to afford crude product, which was purified by prep-HPLC to obtain (R)-2-methyl-N-((R)-1-(10-

methyl-8-oxo-5,8-dihydro-6H-isoquinolino[3,2-f][1,6]naphthyridin-12-yl)ethyl)propane-2-sulfonamide (17 mg, 8% yield) as a white solid. LC-MS: m/z 410.2 $[M+H]^+$.

Step 10:

To a stirred solution of (R)-2-methyl-N-((R)-1-(10-methyl-8-oxo-5,8-dihydro-6H-isoquinolino[3,2-f][1,6]naphthyridin-12-yl)ethyl)propane-2-sulfonamide (17 mg, 41.5 μmol) in EtOH (2.0 mL) was added a solution of 4 M HCl in EtOH (1 mL) and the reaction mixture was stirred at rt for 15 minutes. The mixture was concentrated *in vacuo* to afford (R)-12-(1-aminoethyl)-10-methyl-5,6-dihydro-8H-isoquinolino[3,2-f][1,6]naphthyridin-8-one (15 mg, crude) as an amorphous crystalline solid. LC-MS: m/z 306.2 $[M+H]^+$.

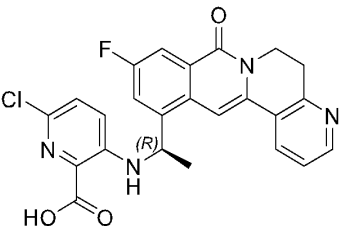
Step 11:

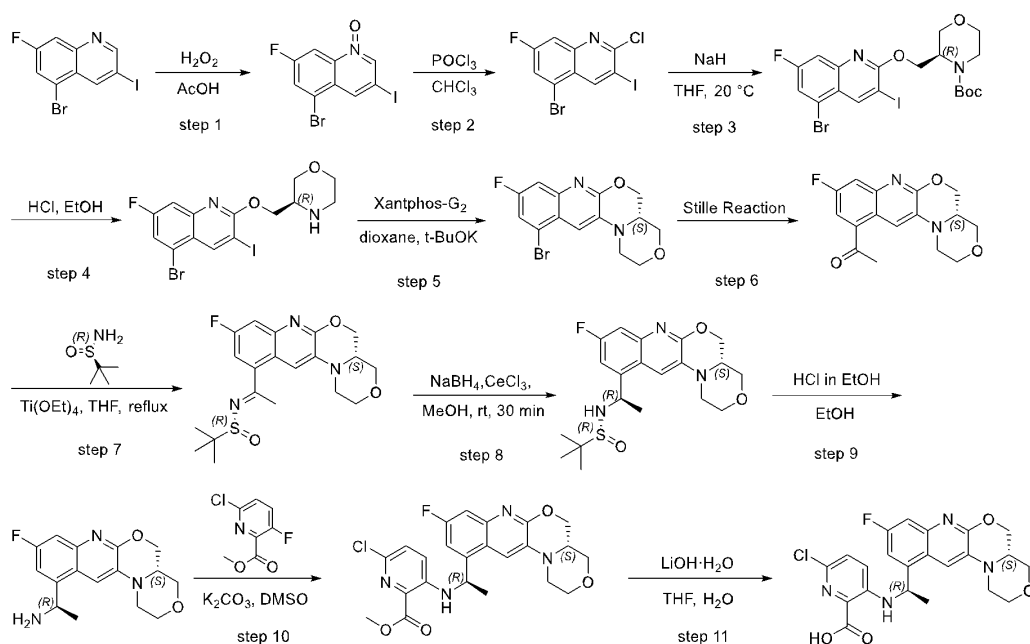
To a stirred solution of (R)-12-(1-aminoethyl)-10-methyl-5,6-dihydro-8H-isoquinolino[3,2-f][1,6]naphthyridin-8-one (15 mg, 43.9 μmol) in DMSO (2 mL) was added DIPEA (28.4 mg, 219.4 μmol), followed by methyl 6-chloro-3-fluoropicolinate (12.5 mg, 65.8 μmol). The mixture was stirred at 100 °C for 15 hours. The reaction mixture was cooled to room temperature, poured into water (10 mL) and extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layers were washed with water (20 mL) and sat. aqueous sodium chloride (20 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to obtain methyl (R)-6-chloro-3-((1-(10-methyl-8-oxo-5,8-dihydro-6H-isoquinolino[3,2-f][1,6]naphthyridin-12-yl)ethyl)amino)picolinate (20 mg, crude) as a brown oil. LC-MS: m/z 475.2 $[M+H]^+$.

Step 12:

To a stirred solution of methyl (R)-6-chloro-3-((1-(10-methyl-8-oxo-5,8-dihydro-6H-isoquinolino[3,2-f][1,6]naphthyridin-12-yl)ethyl)amino)picolinate (20 mg, 42.1 μmol) in THF (2 mL) and water (1 mL) was added LiOH $\cdot$ H₂O (5 mg, 210.6 μmol) at rt. The mixture was then stirred at room temperature for 2 hours. The mixture was cooled to 0~5 °C and diluted with water (5 mL), acidified to pH = 2~3 with 2 N HCl and extracted with ethyl acetate (10 mL $\times$ 3). The combined organic layers were washed with water (15 mL) and sat. aqueous sodium chloride (15 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by prep-HPLC (0.1% formic acid) to give (R)-6-chloro-3-((1-(10-methyl-8-oxo-5,8-dihydro-6H-isoquinolino[3,2-f][1,6]naphthyridin-12-yl)ethyl)amino)picolinic acid (3.5 mg, 18% yield) as an off-white solid. LC-MS: m/z 461.1 $[M+H]^+$.

The following compound has been prepared in analogy to the representative procedures described for **Example 22**.

ID	Structure	LC-MS: m/z [M+H] ⁺
Example 44		465.1

Example 23**Step 1:**

- 5 To a stirred solution of 5-bromo-7-fluoro-3-iodoquinoline (2 g, 5.7 mmol) in AcOH (40 mL) was added H₂O₂ (2.5 mL). The mixture was stirred at 85 °C for 16 hours. LC-MS showed the product was formed. The mixture was poured into sat. NaHCO₃ (aq.) (300 mL) and sat. Na₂S₂O₃ (aq.) (50 mL), extracted with DCM (200 mL × 2). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to
- 10 afford 5-bromo-7-fluoro-3-iodoquinoline 1-oxide (1.3 g, 60% yield) as a white solid. LC-MS: m/z 367.8, 369.8 [M+H]⁺.

Step 2:

- To a stirred mixture of 5-bromo-7-fluoro-3-iodoquinoline 1-oxide (1.3 g, 3.4 mmol) in CHCl₃ (30 mL) was added POCl₃ (2.6 g, 17 mmol). The mixture was stirred at 80 °C for 1.5 hours. LC-MS
- 15 showed the product was formed. The mixture was poured into sat. NaHCO₃ (aq.) (100 mL) and extracted with DCM (100 mL × 2). The combined organic layers were dried over Na₂SO₄, filtered,

and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford 5-bromo-2-chloro-7-fluoro-3-iodoquinoline (700 mg, 53% yield) as a white solid.

Step 3:

To a stirred solution of 5-bromo-2-chloro-7-fluoro-3-iodoquinoline (700 mg, 1.8 mmol) and tert-butyl (R)-3-(hydroxymethyl)morpholine-4-carboxylate (984 mg, 4.5 mmol) in THF (15 mL) was added sodium hydride (217.4 mg, 5.4 mmol, 60% purity) under N₂. The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed the reaction was completed. The mixture was quenched with water (1 mL) to give tert-butyl (R)-3-(((5-bromo-7-fluoro-3-iodoquinolin-2-yl)oxy)methyl)morpholine-4-carboxylate (1 g, crude), which was used to the next step directly without further purification. LC-MS: m/z 567.0, 569.0 [M+H]⁺.

Step 4:

To a stirred solution of tert-butyl (R)-3-(((5-bromo-7-fluoro-3-iodoquinolin-2-yl)oxy)methyl)morpholine-4-carboxylate (1 g, 1.8 mmol) in THF (15 mL) was added a solution of 4 M HCl in EtOH (30 mL). The mixture was stirred at 40 °C for 1 hour. LC-MS showed the product was formed. The mixture was poured into sat. NaHCO₃ (aq.) (250 mL) and extracted with EtOAc (200 mL × 2). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford (R)-3-(((5-bromo-7-fluoro-3-iodoquinolin-2-yl)oxy)methyl)morpholine (840 mg, 99% yield) as a colorless oil. LC-MS: m/z 466.9, 468.9 [M+H]⁺.

Step 5:

To a stirred mixture of (R)-3-(((5-bromo-7-fluoro-3-iodoquinolin-2-yl)oxy)methyl)morpholine (840 mg, 1.8 mmol) in dioxane (30 mL) was added t-BuOK (403.6 mg, 3.6 mmol) and [2-(2-aminophenyl)phenyl]-chloro-palladium;(5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenylphosphane (239.7 mg, 269.8 μmol) at rt. The mixture was stirred at 95 °C for 16 hours under N₂. LC-MS showed the product was formed. The mixture was quenched with water (150 mL) and extracted with EtOAc (100 mL × 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford (S)-11-bromo-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoline (75 mg, 12% yield) as a white solid. LC-MS: m/z 339.0, 341.0 [M+H]⁺.

Step 6:

To a stirred mixture of (S)-11-bromo-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoline (130 mg, 383.3 μmol) in dioxane (5 mL) was added Pd(PPh₃)₂Cl₂ (45.5 mg, 57.5 μmol) and tributyl(1-ethoxyvinyl)stannane (180 mg, 498.3 μmol) under N₂. The mixture was stirred at 105 °C for 3 hours. LC-MS showed the reaction was completed. Then 3 M HCl (2 mL) was added and the resulting mixture was stirred at 20 °C for 0.5 h. The mixture was diluted with water (40 mL), basified with sat. NaHCO₃ (aq.) to pH ~ 9, and extracted with DCM (40 mL × 2). The combined organic layers were dried over Na₂SO₄, filtered, and

concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford (S)-1-(9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinolin-11-yl)ethan-1-one (110 mg, 95% yield) as a yellow solid. LC-MS: *m/z* 303.1 [M+H]⁺.

Step 7:

- 5 A mixture of (S)-1-(9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinolin-11-yl)ethan-1-one (120 mg, 400 μ mol) and (R)-2-methylpropane-2-sulfinamide (144.3 mg, 1.2 mmol) in THF (4 mL) and Ti(OEt)₄ (2 mL) was stirred at 85 °C for 7 hours. LC-MS showed the reaction was completed. The mixture was cooled to 20 °C, diluted with DCM (150 mL) and water (30 mL), and filtered. The filtrate was separated, and the organic layer was dried over Na₂SO₄, filtered
- 10 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford (R)-N-((E)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinolin-11-yl)ethylidene)-2-methylpropane-2-sulfinamide (150 mg, 93% yield) as a yellow solid. LC-MS: *m/z* 406.1 [M+H]⁺.

Step 8:

- 15 To a stirred mixture of (R)-N-((E)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinolin-11-yl)ethylidene)-2-methylpropane-2-sulfinamide (150 mg, 369.9 μ mol) and CeCl₃ (54.7 mg, 222 μ mol) in MeOH (5 mL) was added NaBH₄ (28 mg, 740 μ mol) in portions at rt. The mixture was stirred at 20 °C for 5 minutes. LC-MS showed the product was formed. The mixture was quenched with water (50 mL) and extracted with DCM (40 mL
- 20 $\times$ 2). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford (R)-N-((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinolin-11-yl)ethyl)-2-methylpropane-2-sulfinamide (90 mg, 60% yield) as a white solid. LC-MS: *m/z* 408.1 [M+H]⁺.

Step 9:

- 25 To a stirred solution of (R)-N-((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinolin-11-yl)ethyl)-2-methylpropane-2-sulfinamide (90 mg, 220.9 μ mol) in EtOH (3 mL) was added 4 M HCl in EtOH (1 mL). The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed the reaction was completed. The mixture was basified with sat. NaHCO₃ (aq.) to pH ~ 9, extracted with DCM (40 mL $\times$ 2). The combined organic layers were dried
- 30 over Na₂SO₄, filtered, and concentrated *in vacuo* to afford (R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinolin-11-yl)ethan-1-amine (65 mg, 97% yield) as an off-white solid, which was used to the next step directly without further purification. LC-MS: *m/z* 304.1 [M+H]⁺.

Step 10:

- 35 To a stirred mixture of (R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinolin-11-yl)ethan-1-amine (45 mg, 148.4 μ mol) and methyl 6-chloro-3-fluoropicolinate (70.3 mg, 370.9 μ mol) in DMSO (3 mL) was

added K_2CO_3 (51.3 mg, 370.9 μmol) at rt. Then the mixture was stirred at 110 °C for 4 hours. LC-MS showed the product was formed. The mixture was purified by reverse phase chromatography to afford methyl 6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-

[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinolin-11-yl)ethyl)amino)picolinate (10 mg, 14% yield)

5 as a yellow solid. LC-MS: m/z 473.1 $[M+H]^+$.

Step 11:

To a mixture of methyl 6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-

[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinolin-11-yl)ethyl)amino)picolinate (10 mg, 21.2

μmol) in mixed solvents of THF and water (4 mL, 3:1) was added $LiOH \cdot H_2O$ (2.6 mg, 105.7 μmol).

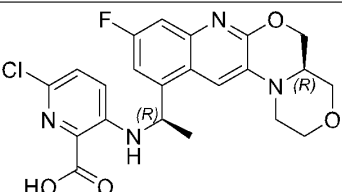
10 The mixture was stirred at 20 °C for 1 hour. LC-MS showed the reaction was completed. The mixture was acidified with HCl (1 M) to pH ~ 5 and concentrated *in vacuo*. The residue was purified by prep-HPLC to afford 6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-

[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinolin-11-yl)ethyl)amino)picolinic acid (3.8 mg, 39% yield) as an off-white solid. LC-MS: m/z 459.1 $[M+H]^+$.

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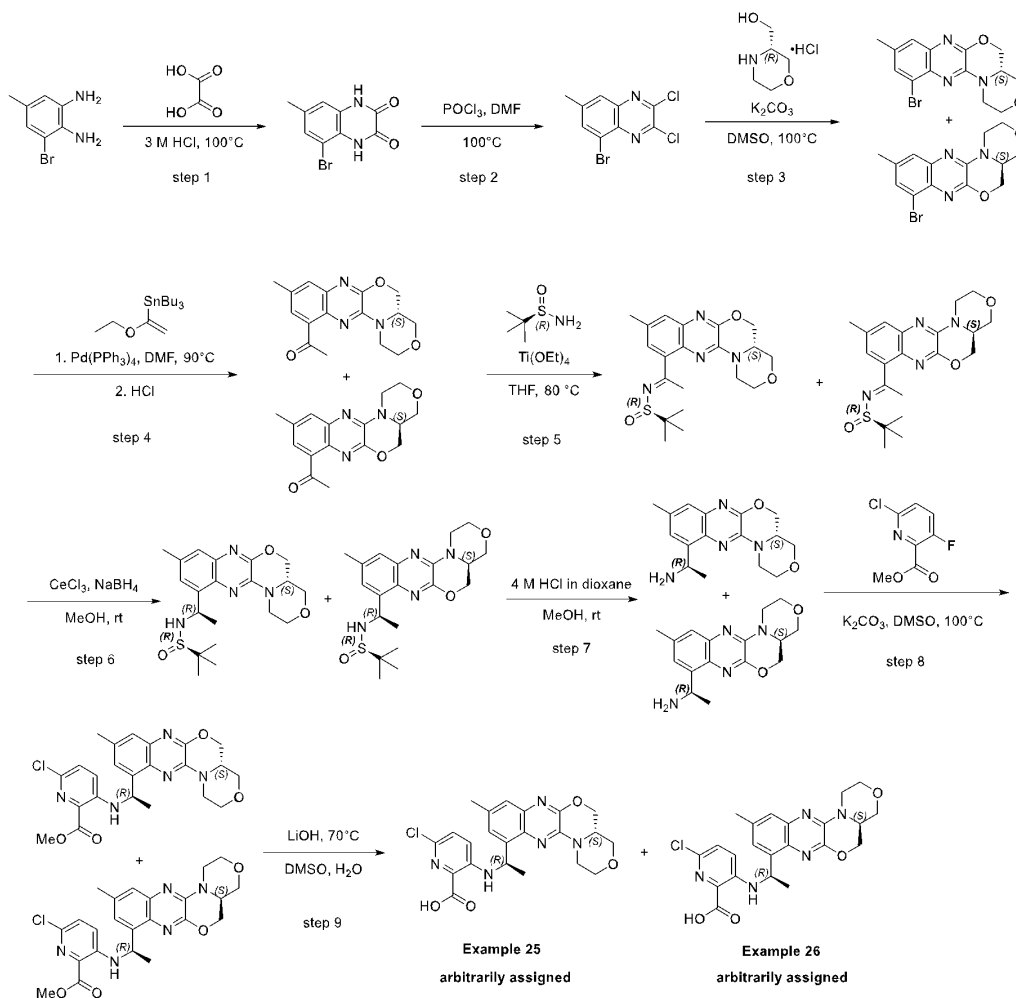
The following compound has been prepared in analogy to the representative procedures described for

Example 23.

ID	Structure	LC-MS: m/z $[M+H]^+$
Example 68		459.1

20

Examples 25 and 26



Step 1:

The mixture of 3-bromo-5-methylbenzene-1,2-diamine (7 g, 34.8 mmol) and oxalic acid (6.3 g, 69.6 mmol) in 3 M HCl aqueous solution (100 mL) was stirred at 100 °C for 24 hours. Then the mixture was filtered, and the filter cake was dried *in vacuo* to afford 5-bromo-7-methyl-1,4-dihydroquinoxaline-2,3-dione (6 g, 68% yield) as a black solid. LC-MS: m/z 254.9 $[M+H]^+$.

Step 2:

The mixture of 5-bromo-7-methyl-1,4-dihydroquinoxaline-2,3-dione (6.4 g, 25.1 mmol), $POCl_3$ (38.5 g, 250.9 mmol, 23.4 mL), and DMF (91.7 mg, 1.3 mmol) in DCE (80 mL) was stirred at 90 °C for 14 hours. Upon completion, the mixture was concentrated *in vacuo* and the residue was basified with sat. $NaHCO_3$ and extracted with DCM (100 mL $\times$ 3). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 0-10% MeOH in DCM to give 5-bromo-2,3-dichloro-7-methylquinoxaline (6 g, 82% yield) as a dark solid.

Step 3:

The mixture of 5-bromo-2,3-dichloro-7-methyl-quinoxaline (1 g, 3.4 mmol), (R)-morpholin-3-ylmethanol hydrochloride (631.35 mg, 4.11 mmol) and K_2CO_3 (1.4 g, 10.3 mmol) in DMSO (30 mL) was stirred at 100 °C for 16 hours. Upon completion, the mixture was diluted with EtOAc (80 mL) and washed with water (30 mL $\times$ 3). The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 0-5% EtOAc in DCM to afford a mixture of (S)-11-bromo-9-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxaline and (S)-8-bromo-10-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxaline (861 mg, 75% yield) as a yellow solid. LC-MS: m/z 336.0 $[M+H]^+$.

10 Step 4:

The mixture of (S)-11-bromo-9-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxaline and (S)-8-bromo-10-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxaline (861 mg, 2.6 mmol), tributyl(1-ethoxyvinyl)stannane (1.4 g, 3.8 mmol) and $Pd(PPh_3)_4$ (296 mg, 256.1 μ mol) in DMF (10 mL) was stirred at 90 °C with microwave irradiation for 3 hours. Upon completion, 3 M HCl (2 mL) was added, and the resulting mixture was stirred at rt for 30 minutes to hydrolyze the ether intermediate into ketone. Then the mixture was basified with sat. $NaHCO_3$, diluted with EtOAc (80 mL) and washed with water (40 mL $\times$ 3). The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 0-20% EtOAc in DCM to give a mixture of (S)-1-(9-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethan-1-one and (S)-1-(10-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-8-yl)ethan-1-one (532 mg, 69% yield) as a yellow solid. LC-MS: m/z 300.1 $[M+H]^+$.

20 Step 5:

The mixture of (S)-1-(9-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethan-1-one and (S)-1-(10-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-8-yl)ethan-1-one (532 mg, 1.8 mmol), (R)-2-methylpropane-2-sulfinamide (430.8 mg, 3.6 mmol) and $Ti(OEt)_4$ (3 mL) in THF (4 mL) was stirred at 80 °C for 16 hours. Upon completion, the mixture was quenched with water and extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 0-60% EtOAc in DCM to afford a mixture of (R)-2-methyl-N-((E)-1-((S)-9-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethylidene)propane-2-sulfinamide and (R)-2-methyl-N-((E)-1-((S)-10-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-8-yl)ethylidene)propane-2-sulfinamide (691 mg, 96% yield) as a yellow solid. LC-MS: m/z 403.2 $[M+H]^+$.

35 Step 6:

To a stirred mixture of (R)-2-methyl-N-((E)-1-((S)-9-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethylidene)propane-2-sulfinamide and (R)-2-methyl-N-((E)-1-((S)-10-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-8-yl)ethylidene)propane-2-sulfinamide (691 mg, 1.7 mmol) and CeCl₃ (423.1 mg, 1.7 mmol) in MeOH (5 mL) was added NaBH₄ (129.9 mg, 3.4 mmol) in portions and the resulting mixture was stirred at rt for 10 minutes. Upon completion, the mixture was quenched with water (20 mL) and extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo* to afford a mixture of (R)-2-methyl-N-((R)-1-((S)-9-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)propane-2-sulfinamide and (R)-2-methyl-N-((R)-1-((S)-10-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-8-yl)ethyl)propane-2-sulfinamide (620 mg, crude) as a yellow solid, which was used in the next step without further purification. LC-MS: m/z 405.2 [M+H]⁺.

Step 7:

To a stirred solution of (R)-2-methyl-N-((R)-1-((S)-9-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)propane-2-sulfinamide and (R)-2-methyl-N-((R)-1-((S)-10-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-8-yl)ethyl)propane-2-sulfinamide (632 mg, 1.6 mmol) in MeOH (3 mL) was dropwise added 4 M HCl in dioxane (0.5 mL) and the resulting mixture was stirred at rt for 10 minutes. Upon completion, the mixture was basified with sat. NaHCO₃ and extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo* to afford a mixture of (R)-1-((S)-9-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethan-1-amine and (R)-1-((S)-10-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-8-yl)ethan-1-amine (590 mg, crude) as a yellow solid, which was used in the next step without further purification. LC-MS: m/z 301.1 [M+H]⁺.

Step 8:

The mixture of (R)-1-((S)-9-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethan-1-amine and (R)-1-((S)-10-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-8-yl)ethan-1-amine (115 mg, 382.9 μmol) and K₂CO₃ (52.9 mg, 382.9 μmol) in DMSO (2 mL) was stirred at 100 °C with microwave irradiation for 1 hour. Upon completion, the mixture was diluted with EtOAc (30 mL) and washed with water (15 mL × 3). The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo* to give a mixture of methyl 6-chloro-3-(((R)-1-((S)-9-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)picolinate and methyl 6-chloro-3-(((R)-1-((S)-10-methyl-1,2,4a,5-tetrahydro-4H-

[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-8-yl)ethyl)amino)picolinate (179.9 mg, crude), which was used in the next step without further purification. LC-MS: m/z 470.1 $[M+H]^+$.

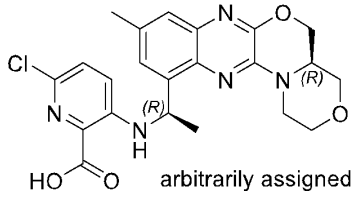
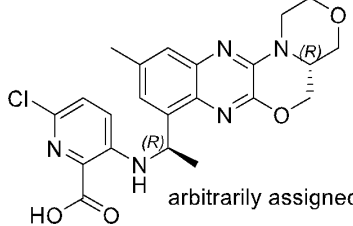
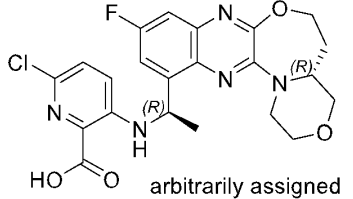
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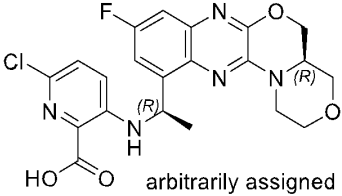
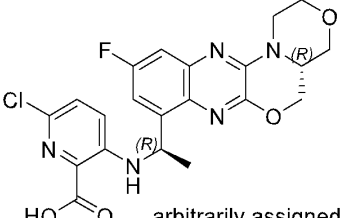
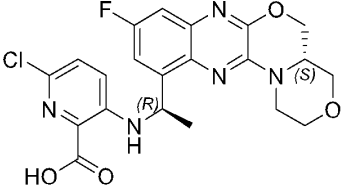
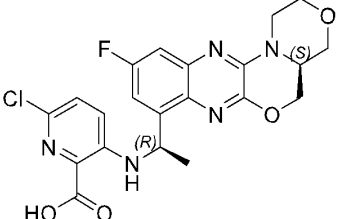
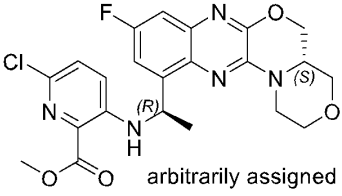
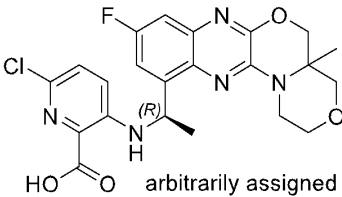
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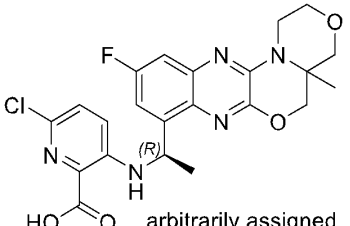
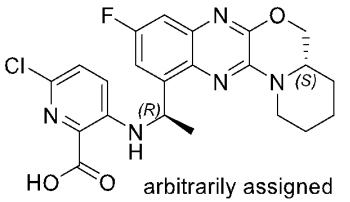
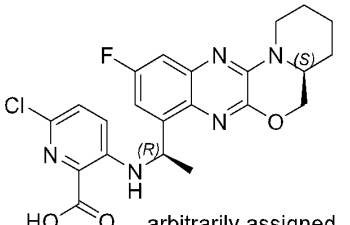
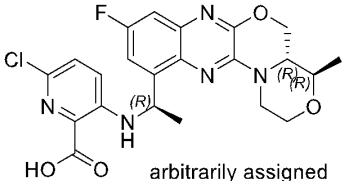
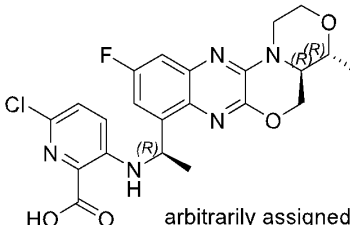
- 5 [1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)picolinate and methyl 6-chloro-3-(((R)-1-((S)-10-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-8-yl)ethyl)amino)picolinate (179.9 mg, 382.8 μ mol) and LiOH·H₂O (9.2 mg, 382.8 μ mol) in mixed solvents of THF and H₂O (3 mL, 2:1) was stirred at 70 °C with microwave irradiation for 20 minutes. Upon completion, the mixture was acidified with 1 M HCl then concentrated *in vacuo*.
- 10 The residue was purified by prep-HPLC to give two products, which were arbitrarily assigned as 6-chloro-3-(((R)-1-((S)-9-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)picolinic acid (22.7 mg, 13% yield, white solid) and 6-chloro-3-(((R)-1-((S)-10-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-8-yl)ethyl)amino)picolinic acid (15.7 mg, 9% yield, white solid). LC-MS: m/z 456.1 $[M+H]^+$.

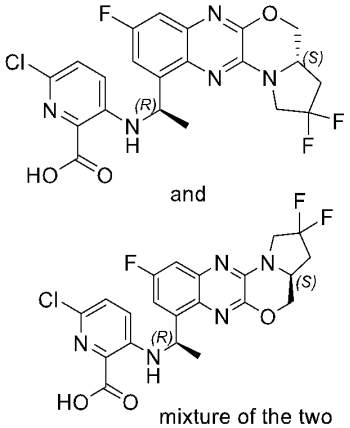
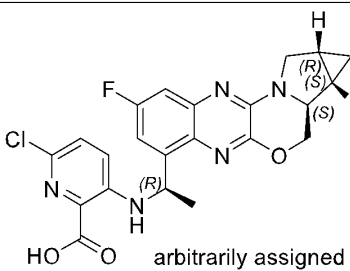
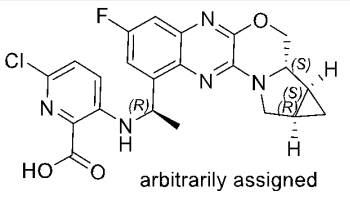
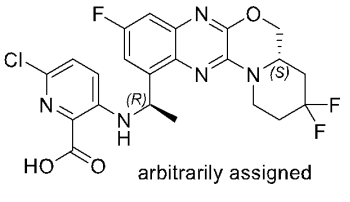
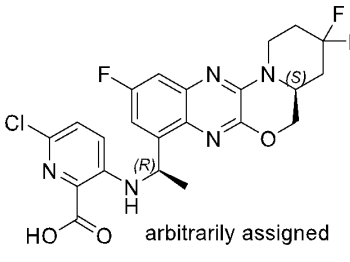
15

The following compounds have been prepared in analogy to the representative procedures described for **Examples 25 and 26**.

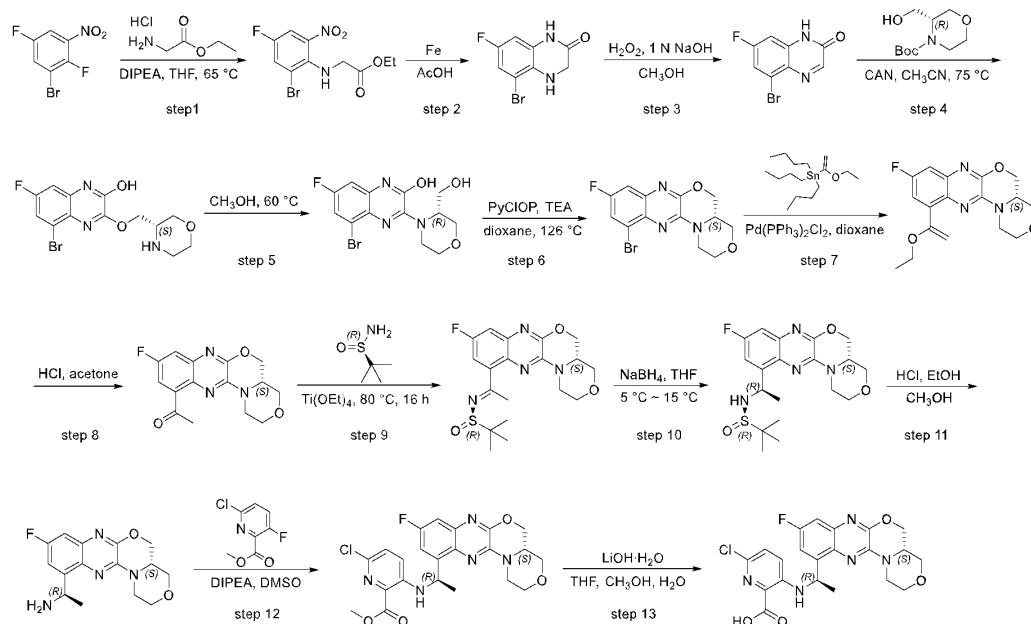
ID	Structure	LC-MS: m/z $[M+H]^+$
Example 27	 arbitrarily assigned	456.1
Example 28	 arbitrarily assigned	456.1
Example 45	 arbitrarily assigned	474.1

Example 46	 arbitrarily assigned	460.1
Example 47	 arbitrarily assigned	460.1
Example 66	 arbitrarily assigned	460.1
Example 67	 arbitrarily assigned	460.1
Example 70	 arbitrarily assigned	473.8
Example 94	 arbitrarily assigned	473.8

Example 95	 HO-C(=O) NH- (R) -C6H4-F arbitrarily assigned	473.8
Example 96	 HO-C(=O) NH- (R) -C6H4-F arbitrarily assigned	458.1
Example 97	 HO-C(=O) NH- (R) -C6H4-F arbitrarily assigned	458.1
Example 98	 HO-C(=O) NH- (R) -C6H4-F arbitrarily assigned	473.7
Example 99	 HO-C(=O) NH- (R) -C6H4-F arbitrarily assigned	473.7

Example 100	 mixture of the two	479.7
Example 190	 arbitrarily assigned	456.1
Example 191	 arbitrarily assigned	456.1
Example 192	 arbitrarily assigned	494.1
Example 193	 arbitrarily assigned	494.1

Example 66

**Step 1:**

To a solution of 1-bromo-2,5-difluoro-3-nitro-benzene (250 g, 1 mol) and DIPEA (474.3 g, 3.7 mol) in THF (2 L) was added ethyl 2-aminoacetate hydrochloride (204.4 g, 1.5 mol). The mixture was stirred at 65 °C for 16 hours before it was cooled to rt. The mixture was diluted with DCM (4 L) and then washed with brine (1 L × 2). The organic phase was dried over Na₂SO₄, filtered and concentrated to afford ethyl 2-(2-bromo-4-fluoro-6-nitro-anilino)acetate (270 g, crude) as a yellow solid. LC-MS: m/z 321.0 [M+H]⁺.

Step 2:

A mixture of ethyl 2-(2-bromo-4-fluoro-6-nitro-anilino)acetate (270 g, 841.1 mmol) and Fe (235.5 g, 4.2 mol) in AcOH (2 L) was stirred at 85 °C for 10 hours under N₂. The mixture was cooled to rt before it was concentrated under reduced pressure to afford a residue. The residue was suspended in DCM (3 L) and then filtered. The organic phase was washed with aq. NaHCO₃ (400 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated to afford 5-bromo-7-fluoro-3,4-dihydro-1H-quinoxalin-2-one (175 g, crude) as a light yellow solid. LC-MS: m/z 244.9 [M+H]⁺.

Step 3:

To a solution of 5-bromo-7-fluoro-3,4-dihydro-1H-quinoxalin-2-one (175 g, 714.2 mmol) in aq. NaOH (1 N, 1500 mL) and methanol (1500 mL) was added hydrogen peroxide (283.3 g, 2.5 mol, 30% purity). The mixture was stirred at 85 °C for 10 hours before it was cooled to rt. The mixture was concentrated and adjusted pH to 3 with 1 N HCl (aq.). The mixture was filtered and the filter cake was washed with water (500 mL). The filter cake was purified by triturated eluting with

CH₃OH (300 mL) to afford 5-bromo-7-fluoro-1H-quinoxalin-2-one (87 g, 50% yield) as a yellow solid. LC-MS: m/z 242.8 [M+H]⁺.

Step 4:

To a solution of 5-bromo-7-fluoro-1H-quinoxalin-2-one (26.5 g, 109 mmol) in CH₃CN (400 mL) was added CAN (179.3 g, 327.1 mmol) and tert-butyl (3R)-3-(hydroxymethyl)morpholine-4-carboxylate (47.4 g, 218.1 mmol). The mixture was stirred at 75 °C for 2 hours. The mixture was concentrated and then diluted with EtOAc (3 L). The mixture was adjusted to pH 7 with 10% NaHCO₃ (aq.). The suspension was filtered. The aqueous phase was extracted with EtOAc (1.5 L × 3) and a mixed solvent of CH₂Cl₂ (500 mL) and CH₃OH (50 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to afford crude product which was combined with the filter cake to afford 5-bromo-7-fluoro-3-[(3S)-morpholin-3-yl]methoxy]-1H-quinoxalin-2-one (300 g, crude) as a yellow solid. LC-MS: m/z 359.8 [M+H]⁺.

Step 5:

A solution of 5-bromo-7-fluoro-3-[(3S)-morpholin-3-yl]methoxy]-1H-quinoxalin-2-one (103.3 g, 288.4 mmol) in methanol (1.2 L) was stirred at 70 °C for 16 hours. The mixture was filtered. The filter cake was suspended in CH₃OH (3 L) and the mixture was stirred at 20 °C for 0.5 hour. The mixture was filtered and the filter cake was washed with CH₃OH (500 mL). to give crude product. The crude was purified by column chromatography on silica gel to afford 5-bromo-7-fluoro-3-[(3R)-3-(hydroxymethyl)morpholin-4-yl]-1H-quinoxalin-2-one (33.8 g) as a yellow solid. LC-MS: m/z 357.8 [M+H]⁺.

Step 6:

To a solution of 5-bromo-7-fluoro-3-[(3R)-3-(hydroxymethyl)morpholin-4-yl]-1H-quinoxalin-2-one (16.4 g, 45.8 mmol) in dioxane (167 mL) was added TEA (34.7 g, 343.4 mmol) and PyCLOP (28.9 g, 68.7 mmol). The mixture was degassed with a stream of N₂ for three times and then stirred at 127 °C for 16 hours. The mixture was concentrated, diluted with DCM (1.6 L) and washed with brine (400 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by column chromatography on silica gel to afford (7S)-16-bromo-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaene (30.7 g, 98.5% yield) as a yellow solid. LC-MS: m/z 339.8 [M+H]⁺.

Step 7:

To a solution of (7S)-16-bromo-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaene (14.8 g, 43.6 mmol) in dioxane was added tributyl(1-ethoxyvinyl)stannane (23.6 g, 65.4 mmol) and Pd(PPh₃)₂Cl₂ (6.1 g, 8.7 mmol). The mixture was degassed with a stream of N₂ for three times and then stirred at 100 °C for 16 hours. The mixture was quenched with KF solution (150 mL) and filtered. The filter cake was suspended in DCM (1.5 L) and stirred at 20 °C for 0.5 hour. The mixture was filtered. The filtrate was washed with water (300 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated to afford crude

product. The crude was purified by column chromatography on silica gel to afford (7S)-16-(1-ethoxyvinyl)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaene (30.3 g, crude) as a yellow solid. LC-MS: m/z 331.9 [M+H]⁺.

Step 8:

- 5 To a solution of (7S)-16-(1-ethoxyvinyl)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaene (30.3 g, 91.4 mmol) in acetone (300 mL) was added 2 N HCl (aq., 90 mL). The mixture was stirred at 20 °C for 5 minutes, diluted with DCM (1.5 L) and washed with 10% NaHCO₃ (aq., 300 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by column
- 10 chromatography on silica gel to afford 1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethanone (26 g, 93.7% yield) as a yellow solid LC-MS: m/z 303.9 [M+H]⁺.

Step 9:

- To a solution of 1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-
- 15 1(18),10,12(17),13,15-pentaen-16-yl]ethanone (10 g, 32.9 mmol) in titanium ethoxide (70 mL) and THF (80 mL) was added (R)-2-methylpropane-2-sulfinamide (11.9 g, 98.9 mmol). The mixture was stirred at 80 °C for 16 hours under N₂. The mixture was diluted with EtOAc (1.2 L) and water (360 mL). The mixture was stirred at 20 °C for 0.5 hour, filtered and the organic layer was washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude was
- 20 purified by column chromatography on silica gel to afford (R)-N-((E)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethylidene)-2-methylpropane-2-sulfinamide (25.7 g, 95.8% yield) as a yellow solid. LC-MS: m/z 406.9 [M+H]⁺.

Step 10:

- To a solution of (R)-N-((E)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-
- 25 [1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethylidene)-2-methylpropane-2-sulfinamide (12.8 g, 31.5 mmol) and CeCl₃ (3.1 g, 12.6 mmol) in methanol (160 mL) was added NaBH₄ (1.8 g, 47.2 mmol) at 5-15 °C. The mixture was then stirred at 5-15 °C for 20 minutes, diluted with DCM (1.2 L) and washed with brine (200 mL × 2). The organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by column chromatography
- 30 on silica gel to afford (R)-N-[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]-2-methylpropane-2-sulfinamide (22 g, 85.5% yield) as a yellow solid. LC-MS: m/z 406.9 [M+H]⁺.

Step 11:

- To a solution of (R)-N-[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-
- 35 triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]-2-methylpropane-2-sulfinamide (16 g, 39.1 mmol) in methanol (170 mL) was added a solution of HCl in EtOH (4 N, 15 mL). The mixture was stirred at 20 °C for 5 minutes. The mixture was diluted with water

(150 mL), adjusted to pH 7 with 10% NaHCO₃ (aq.) and extracted with DCM (500 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to afford (1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethanamine (12.4 g, crude) as a yellow solid. LC-MS: m/z 304.9 [M+H]⁺.

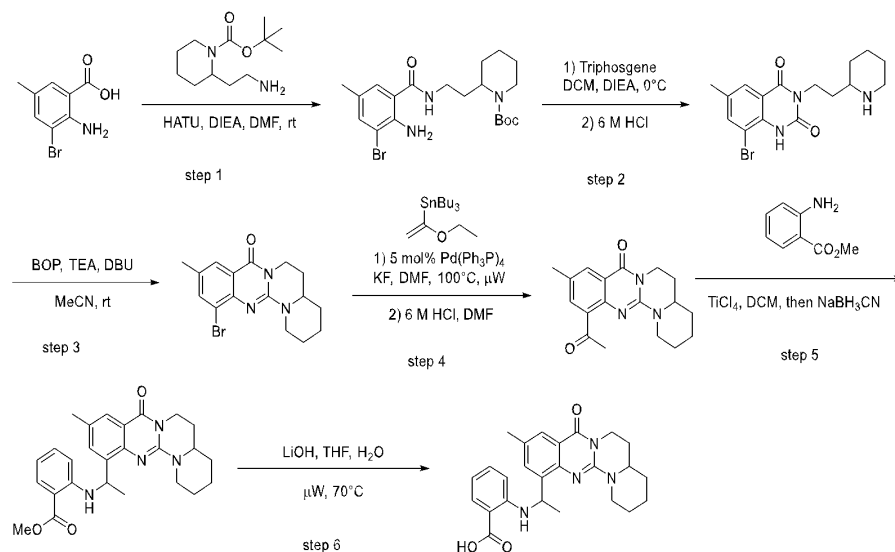
5 **Step 12:**

To a solution of (1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethanamine (6.2 g, 20.3 mmol) and TEA (5.4 g, 52.9 mmol) in DMSO (60 mL) was added methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (5.8 g, 30.6 mmol). The mixture was stirred at 100 °C for 16 hours. The mixture was diluted with EtOAc (700 mL) and
 10 washed with brine (150 mL × 4). The organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by column chromatography on silica gel to afford methyl 6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)picolinate (15.7 g, 81.3% yield) as a yellow solid. LC-MS: m/z 473.8 [M+H]⁺.

15 **Step 13:**

To a solution of methyl 6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)picolinate (7.5 g, 15.8 mmol) in THF (150 mL), methanol (30 mL) and water (30 mL) was added LiOH·H₂O (3.3 g, 79.1 mmol). The mixture was stirred at 20 °C for 50 minutes. The mixture was adjusted to pH = 5 with 1N HCl
 20 (aq.), diluted with brine (150 mL) and extracted with EtOAc (300 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by reverse phase chromatography to afford 6-chloro-3-(((1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl)amino)pyridine-2-carboxylic acid (10.2 g, 70.1% yield) as a light yellow solid. LC-MS: m/z
 25 459.8 [M+H]⁺.

Example 29



Step 1:

To a stirred mixture of 2-amino-3-bromo-5-methylbenzoic acid (920.2 mg, 4 mmol), tert-butyl 2-(2-aminoethyl)piperidine-1-carboxylate (1 g, 4.4 mmol) and HATU (2.3 g, 6 mmol) in anhydrous DMF (15 mL) was added DIPEA (1.0 g, 8.0 mmol) and the resulting mixture was stirred at rt for 1 hour. Upon completion, the mixture was diluted with EtOAc (50 mL) and washed with water (25 mL $\times$ 3). The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford tert-butyl 2-[2-[(2-amino-3-bromo-5-methylbenzoyl)amino]ethyl]piperidine-1-carboxylate (1.5 g, 85% yield) as a white solid. LC-MS: m/z 440.1 $[\text{M}+\text{H}]^+$.

Step 2:

To a stirred mixture of tert-butyl 2-[2-[(2-amino-3-bromo-5-methylbenzoyl)amino]ethyl]piperidine-1-carboxylate (1.5 g, 3.4 mmol) and DIPEA (2.2 g, 17.1 mmol, 3 mL) in DCM (20 mL) at 0 °C was dropwise added a solution of triphosgene (506 mg, 1.7 mmol) in DCM (2 mL) and the resulting mixture was stirred at 0 °C for 1 hour. Then the mixture was quenched with water, followed by treatment of 6 M HCl at 60 °C for 1 hour to remove Boc protection. Upon completion, the mixture was basified with sat. NaHCO_3 and extracted with DCM (50 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo* to afford 8-bromo-6-methyl-3-(2-(piperidin-2-yl)ethyl)quinazoline-2,4(1H,3H)-dione (300 mg, 24% yield) as a white solid. LC-MS: m/z 366.0 $[\text{M}+\text{H}]^+$.

Step 3:

The mixture of 8-bromo-6-methyl-3-(2-(piperidin-2-yl)ethyl)quinazoline-2,4(1H,3H)-dione (300 mg, 0.8 mmol), 1H-benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) (470 mg, 1.1 mmol) and DBU (187 mg, 1.2 mmol) in MeCN (15 mL) was stirred at rt for 2 hours.

Then the mixture was concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford 12-bromo-10-methyl-2,3,4,4a,5,6-hexahydro-1H,8H-pyrido[1',2':3,4]pyrimido[2,1-b]quinazolin-8-one (150 mg, 54% yield) as a white solid. LC-MS: m/z 348.0 [M+H]⁺.

Step 4:

- 5 The mixture of 12-bromo-10-methyl-2,3,4,4a,5,6-hexahydro-1H,8H-pyrido[1',2':3,4]pyrimido[2,1-b]quinazolin-8-one (50 mg, 143.6 μ mol), Pd(PPh₃)₄ (16.6 mg, 14.4 μ mol) and KF (25 mg, 430.7 μ mol) in DMF (4 mL) was stirred at 100 °C with microwave irradiation for 1 hour. Then 6 M HCl (1 mL) was added, and the mixture was stirred at rt for 30 minutes. The mixture was basified with sat. NaHCO₃ and extracted with EtOAc (15 mL $\times$ 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford 12-acetyl-10-methyl-2,3,4,4a,5,6-hexahydro-1H,8H-pyrido[1',2':3,4]pyrimido[2,1-b]quinazolin-8-one (40 mg, 89% yield) as a colorless foam. LC-MS: m/z 312.1 [M+H]⁺.

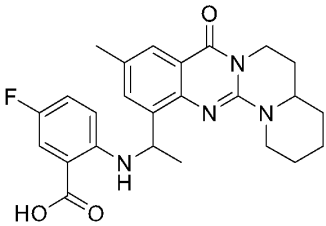
Step 5:

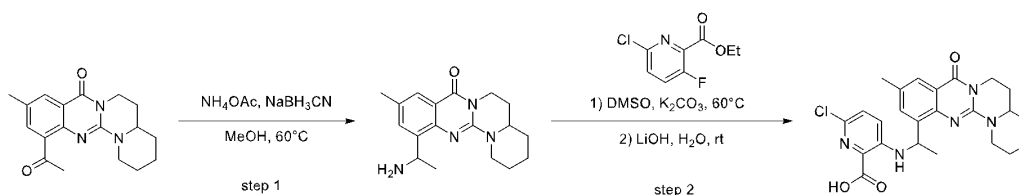
- 15 To a stirred mixture of methyl 2-aminobenzoate (750.00 mg, 4.96 mmol) 12-acetyl-10-methyl-2,3,4,4a,5,6-hexahydro-1H,8H-pyrido[1',2':3,4]pyrimido[2,1-b]quinazolin-8-one (30 mg, 96.4 μ mol) in anhydrous DCM (4 mL) at 0 °C was added TiCl₄ (2 mL) and the resulting mixture was stirred at rt for 1 hour. Then NaBH₃CN (121 mg, 1.9 mmol) was added in portions and the resulting mixture was stirred at rt for 1 hour. Upon completion, water (20 mL) was added to quench the reaction and the mixture was extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give methyl 2-((1-(10-methyl-8-oxo-2,3,4,4a,5,6-hexahydro-1H,8H-pyrido[1',2':3,4]pyrimido[2,1-b]quinazolin-12-yl)ethyl)amino)benzoate (28 mg, 65% yield) as a colorless foam. LC-MS: m/z 447.2 [M+H]⁺.

25 **Step 6:**

- The mixture of methyl 2-((1-(10-methyl-8-oxo-2,3,4,4a,5,6-hexahydro-1H,8H-pyrido[1',2':3,4]pyrimido[2,1-b]quinazolin-12-yl)ethyl)amino)benzoate (28 mg, 62.8 μ mol) and LiOH·H₂O (15 mg, 0.6 mmol) in mixed solvents of THF and H₂O (2 mL, 2:1) was stirred at 70 °C with microwave irradiation for 1 hour. Upon completion, the mixture was concentrated *in vacuo* and the residue was purified by prep-HPLC to give 2-((1-(10-methyl-8-oxo-2,3,4,4a,5,6-hexahydro-1H,8H-pyrido[1',2':3,4]pyrimido[2,1-b]quinazolin-12-yl)ethyl)amino)benzoic acid (5 mg, 18% yield) as a white solid. LC-MS: m/z 433.2 [M+H]⁺.

- The following compound has been prepared in analogy to the representative procedures described for
35 **Example 29.**

ID	Structure	LC-MS: m/z [M+H] ⁺
Example 30		451.2

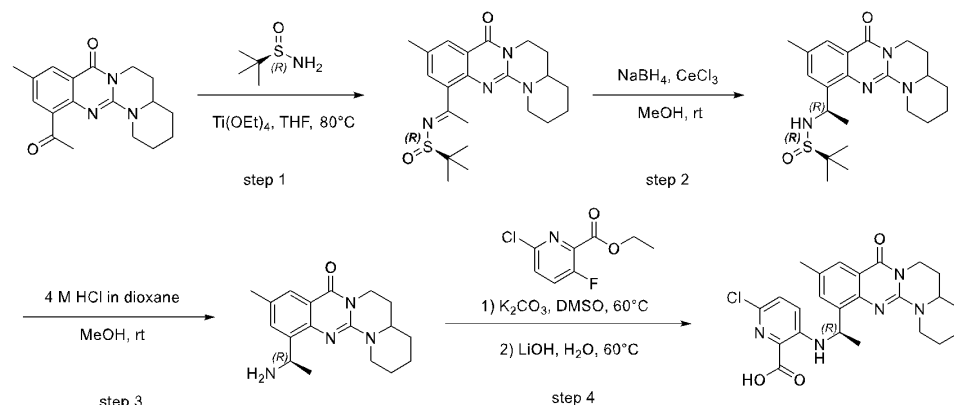
Example 31**Step 1:**

- 5 To a stirred mixture of 12-acetyl-10-methyl-2,3,4,4a,5,6-hexahydro-1H,8H-pyrido[1',2':3,4]pyrimido[2,1-b]quinazolin-8-one (50 mg, 161 μ mol) and NH_4OAc (123.8 mg, 1.6 mmol) in MeOH (3 mL) at 60 °C was added sodium cyanoborohydride (100.9 mg, 1.6 mmol) in portions and the resulting mixture was stirred at 60 °C for 1 hour. Upon completion, the reaction was quenched with water and the mixture was extracted with DCM (15 mL $\times$ 3). The combined organic
- 10 layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo* to give 12-(1-aminoethyl)-10-methyl-2,3,4,4a,5,6-hexahydro-1H,8H-pyrido[1',2':3,4]pyrimido[2,1-b]quinazolin-8-one (50 mg, crude) as a white solid, which was used in the next step without further purification. LC-MS: m/z 313.2 [M+H]⁺.

Step 2:

- 15 The mixture of 12-(1-aminoethyl)-10-methyl-2,3,4,4a,5,6-hexahydro-1H,8H-pyrido[1',2':3,4]pyrimido[2,1-b]quinazolin-8-one (20 mg, 64 μ mol), ethyl 6-chloro-3-fluoropicolinate (26 mg, 128 μ mol) and K_2CO_3 (17.7 mg, 128 μ mol) in DMSO (1 mL) was stirred at 60 °C for 8 hours. After the completion of the first step, a solution of $\text{LiOH}\cdot\text{H}_2\text{O}$ (7.4 mg, 320 μ mol) in H_2O (1 mL) was added and the mixture was stirred at rt overnight. Then the mixture was acidified with 3.0 M HCl, and
- 20 the mixture was concentrated *in vacuo*. The residue was purified by prep-HPLC to give 6-chloro-3-((1-(10-methyl-8-oxo-2,3,4,4a,5,6-hexahydro-1H,8H-pyrido[1',2':3,4]pyrimido[2,1-b]quinazolin-12-yl)ethyl)amino)picolinic acid (2 mg, 7% yield) as a white solid. LC-MS: m/z 467.2 [M+H]⁺.

Example 32



Step 1:

The mixture of 12-acetyl-10-methyl-2,3,4,4a,5,6-hexahydro-1H,8H-pyrido[1',2':3,4]pyrimido[2,1-b]quinazolin-8-one (250 mg, 0.8 mmol), (R)-2-methylpropane-2-sulfonamide (194 mg, 1.6 mmol) and Ti(OEt)₄ (2 mL) in THF (2 mL) was stirred at 80 °C for 16 hours. Upon completion, the reaction was quenched with water and the mixture was extracted with EtOAc (20 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo* to afford (R)-2-methyl-N-((E)-1-(10-methyl-8-oxo-2,3,4,4a,5,6-hexahydro-1H,8H-pyrido[1',2':3,4]pyrimido[2,1-b]quinazolin-12-yl)ethylidene)propane-2-sulfonamide (331 mg, crude), which was used in the next step without further purification. LC-MS: m/z 415.2 [M+H]⁺.

Step 2:

To a stirred mixture of (NE,R)-2-methyl-N-[1-(14-methyl-11-oxo-2,10,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),12(17),13,15-tetraen-16-yl)ethylidene]propane-2-sulfonamide (331 mg, 0.8 mmol) and CeCl₃ (148 mg, 0.6 mmol) in MeOH (4 mL) was carefully added NaBH₄ (61 mg, 1.6 mmol) in portions and the resulting mixture was stirred at rt for 30 minutes. Then the reaction was quenched with water and the mixture was extracted with DCM (20 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 0-10% MeOH in DCM to afford (R)-2-methyl-N-((1R)-1-(10-methyl-8-oxo-2,3,4,4a,5,6-hexahydro-1H,8H-pyrido[1',2':3,4]pyrimido[2,1-b]quinazolin-12-yl)ethyl)propane-2-sulfonamide (313 mg, 94% yield) as a yellow solid. LC-MS: m/z 417.2 [M+H]⁺.

Step 3:

To a stirred mixture of (R)-2-methyl-N-((1R)-1-(10-methyl-8-oxo-2,3,4,4a,5,6-hexahydro-1H,8H-pyrido[1',2':3,4]pyrimido[2,1-b]quinazolin-12-yl)ethyl)propane-2-sulfonamide (313 mg, 751 μmol) in MeOH (5 mL) was added 4 M HCl in dioxane (2 mL) and the resulting mixture was stirred at rt for 30 minutes. Then the mixture was basified with sat. NaHCO₃ and extracted with DCM (20 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo* to

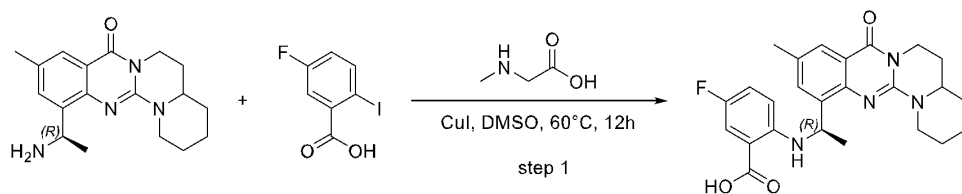
afford 12-((R)-1-aminoethyl)-10-methyl-2,3,4,4a,5,6-hexahydro-1H,8H-pyrido[1',2':3,4]pyrimido[2,1-b]quinazolin-8-one (370 mg, crude), which was used in the next step without further purification. LC-MS: m/z 313.2 $[M+H]^+$.

Step 4:

- 5 The mixture of ethyl 6-chloro-3-fluoro-pyridine-2-carboxylate (20.3 mg, 100 μ mol), 12-((R)-1-aminoethyl)-10-methyl-2,3,4,4a,5,6-hexahydro-1H,8H-pyrido[1',2':3,4]pyrimido[2,1-b]quinazolin-8-one (30 mg, 96 μ mol) and K_2CO_3 (56 mg, 400 μ mol) in DMSO (2 mL) was stirred at 60 °C for 9 hours. Upon completion, a solution of $LiOH \cdot H_2O$ (50 mg, 2.2 mmol) in water (1 mL) was added and the resulting mixture was stirred at 60 °C for 2 hours. Then the mixture was acidified with 3 M HCl
- 10 and extracted with DCM (20 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by prep-HPLC to afford 6-chloro-3-(((1R)-1-(10-methyl-8-oxo-2,3,4,4a,5,6-hexahydro-1H,8H-pyrido[1',2':3,4]pyrimido[2,1-b]quinazolin-12-yl)ethyl)amino)picolinic acid (3.2 mg, 7% yield) as a white solid. LC-MS: m/z 468.1 $[M+H]^+$.

15

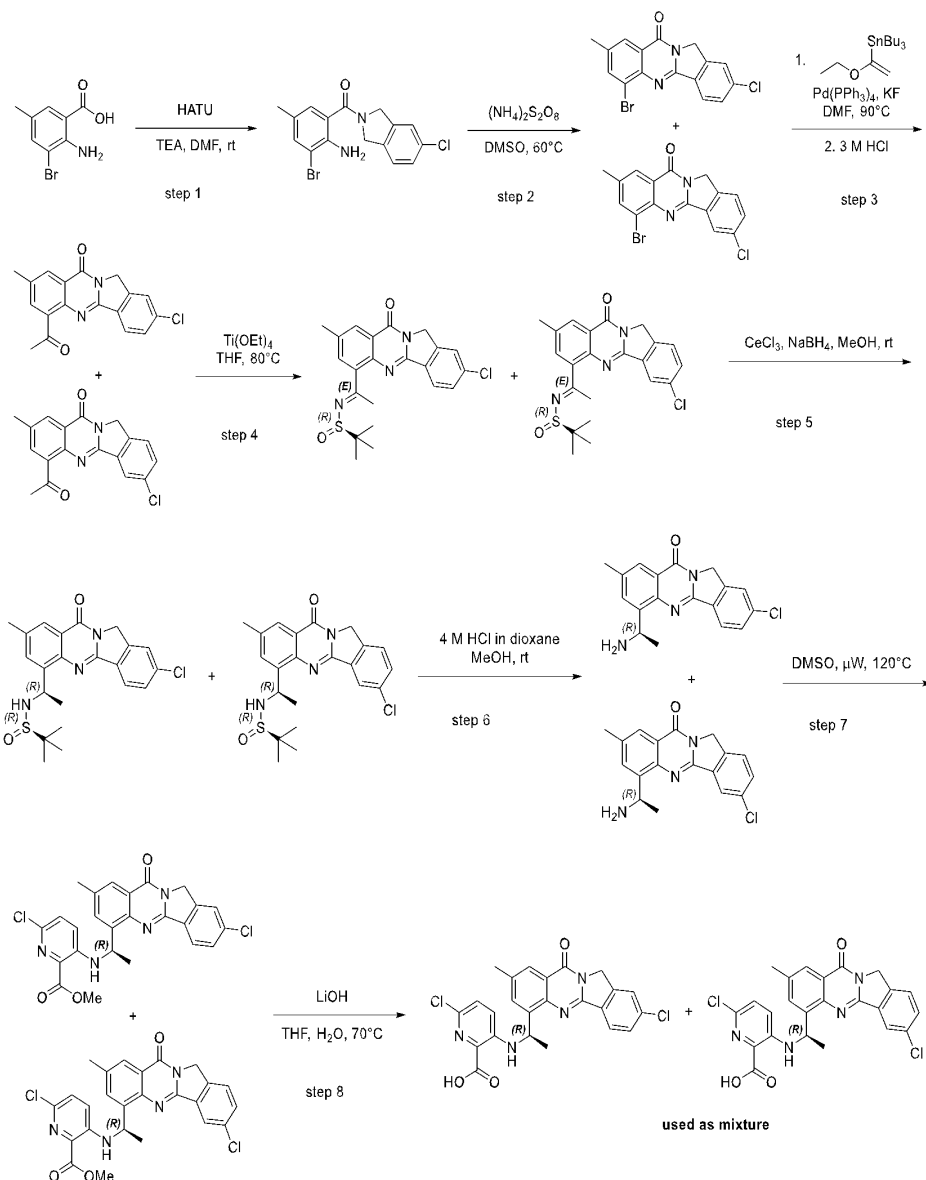
Example 33



Step 1:

- The mixture of CuI (5.3 mg, 28 μ mol) and sarcosine (2.7 mg, 30 μ mol) in DMSO (1 mL) was stirred at
- 20 rt for 15 minutes. Then 12-((R)-1-aminoethyl)-10-methyl-2,3,4,4a,5,6-hexahydro-1H,8H-pyrido[1',2':3,4]pyrimido[2,1-b]quinazolin-8-one (35 mg, 112 μ mol), 5-fluoro-2-iodo-benzoic acid (297 mg, 1.1 mmol) and K_2CO_3 (55 mg, 400 μ mol) was added and the resulting mixture was stirred at 60 °C for 36 hours. Then the mixture was acidified with 3 M HCl and extracted with DCM (20 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo*.
- 25 The residue was purified by prep-HPLC to afford 5-fluoro-2-(((1R)-1-(10-methyl-8-oxo-2,3,4,4a,5,6-hexahydro-1H,8H-pyrido[1',2':3,4]pyrimido[2,1-b]quinazolin-12-yl)ethyl)amino)benzoic acid (7.1 mg, 14% yield) as a white solid. LC-MS: m/z 451.2 $[M+H]^+$.

Example 34



5

Step 1:

The mixture of 2-amino-3-bromo-5-methylbenzoic acid (1.65 g, 7.2 mmol), 5-chloroisindoline (1 g, 6.5 mmol), HATU (3.7 g, 9.8 mmol) and TEA (2 g, 19.5 mmol) in DMF (20 mL) was stirred at rt for 2 hours. The mixture was diluted with EtOAc (80 mL) and washed with water (30 mL $\times$ 3). The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford (2-amino-3-bromo-5-methylphenyl)(5-chloroisindolin-2-yl)methanone (1.6 g, 67% yield) as a white solid. LC-MS: m/z 365.0 $[\text{M}+\text{H}]^+$.

Step 2:

The mixture of (2-amino-3-bromo-5-methylphenyl)(5-chloroisindolin-2-yl)methanone (1.6 g, 4.4 mmol) and (NH₄)₂S₂O₈ (4 g, 17.5 mmol) in DMSO (30 mL) was stirred at 60 °C for 2 hours. The mixture was diluted with water (60 mL) and precipitation was collected by filtration. The filter cake
5 was dried *in vacuo* to give a mixture of 6-bromo-2-chloro-8-methylisindolo[1,2-b]quinazolin-10(12H)-one and 6-bromo-3-chloro-8-methylisindolo[1,2-b]quinazolin-10(12H)-one (total 1.4 g, 88% yield) which was used as a mixture until the final step. LC-MS: m/z 360.9 [M+H]⁺.

Step 3:

The mixture of 6-bromo-2-chloro-8-methylisindolo[1,2-b]quinazolin-10(12H)-one, 6-bromo-3-
10 chloro-8-methylisindolo[1,2-b]quinazolin-10(12H)-one (mixture of the two, 720 mg, 2 mmol), tributyl(1-ethoxyvinyl)stannane (1.1 g, 3 mmol), Pd(PPh₃)₄ (231 mg, 200 μmol) and KF (232 mg, 4 mmol) in DMF (15 mL) was stirred at 90 °C for 16 hours. Upon completion, 3 M HCl (5 mL) was added to hydrolyze the ether intermediate into ketone product. Upon completion, the mixture was basified with sat. NaHCO₃ and extracted with EtOAc (50 mL × 3). The combined organic layers were
15 dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 0-5% MeOH in DCM to afford a mixture of 6-acetyl-2-chloro-8-methylisindolo[1,2-b]quinazolin-10(12H)-one and 6-acetyl-3-chloro-8-methylisindolo[1,2-b]quinazolin-10(12H)-one (total 412 mg, 63% yield). LC-MS: m/z 325.0 [M+H]⁺.

Step 4:

The mixture of 6-acetyl-2-chloro-8-methylisindolo[1,2-b]quinazolin-10(12H)-one and 6-acetyl-3-
20 chloro-8-methylisindolo[1,2-b]quinazolin-10(12H)-one (mixture of the two, 412 mg, 1.3 mmol), (R)-2-methylpropane-2-sulfinamide (307 mg, 2.5 mmol) and titanium (IV) ethoxide (6 mL) in THF (6 mL) was stirred at 80 °C for 16 hours. The reaction was quenched with water (30 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered,
25 and concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford a mixture of (R,E)-N-(1-(2-chloro-8-methyl-10-oxo-10,12-dihydroisindolo[1,2-b]quinazolin-6-yl)ethylidene)-2-methylpropane-2-sulfinamide and (R,E)-N-(1-(3-chloro-8-methyl-10-oxo-10,12-dihydroisindolo[1,2-b]quinazolin-6-yl)ethylidene)-2-methylpropane-2-sulfinamide (mixture of the two, 131 mg, 24% yield). LC-MS: m/z 428.1 [M+H]⁺.

Step 5:

To a stirred mixture of (R,E)-N-(1-(2-chloro-8-methyl-10-oxo-10,12-dihydroisindolo[1,2-
b]quinazolin-6-yl)ethylidene)-2-methylpropane-2-sulfinamide and (R,E)-N-(1-(3-chloro-8-methyl-10-
oxo-10,12-dihydroisindolo[1,2-b]quinazolin-6-yl)ethylidene)-2-methylpropane-2-sulfinamide
(mixture of the two, 131 mg, 306 μmol) and CeCl₃ (75 mg, 306 μmol) in MeOH (5 mL) was
35 added NaBH₄ (23 mg, 612 μmol) in portions. The resulting mixture was stirred at rt for 30 minutes. The mixture was quenched with water (15 mL) and extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo* to give a

mixture of (R)-N-((R)-1-(2-chloro-8-methyl-10-oxo-10,12-dihydroisoindolo[1,2-b]quinazolin-6-yl)ethyl)-2-methylpropane-2-sulfinamide and (R)-N-((R)-1-(3-chloro-8-methyl-10-oxo-10,12-dihydroisoindolo[1,2-b]quinazolin-6-yl)ethyl)-2-methylpropane-2-sulfinamide (mixture of the two, 130 mg), which was used in the next step without further purification. LC-MS: m/z 430.1 [M+H]⁺.

5 **Step 6:**

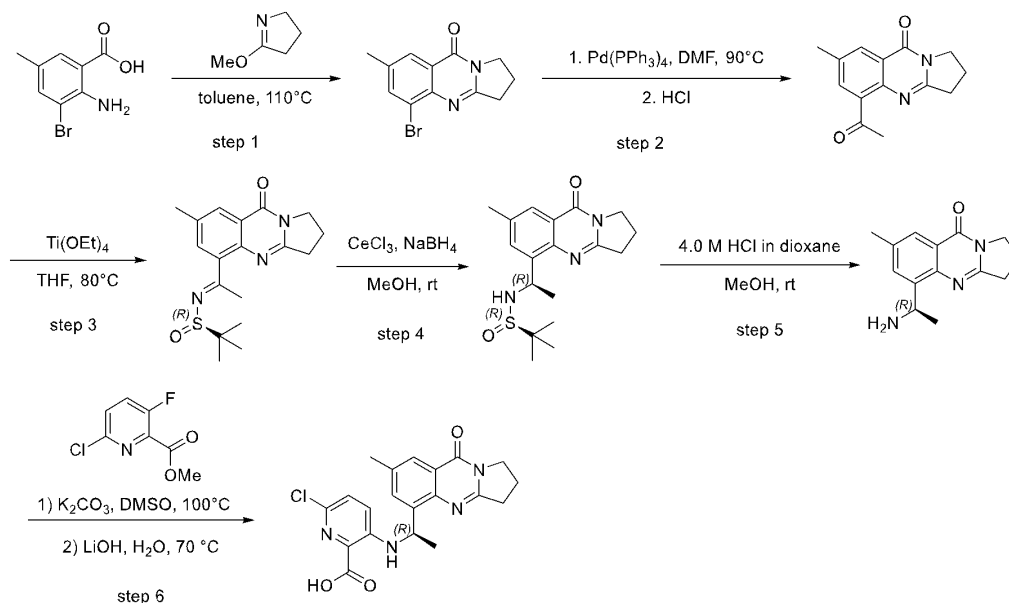
To a stirred mixture of (R)-N-((R)-1-(2-chloro-8-methyl-10-oxo-10,12-dihydroisoindolo[1,2-b]quinazolin-6-yl)ethyl)-2-methylpropane-2-sulfinamide and (R)-N-((R)-1-(3-chloro-8-methyl-10-oxo-10,12-dihydroisoindolo[1,2-b]quinazolin-6-yl)ethyl)-2-methylpropane-2-sulfinamide (mixture of the two, 130 mg, 0.3 mmol) in MeOH was dropwise added 4 M HCl in dioxane (1 mL) and the
10 resulting mixture was stirred at rt for 20 minutes. The mixture was basified with sat. NaHCO₃ and extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo* to give a mixture of (R)-6-(1-aminoethyl)-2-chloro-8-methylisoindolo[1,2-b]quinazolin-10(12H)-one and (R)-6-(1-aminoethyl)-3-chloro-8-methylisoindolo[1,2-b]quinazolin-10(12H)-one (mixture of the two, 100 mg), which was used in the
15 next step without further purification. LC-MS: m/z 326.1 [M+H]⁺.

Step 7:

The mixture of (R)-6-(1-aminoethyl)-2-chloro-8-methylisoindolo[1,2-b]quinazolin-10(12H)-one, (R)-6-(1-aminoethyl)-3-chloro-8-methylisoindolo[1,2-b]quinazolin-10(12H)-one (mixture of the two, 50 mg, 153 μmol) and methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (58.2 mg, 306.9 μmol) in DMSO
20 (2 mL) was stirred at 120 °C with microwave irradiation for 1 hour. The mixture was diluted with EtOAc (20 mL) and washed with water (10 mL × 3). The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo* to give a crude mixture of methyl (R)-6-chloro-3-((1-(2-chloro-8-methyl-10-oxo-10,12-dihydroisoindolo[1,2-b]quinazolin-6-yl)ethyl)amino)picolinate and methyl (R)-6-chloro-3-((1-(3-chloro-8-methyl-10-oxo-10,12-dihydroisoindolo[1,2-b]quinazolin-6-yl)ethyl)amino)picolinate, which was used in the next step without further purification. LC-MS: m/z
25 495.0 [M+H]⁺.

Step 8:

The mixture of methyl (R)-6-chloro-3-((1-(2-chloro-8-methyl-10-oxo-10,12-dihydroisoindolo[1,2-b]quinazolin-6-yl)ethyl)amino)picolinate, methyl (R)-6-chloro-3-((1-(3-chloro-8-methyl-10-oxo-10,12-dihydroisoindolo[1,2-b]quinazolin-6-yl)ethyl)amino)picolinate (mixture of the two, 10 mg, 20 μmol) and LiOH·H₂O (9.7 mg, 404 μmol) in mixed solvents of THF and water (2 mL, 2:1) was stirred
30 at 70 °C with microwave irradiation for 15 minutes. The mixture was acidified with 1 N HCl then concentrated *in vacuo*. The residue was purified by prep-HPLC eluting with 20-95% MeCN in water to afford a mixture of (R)-6-chloro-3-((1-(2-chloro-8-methyl-10-oxo-10,12-dihydroisoindolo[1,2-b]quinazolin-6-yl)ethyl)amino)picolinic acid and (R)-6-chloro-3-((1-(3-chloro-8-methyl-10-oxo-10,12-dihydroisoindolo[1,2-b]quinazolin-6-yl)ethyl)amino)picolinic acid (mixture of the two, 1.7 mg, 18 yield) as a white solid. LC-MS: m/z 481.0 [M+H]⁺.
35

Example 35**Step 1:**

- 5 The mixture of 2-amino-3-bromo-5-methylbenzoic acid (2.3 g, 10.0 mmol) and 5-methoxy-3,4-dihydro-2H-pyrrole (3 g, 30 mmol) in toluene (30 mL) was stirred at 110 °C for 16 hours. The mixture was concentrated *in vacuo* and the residue was purified by silica gel chromatography eluting with 0-10% EtOAc in DCM to give 5-bromo-7-methyl-2,3-dihydro-1H-pyrrolo[2,1-b]quinazolin-9-one (700 mg, 25% yield) as a yellow solid. LC-MS: *m/z* 279.0 [M+H]⁺.

Step 2:

- 10 The mixture of 5-bromo-7-methyl-2,3-dihydro-1H-pyrrolo[2,1-b]quinazolin-9-one (350 mg, 1.3 mmol), tributyl(1-ethoxyvinyl)stannane (679 mg, 1.9 mmol) and Pd(PPh₃)₄ (1.5 g, 1.3 mmol) in DMF (10 mL) was stirred at 90 °C with microwave irradiation for 3 hours. Upon completion, the reaction was quenched with 3 M HCl (4 mL), and the mixture was stirred at rt for 2 hours to hydrolyze the ether intermediate to ketone. Upon completion, the mixture was basified with sat. NaHCO₃ and
 15 extracted with EtOAc (50 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 0-10% EtOAc in DCM to give 5-acetyl-7-methyl-2,3-dihydro-1H-pyrrolo[2,1-b]quinazolin-9-one (200 mg, 66% yield) as a yellow solid. LC-MS: *m/z* 243.1 [M+H]⁺.

Step 3:

- 20 The mixture of 5-acetyl-7-methyl-2,3-dihydro-1H-pyrrolo[2,1-b]quinazolin-9-one (200 mg, 826 μmol), (R)-2-methylpropane-2-sulfonamide (200 mg, 1.7 mmol) and titanium (IV) ethoxide (2 mL) in THF (4 mL) was stirred at 80 °C for 16 hours. Upon completion, the mixture was quenched with water (20 mL) and extracted with EtOAc (50 mL × 4). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by silica gel

chromatography eluting with 0-80% EtOAc in DCM to give (R,E)-2-methyl-N-(1-(7-methyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethylidene)propane-2-sulfinamide (250 mg, 87% yield) as a yellow solid. LC-MS: m/z 346.1 $[M+H]^+$.

Step 4:

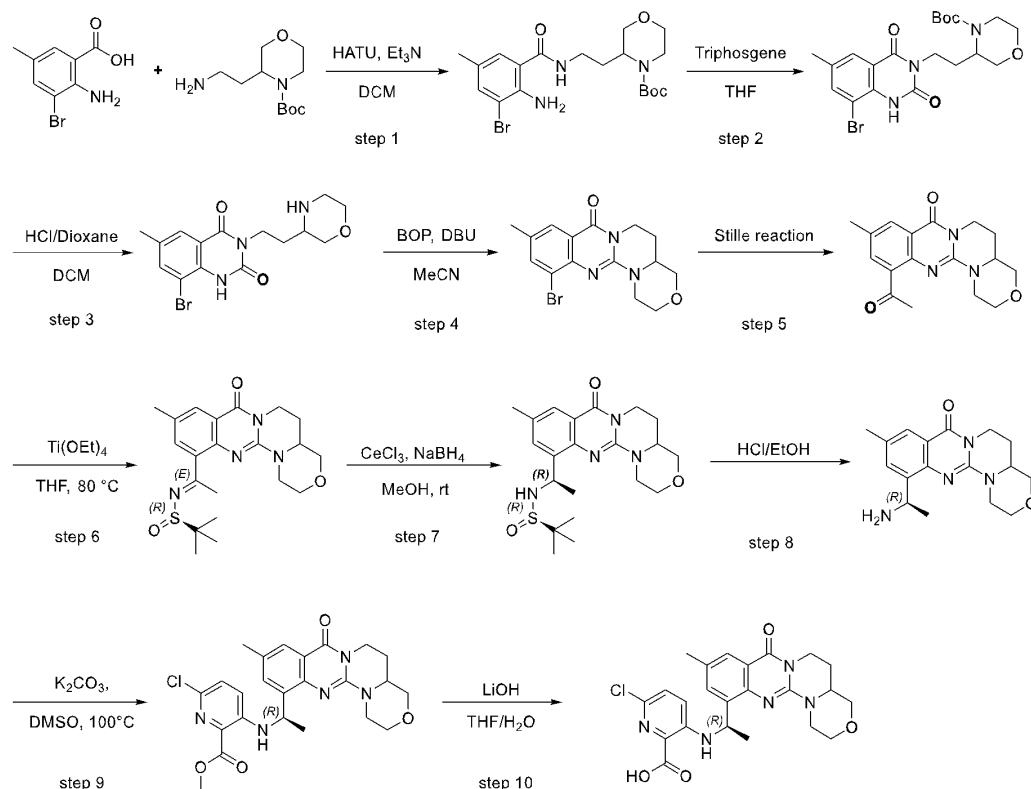
- 5 To a stirred mixture of (R,E)-2-methyl-N-(1-(7-methyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethylidene)propane-2-sulfinamide (250 mg, 0.7 mmol) and $CeCl_3$ (250 mg, 1.0 mmol) in MeOH (5 mL) was added $NaBH_4$ (77 mg, 2.0 mmol) in portions and the resulting mixture was stirred at rt for 10 minutes. Upon completion, the mixture was quenched with water (10 mL) and extracted with DCM (20 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 ,
10 filtered, and concentrated *in vacuo* to give (R)-2-methyl-N-((R)-1-(7-methyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethyl)propane-2-sulfinamide (297 mg, crude), which was used in the next step without further purification. LC-MS: m/z 348.1 $[M+H]^+$.

Step 5:

- 15 To a stirred mixture of (R)-2-methyl-N-((R)-1-(7-methyl-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethyl)propane-2-sulfinamide (297 mg, 854 μ mol) in MeOH (4 mL) was added 4 M HCl in 1,4-dioxane (1 mL) and the resulting mixture was stirred at rt for 10 minutes. Upon completion, the mixture was quenched with sat. $NaHCO_3$ (10 mL) and extracted with DCM (20 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo* to give (R)-5-(1-aminoethyl)-7-methyl-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (227
20 mg, crude), which was used in the next step without further purification. LC-MS: m/z 244.1 $[M+H]^+$.

Step 6:

- The mixture of methyl 6-chloro-3-fluoropicolinate (129 mg, 678 μ mol), (R)-5-(1-aminoethyl)-7-methyl-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (110 mg, 452 μ mol) and K_2CO_3 (62.5 mg, 452 μ mol) in DMSO (2 mL) was stirred at 100 °C with microwave irradiation for 1 hour. Upon
25 completion, 2 M $LiOH \cdot H_2O$ (aq. 1 mL) was added, and mixture was stirred at 70 °C with microwave irradiation for 10 minutes to hydrolyze the ester intermediate. Then the reaction was quenched with 6 M HCl (0.5 mL) and the mixture was directly purified by prep-HPLC eluting with 10-90% MeCN in water to give 6-chloro-3-[[[(1R)-1-(7-methyl-9-oxo-2,3-dihydro-1H-pyrrolo[2,1-b]quinazolin-5-yl)ethyl]amino]pyridine-2-carboxylic acid (50 mg, 27.8% yield) as a white solid. LC-MS: m/z 399.1
30 $[M+H]^+$.

Example 36**Step 1:**

To a stirred mixture of 2-amino-3-bromo-5-methylbenzoic acid (600 mg, 2.6 mmol) in DCM (20 mL) was added HATU (1.29 g, 3.4 mmol), triethylamine (527.8 mg, 5.2 mmol), and tert-butyl 3-(2-aminoethyl)-4-morpholinecarboxylate (600.6 mg, 2.6 mmol). The mixture was stirred at 20 °C for 1 hour. LC-MS showed the product was formed. The mixture was dissolved in water (50 mL) and extracted with DCM (40 mL × 2). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluting with EtOAc/pet.ether from 0 to 30%) to afford tert-butyl 3-(2-(2-amino-3-bromo-5-methylbenzamido)ethyl)morpholine-4-carboxylate (1.1 g, 91% yield) as a white solid. LC-MS: m/z 442.1, 444.1 [M+H]⁺.

Step 2:

To a stirred mixture of tert-butyl 3-[2-[(2-amino-3-bromo-5-methyl-benzoyl)amino]ethyl]morpholine-4-carboxylate (1.05 g, 2.4 mmol) in THF (25 mL) was added triethylamine (2.40 g, 23.7 mmol). Then triphosgene (493.1 mg, 1.7 mmol) in THF (5 mL) was added dropwise at 0 °C. The mixture was stirred at 20 °C for 1 hour. LC-MS showed the starting material was consumed up. The mixture was poured into sat. NaHCO₃ (80 mL) and extracted with EtOAc (80 mL × 2). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford tert-butyl 3-(2-(8-bromo-

2-hydroxy-6-methyl-4-oxoquinazolin-3(4H)-yl)ethyl)morpholine-4-carboxylate (1.1 g, 99% yield) as a brown solid. LC-MS: m/z 368.0, 370.0 $[M+H]^+$.

Step 3:

To a stirred solution of tert-butyl 3-[2-(8-bromo-2-hydroxy-6-methyl-4-oxo-quinazolin-3-yl)ethyl]morpholine-4-carboxylate (1.1 g, 2.4 mmol) in DCM (20 mL) was added a solution of HCl in dioxane (4 M, 6 mL). The mixture was stirred at 20 °C for 1 hour. LC-MS showed the reaction was completed. The mixture was basified with sat. NaHCO_3 , and extracted with DCM (30 mL $\times$ 2). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to afford 8-bromo-2-hydroxy-6-methyl-3-(2-morpholin-3-ylethyl)quinazolin-4-one (850 mg, 98% yield) as a yellow solid. LC-MS: m/z 368.0, 370.0 $[M+H]^+$.

Step 4:

To a stirred mixture of 8-bromo-2-hydroxy-6-methyl-3-(2-morpholin-3-ylethyl)quinazolin-4-one (850 mg, 2.3 mmol) in MeCN (20 mL) was added BOP (1.5 g, 3.5 mmol) and DBU (702.8 mg, 4.6 mmol). The mixture was stirred at 20 °C for 0.5 hour, then at 80 °C for 2.5 hours. LC-MS showed the product was formed. The mixture was dissolved in water (100 mL) and extracted with DCM (100 mL $\times$ 2). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford 12-bromo-10-methyl-1,2,4,4a,5,6-hexahydro-8H-[1,4]oxazino[4',3':3,4]pyrimido[2,1-b]quinazolin-8-one (600 mg, 74% yield) as a yellow solid. LC-MS: m/z 350.0, 352.0 $[M+H]^+$.

Step 5:

To a stirred mixture of 12-bromo-10-methyl-1,2,4,4a,5,6-hexahydro-8H-[1,4]oxazino[4',3':3,4]pyrimido[2,1-b]quinazolin-8-one (600 mg, 1.7 mmol) and tributyl(1-ethoxyvinyl)stannane (804.4 mg, 2.23 mmol) in dioxane (12 mL) was added $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (180.4 mg, 257 μmol) under N_2 . The mixture was stirred at 105 °C for 5 hours. LC-MS showed the product was formed. The mixture was cooled to 20 °C. Then HCl (8 mL, 1 M) was added to the mixture, the mixture was stirred at 20 °C for 0.5 hour. LC-MS showed the reaction was completed. The mixture was diluted in water (60 mL), basified with sat. NaHCO_3 aqueous to pH~9, and extracted with DCM (50 mL $\times$ 2). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford 12-acetyl-10-methyl-1,2,4,4a,5,6-hexahydro-8H-[1,4]oxazino[4',3':3,4]pyrimido[2,1-b]quinazolin-8-one (350 mg, 65% yield) as a yellow solid. LC-MS: m/z 314.1 $[M+H]^+$.

Step 6:

A mixture of 12-acetyl-10-methyl-1,2,4,4a,5,6-hexahydro-8H-[1,4]oxazino[4',3':3,4]pyrimido[2,1-b]quinazolin-8-one (350 mg, 1.1 mmol) and (R)-2-methylpropane-2-sulfinamide (270.7 mg, 2.2 mmol) in $\text{Ti}(\text{OEt})_4$ (4 mL) and THF (8 mL) was stirred at 80 °C for 16 hours. LC-MS showed the reaction was completed. The mixture was diluted in DCM (150 mL) and water (30 mL) and then filtered. The filtrate was separated, and the combined organic layer was dried over Na_2SO_4 , filtered,

and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford (R)-2-methyl-N-((E)-1-(10-methyl-8-oxo-1,2,4,4a,5,6-hexahydro-8H-[1,4]oxazino[4',3':3,4]pyrimido[2,1-b]quinazolin-12-yl)ethylidene)propane-2-sulfonamide (350 mg, 75% yield) as a yellow solid. LC-MS: m/z 417.1 [M+H]⁺.

5 **Step 7:**

To a mixture of (R)-2-methyl-N-((E)-1-(10-methyl-8-oxo-1,2,4,4a,5,6-hexahydro-8H-[1,4]oxazino[4',3':3,4]pyrimido[2,1-b]quinazolin-12-yl)ethylidene)propane-2-sulfonamide (350 mg, 840.2 μmol) and CeCl₃ (124.3 mg, 504.2 μmol) in MeOH (10 mL) was added NaBH₄ (63.6 mg, 1.7 mmol) in portions. The mixture was stirred at 20 °C for 10 minutes. LC-MS showed the product was formed. The reaction was quenched with water (50 mL) and the mixture was extracted with DCM (40 mL × 2). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*, the residue was purified by flash column chromatography on silica gel to afford (R)-2-methyl-N-((1R)-1-(10-methyl-8-oxo-1,2,4,4a,5,6-hexahydro-8H-[1,4]oxazino[4',3':3,4]pyrimido[2,1-b]quinazolin-12-yl)ethyl)propane-2-sulfonamide (280 mg, 80% yield) as a white solid. LC-MS: m/z 419.1 [M+H]⁺.

Step 8:

To a stirred solution of (R)-2-methyl-N-((1R)-1-(10-methyl-8-oxo-1,2,4,4a,5,6-hexahydro-8H-[1,4]oxazino[4',3':3,4]pyrimido[2,1-b]quinazolin-12-yl)ethyl)propane-2-sulfonamide (80 mg, 191.1 μmol) in EtOH (3 mL) was added 4 M HCl in EtOH (1 mL). The mixture was stirred at 20 °C for 0.5 hour. LC-MS showed the reaction was completed. The mixture was basified with sat. NaHCO₃ to pH~9, and then extracted with DCM (40 mL × 2). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford 12-((R)-1-aminoethyl)-10-methyl-1,2,4,4a,5,6-hexahydro-8H-[1,4]oxazino[4',3':3,4]pyrimido[2,1-b]quinazolin-8-one (60 mg, 100% yield) as a yellow solid which was used in the next step directly without further purification. LC-MS: m/z 315.2 [M+H]⁺.

Step 9:

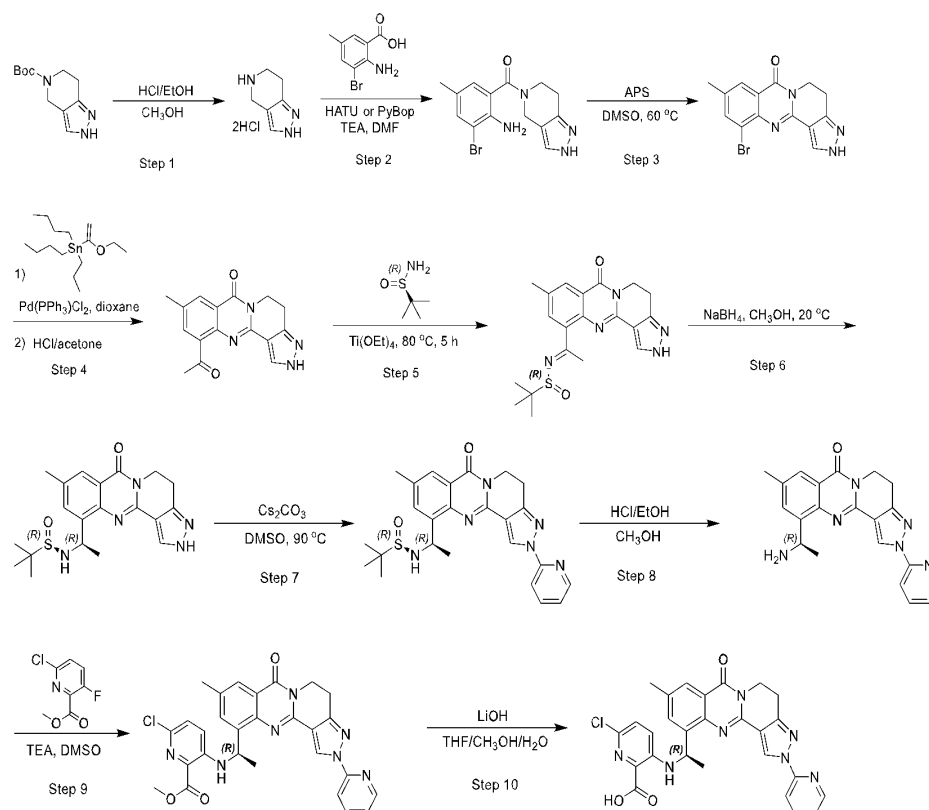
To a stirred mixture of 12-((R)-1-aminoethyl)-10-methyl-1,2,4,4a,5,6-hexahydro-8H-[1,4]oxazino[4',3':3,4]pyrimido[2,1-b]quinazolin-8-one (60 mg, 190.9 μmol) and methyl 6-chloro-3-fluoropicolinate (90.5 mg, 477.1 μmol) in DMSO (3 mL) was added K₂CO₃ (79.1 mg, 572.6 μmol). Then the mixture was stirred at 105 °C for 2 hours. LC-MS showed the product was formed. The mixture was purified by reverse phase chromatography to afford methyl 6-chloro-3-(((1R)-1-(10-methyl-8-oxo-1,2,4,4a,5,6-hexahydro-8H-[1,4]oxazino[4',3':3,4]pyrimido[2,1-b]quinazolin-12-yl)ethyl)amino)picolinate (70 mg, 76% yield) as a white solid. LC-MS: m/z 484.1 [M+H]⁺.

Step 10:

To a mixture of methyl 6-chloro-3-(((1R)-1-(10-methyl-8-oxo-1,2,4,4a,5,6-hexahydro-8H-[1,4]oxazino[4',3':3,4]pyrimido[2,1-b]quinazolin-12-yl)ethyl)amino)picolinate (70 mg, 144.6 μmol) in THF (3 mL) and water (1 mL) was added LiOH·H₂O (17.3 mg, 723.2 μmol). The mixture

was stirred at 50 °C for 1 hour. LC-MS showed the reaction was completed. The mixture was acidified with HCl (1 M) to pH ~ 5 and then concentrated *in vacuo*. The residue was purified by prep-HPLC to afford 6-chloro-3-[[[(1R)-1-(14-methyl-11-oxo-5-oxa-2,10,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),12(17),13,15-tetraen-16-yl)ethyl]amino]pyridine-2-carboxylic acid (25.6 mg, 38% yield) as a white solid. LC-MS: m/z 470.1 [M+H]⁺.

Example 37



Step 1:

To a stirred solution of tert-butyl 2,4,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carboxylate (4 g, 17.9 mmol) in methanol (40 mL) was added 4 M HCl in EtOH (40 mL). The mixture was stirred at 20 °C for 16 hours. The mixture was concentrated *in vacuo* to afford 4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine dihydrochloride (3 g, crude) as a yellow solid, which was used in the next step without further purification.

Step 2:

Method 1:

To a stirred solution of 2-amino-3-bromo-5-methylbenzoic acid (1.4 g, 6.1 mmol), HATU (2.7 g, 7.3 mmol) and N,N-diethylethanamine (2.1 g, 21.3 mmol) in DMF was added 4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine (971.3 mg, 6.1 mmol). The mixture was stirred at 20 °C for 2 hours. The

mixture was poured into water (150 mL) and a yellow solid was precipitated out. The mixture was filtered, and the aqueous phase was extracted with EtOAc (200 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford the product as yellow oil. The crude was purified by column chromatography on silica gel eluting with CH₂Cl₂: CH₃OH = 20: 1 to afford the product (2-amino-3-bromo-5-fluoro-phenyl)-(2,4,6,7-tetrahydropyrazolo[4,3-c]pyridin-5-yl)methanone (820 mg, 40% yield) as a light yellow solid. LC-MS: m/z 337.0 [M+H]⁺.

Method 2:

To a stirred solution of 2-amino-3-bromo-5-methyl-benzoic acid (2.4 g, 10.4 mmol), N,N-diethylethanamine (3.1 g, 31.3 mmol) and PyBOP (6.5 g, 12.5 mmol) in DMF (40 mL) was added 4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine (1.2 g, 8.0 mmol). The mixture was stirred at 20 °C for 1.5 hours. The mixture was poured into water (150 mL) and then filtered. The filtrate was extracted with EtOAc (100 mL × 3), and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford crude product. The residue was purified by column chromatography on silica gel eluting with CH₂Cl₂: CH₃OH = 20: 1 to afford the product (2-amino-3-bromo-5-methyl-phenyl)-(2,4,6,7-tetrahydropyrazolo[4,3-c]pyridin-5-yl)methanone (2.3 g, 66% yield) as a light yellow solid. LC-MS: m/z 337.0 [M+H]⁺.

Step 3:

To a stirred solution of (2-amino-3-bromo-5-methyl-phenyl)-(2,4,6,7-tetrahydropyrazolo[4,3-c]pyridin-5-yl)methanone (3.1 g, 9.2 mmol) in DMSO (50 mL) was added (NH₄)₂S₂O₈ (8.4 g, 36.9 mmol). The mixture was stirred at 60 °C for 10 hours. The mixture was poured into water (150 mL) and a yellow solid was precipitated out. The mixture was filtered, and the filter cake was dried *in vacuo* to afford the product as a yellow solid. The crude product was purified by column chromatography on silica gel eluting with CH₂Cl₂: CH₃OH = 20: 1 to afford the product 7-bromo-5-methyl-1,9,13,14-tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-3(8),4,6,9,11,14-hexaen-2-one (950 mg, 31% yield) as a yellow solid. LC-MS: m/z 331.0 [M+H]⁺.

Step 4:

To a stirred solution of 7-bromo-5-methyl-1,9,13,14-tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-3(8),4,6,9,11,14-hexaen-2-one (950 mg, 2.8 mmol) in dioxane (20 mL) was added tributyl(1-ethoxyvinyl)stannane (1.5 g, 4.3 mmol) and Pd(PPh₃)₂Cl₂ (402.7 mg, 573.7 μmol). The mixture was degassed with a stream of N₂ for three times and then stirred at 100 °C for 16 hours. The mixture was quenched with KF solution (50 mL) and extracted with CH₂Cl₂ (150 mL × 2). The combined extracts were washed with brine (50 mL) and dried over anhydrous Na₂SO₄. Solvent was evaporated to afford crude product. The crude was purified by column chromatography on silica gel eluting with CH₂Cl₂: CH₃OH = 20: 1 to afford the product 7-(1-ethoxyvinyl)-5-methyl-1,9,13,14-tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-3(8),4,6,9,11,14-hexaen-2-one (500 mg, 54% yield) as a yellow solid. LC-MS: m/z 323.1 [M+H]⁺. To a stirred solution of 7-(1-ethoxyvinyl)-5-methyl-1,9,13,14-tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-3(8),4,6,9,11,14-hexaen-2-one (500 mg, 1.5

mmol) in acetone (20 mL) was added 2 M HCl (5 mL). The mixture was stirred at 20 °C for 0.5 hour. The mixture was diluted with CH₂Cl₂ (120 mL), washed with sat. NaHCO₃ (50 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford crude product. The crude was purified by column chromatography on silica gel eluting with CH₂Cl₂: CH₃OH = 20: 1 to afford the product 7-acetyl-5-methyl-1,9,13,14-tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-3(8),4,6,9,11,14-hexaen-2-one (450 mg, 98 % yield) as a yellow solid.

Step 5:

To a stirred solution of 7-acetyl-5-methyl-1,9,13,14-tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-3(8),4,6,9,11,14-hexaen-2-one (450 mg, 1.5 mmol) in titanium ethoxide (4 mL) was added (R)-2-methylpropane-2-sulfinamide (555.9 mg, 4.6 mmol). The mixture was stirred at 80 °C for 5 hours under N₂ protection. The mixture was diluted with EtOAc (200 mL) and then water (50 mL) was added. The mixture was stirred at 20 °C for 0.5 hours. The mixture was filtered, and the organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford crude product. The crude was purified by column chromatography on silica gel eluting with CH₂Cl₂: CH₃OH = 20: 1 to afford the product (NZ,R)-2-methyl-N-[1-(5-methyl-2-oxo-1,9,13,14-tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-3(8),4,6,9,11,14-hexaen-7-yl)ethylidene]propane-2-sulfinamide (430 mg, 71% yield) as a yellow solid. LC-MS: m/z 398.2 [M+H]⁺

Step 6:

To a stirred solution of (NZ,R)-2-methyl-N-[1-(5-methyl-2-oxo-1,9,13,14-tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-3(8),4,6,9,11,14-hexaen-7-yl)ethylidene]propane-2-sulfinamide (430 mg, 1.1 mmol) and CeCl₃ (159.9 mg, 649.0 μmol) in methanol (11.9 mL) was added NaBH₄ (90.0 mg, 2.4 mmol). The mixture was stirred at 20 °C for 15 minutes. The mixture was diluted with CH₂Cl₂ (70 mL) and then washed with brine (30 mL × 2). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford crude product. The crude was purified by column chromatography on silica gel eluting with CH₂Cl₂: CH₃OH = 20: 1 to afford the product (R)-2-methyl-N-[(1R)-1-(5-methyl-2-oxo-1,9,13,14-tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-3(8),4,6,9,11,14-hexaen-7-yl)ethyl]propane-2-sulfinamide (340 mg, 79% yield) as a white solid. LC-MS: m/z 400.2 [M+H]⁺.

Step 7:

To a stirred solution of (R)-2-methyl-N-[(1R)-1-(5-methyl-2-oxo-1,9,13,14-tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-3(8),4,6,9,11,14-hexaen-7-yl)ethyl]propane-2-sulfinamide (55 mg, 137.6 μmol) in DMSO (3 mL) was added 2-fluoropyridine (66.8 mg, 688.3 μmol) and Cs₂CO₃ (134.5 mg, 413.0 μmol). The mixture was stirred at 90 °C for 16 hours under N₂ protection. The mixture was diluted with EtOAc (100 mL) and washed with water (30 mL × 3). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford crude product. The crude was purified by column chromatography on silica gel eluting with CH₂Cl₂: CH₃OH = 20: 1 to afford the product (R)-2-methyl-N-[(1R)-1-[5-methyl-2-oxo-13-(2-pyridyl)-1,9,13,14-

tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-3(8),4,6,9,11,14-hexaen-7-yl]ethyl]propane-2-sulfinamide (60 mg, 91% yield) as a white solid. LC-MS: m/z 477.2 [M+H]⁺.

Step 8:

To a stirred solution of (R)-2-methyl-N-[(1R)-1-[5-methyl-2-oxo-13-(2-pyridyl)-1,9,13,14-tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-3(8),4,6,9,11,14-hexaen-7-yl]ethyl]propane-2-sulfinamide (60 mg, 125.8 μmol) in methanol (6 mL) was added 4 M HCl in EtOH (0.5 mL). The mixture was stirred at 20 °C for 5 minutes. The mixture was diluted with CH₂Cl₂ (100 mL) and washed with sat. NaHCO₃ (50 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford crude product 7-[(1R)-1-aminoethyl]-5-methyl-13-(2-pyridyl)-1,9,13,14-tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-3(8),4,6,9,11,14-hexaen-2-one (50 mg, crude) as a white solid. LC-MS: m/z 373.2 [M+H]⁺.

Step 9:

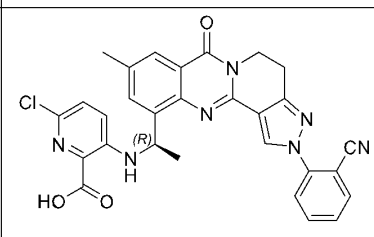
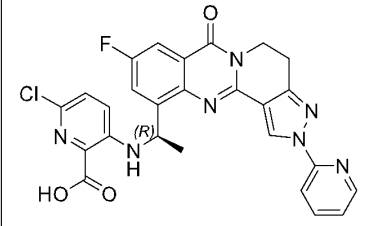
To a stirred solution of 7-[(1R)-1-aminoethyl]-5-methyl-13-(2-pyridyl)-1,9,13,14-tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-3(8),4,6,9,11,14-hexaen-2-one (50 mg, 134.2 μmol) and triethylamine (48.6 mg, 480.5 μmol) in DMSO (3 mL) was added methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (34.1 mg, 180.2 μmol). The mixture was stirred at 100 °C for 16 hours. The mixture was diluted with EtOAc (100 mL) and washed with brine (30 mL × 3). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford crude product. The crude was purified by column chromatography on silica gel eluting with CH₂Cl₂: CH₃OH= 20: 1 to afford the product methyl 6-chloro-3-[[[(1R)-1-[5-methyl-2-oxo-13-(2-pyridyl)-1,9,13,14-tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-3(8),4,6,9,11,14-hexaen-7-yl]ethyl]amino]pyridine-2-carboxylate (30 mg, 46% yield) as a white solid. LC-MS: m/z 542.2 [M+H]⁺.

Step 10:

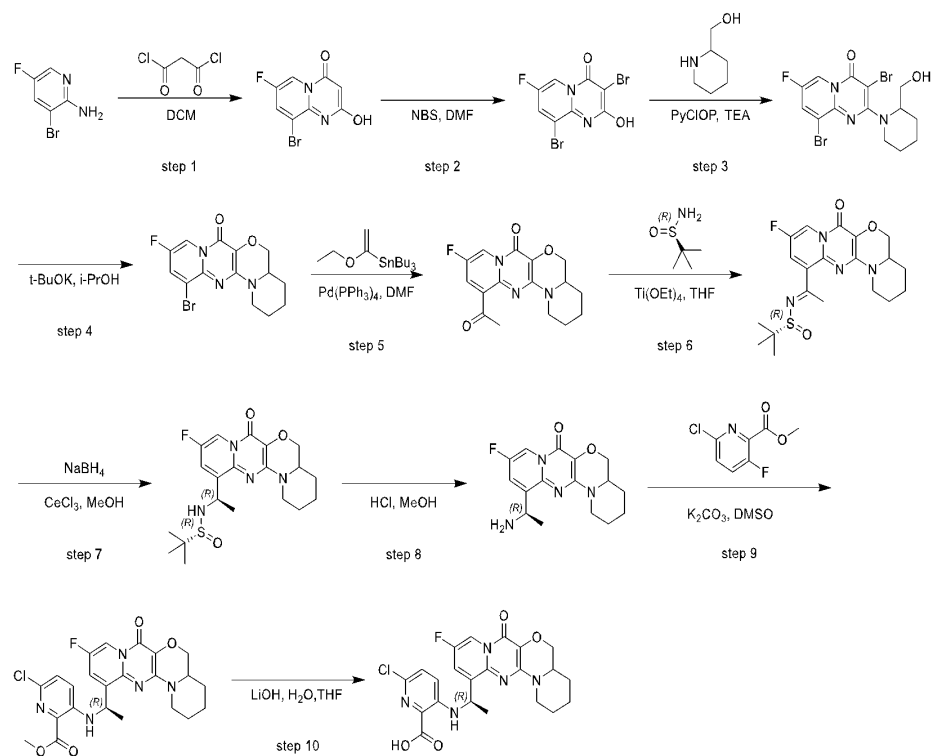
To a stirred solution of methyl 6-chloro-3-[[[(1R)-1-[5-methyl-2-oxo-13-(2-pyridyl)-1,9,13,14-tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-3(8),4,6,9,11,14-hexaen-7-yl]ethyl]amino]pyridine-2-carboxylate (30 mg, 55.3 μmol) in mixed solvents of THF, methanol and water (6 mL, 4:1:1) was added LiOH (11.6 mg, 276.7 μmol). The mixture was stirred at 20 °C for 20 minutes. The mixture was basified to PH = 5 with sat. NaHCO₃, diluted with brine (20 mL) and extracted with CH₂Cl₂ (60 mL × 2). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford crude product. The crude was purified by prep-HPLC (A:0.05%FA in water, B: CH₃CN, Gradient: 10 ~ 85% of B) to afford the product 6-chloro-3-[[[(1R)-1-[5-methyl-2-oxo-13-(2-pyridyl)-1,9,13,14-tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-3(8),4,6,9,11,14-hexaen-7-yl]ethyl]amino]pyridine-2-carboxylic acid (10.2 mg, 35% yield) as a white solid. LC-MS: m/z 528.2 [M+H]⁺.

35

The following compounds have been prepared in analogy to the representative procedures described for **Example 37**.

ID	Structure	LC-MS: m/z [M+H] ⁺
Example 38		552.2
Example 48		531.7

5 Example 39:



Step 1:

To a stirred solution of 3-bromo-5-fluoro-pyridin-2-amine (4.0 g, 20.9 mmol) in DCM (80 mL) was added propanedioyl dichloride (3.5 g, 25.1 mmol) at 0 °C. The mixture was then stirred at 20 °C for 12 hours. The light yellow precipitation was collected by filtration, washed with dichloromethane (3 × 100 mL) and water (50 mL), dried *in vacuo* to afford 9-bromo-7-fluoro-2-hydroxy-pyrido[1,2-a]pyrimidin-4-one (3.0 g, 55% yield) as a yellow solid. LC-MS: m/z 258.9 [M+H]⁺.

Step 2:

To a stirred solution of 9-bromo-7-fluoro-2-hydroxy-pyrido[1,2-a]pyrimidin-4-one (2.0 g, 7.7 mmol) in DMF (20 mL) was added NBS (1.3 g, 7.7 mmol) at 0 °C, the mixture was stirred at 0 °C under N₂ for 5 minutes. The mixture was diluted with water (100 mL) and extracted with DCM (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 0-5% methanol in dichloromethane to give 3,9-dibromo-7-fluoro-2-hydroxy-pyrido[1,2-a]pyrimidin-4-one (2.4 g, 92% yield) as yellow solid. LC-MS: m/z 336.8 [M+H]⁺.

Step 3:

To a stirred solution of 3,9-dibromo-7-fluoro-2-hydroxy-pyrido[1,2-a]pyrimidin-4-one (1.5 g, 4.4 mmol) in dioxane (10 mL) was added PyClOP (1.8 g, 4.4 mmol) and TEA (2.7 g, 26.6 mmol) at 20 °C. The resulting mixture was stirred at 100 °C with microwave irradiation for 30 minutes, then 2-piperidylmethanol (1.5 g, 13.3 mmol) was added, and the mixture was stirred at 100 °C under N₂ for 20 hours. The mixture was diluted with water (50 mL), and extracted with DCM (100 mL). The organic layer was washed with brine (100 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with methanol in dichloromethane 0-5% to give 3,9-dibromo-7-fluoro-2-[2-(hydroxymethyl)-1-piperidyl]pyrido[1,2-a]pyrimidin-4-one (1.2 g, 62% yield) as yellow solid. LC-MS: m/z 433.9 [M+H]⁺.

Step 4:

To a stirred solution of 3,9-dibromo-7-fluoro-2-[2-(hydroxymethyl)-1-piperidyl]pyrido[1,2-a]pyrimidin-4-one (800 mg, 1.8 mmol) in *i*-PrOH (40 mL) was added t-BuOK (413 mg, 3.6 mmol) at 0 °C. The resulting mixture was stirred at 50 °C under N₂ for 30 minutes. The mixture was quenched with sat. NH₄Cl (10 mL), diluted with water (100 mL), and extracted with DCM (2 × 100 mL). The organic layer was washed with brine (100 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with methanol in dichloromethane 0-5% to give 16-bromo-14-fluoro-9-oxa-2,12,18-triazatetracyclo[8.8.0.02,7.012,17]octadeca-1(10),13,15,17-tetraen-11-one (130 mg, 20% yield) as yellow solid. LC-MS: m/z 354.0 [M+H]⁺.

Step 5:

To a stirred solution of 16-bromo-14-fluoro-9-oxa-2,12,18-triazatetracyclo[8.8.0.02,7.012,17]octadeca-1(10),13,15,17-tetraen-11-one (130 mg, 367 μmol) in DMF (3 mL) was added Pd(PPh₃)₄ (84 mg, 73 μmol) and tributyl(1-ethoxyvinyl)stannane (159 mg,

440 μmol) at 20 °C. The resulting mixture was stirred at 100 °C with microwave irradiation for 2 hours. The mixture was diluted with DCM (50 mL), and then quenched with sat. aqueous KF (50 mL). The mixture was stirred at 20 °C for 1 hour, then filtered. The filtrate was separated, and the organic layer was concentrated *in vacuo*, then dissolved in acetone (30 mL) and 4 M HCl in dioxane (3 mL) was added. The mixture was stirred at 20 °C for 30 minutes. Then the mixture was diluted with water (50 mL) and extracted with DCM (100 mL). The organic layer was dried with brine (50 mL) and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with methanol in dichloromethane 0-10% to give 16-acetyl-14-fluoro-9-oxa-2,12,18-triazatetracyclo[8.8.0.02,7.012,17]octadeca-1(10),13,15,17-tetraen-11-one (110 mg, 94% yield) as yellow solid. LC-MS: m/z 318.1 $[\text{M}+\text{H}]^+$.

Step 6:

To a stirred solution of 16-acetyl-14-fluoro-9-oxa-2,12,18-triazatetracyclo[8.8.0.02,7.012,17]octadeca-1(10),13,15,17-tetraen-11-one (110 mg, 347 μmol) in THF (10 mL) was added $\text{Ti}(\text{OEt})_4$ (2.2 mL) and (R)-2-methylpropane-2-sulfinamide (126 mg, 1.0 mmol) at 20 °C and the resulting mixture was stirred at 85 °C for 12 hours. The mixture was diluted with EA (200 mL) and quenched with water (50 mL). The mixture was then filtered, and the filtrate was washed with brine (100 mL), dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 0-100% EA in PE to give (NE,R)-N-[1-(14-fluoro-11-oxo-9-oxa-2,12,18-triazatetracyclo[8.8.0.02,7.012,17]octadeca-1(10),13,15,17-tetraen-16-yl)ethylidene]-2-methyl-propane-2-sulfinamide (100 mg, 69% yield) as a yellow solid. LC-MS: m/z 421.1 $[\text{M}+\text{H}]^+$.

Step 7:

To a stirred mixture of (NE,R)-N-[1-(14-fluoro-11-oxo-9-oxa-2,12,18-triazatetracyclo[8.8.0.02,7.012,17]octadeca-1(10),13,15,17-tetraen-16-yl)ethylidene]-2-methyl-propane-2-sulfinamide (100 mg, 238 μmol) and CeCl_3 (58.6 mg, 238 μmol) in MeOH (10 mL) was added NaBH_4 (18 mg, 476 μmol) in portions at 25 °C, and the resulting mixture was stirred at 25 °C for 10 minutes. The reaction was quenched with water (50 mL), and the mixture was extracted with DCM (2×100 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 0-5% methanol in dichloromethane to give N-((1R)-1-(10-fluoro-7-oxo-1,2,3,4,4a,5-hexahydro-7H-pyrido[1,2-d]pyrido[1',2':1,2]pyrimido[5,4-b][1,4]oxazin-12-yl)ethyl)-2-methylpropane-2-sulfinamide (80 mg, 80% yield) as a yellow solid. LC-MS: m/z 423.1 $[\text{M}+\text{H}]^+$.

Step 8:

To a stirred solution of N-((1R)-1-(10-fluoro-7-oxo-1,2,3,4,4a,5-hexahydro-7H-pyrido[1,2-d]pyrido[1',2':1,2]pyrimido[5,4-b][1,4]oxazin-12-yl)ethyl)-2-methylpropane-2-sulfinamide (80 mg, 189.34 μmol) in MeOH (5 mL) was dropwise added 4.0 M HCl in ethanol (470 μL) at 0 °C and the resulting mixture was stirred at 0 °C for 30 minutes. The mixture was diluted with EA (30 mL) and

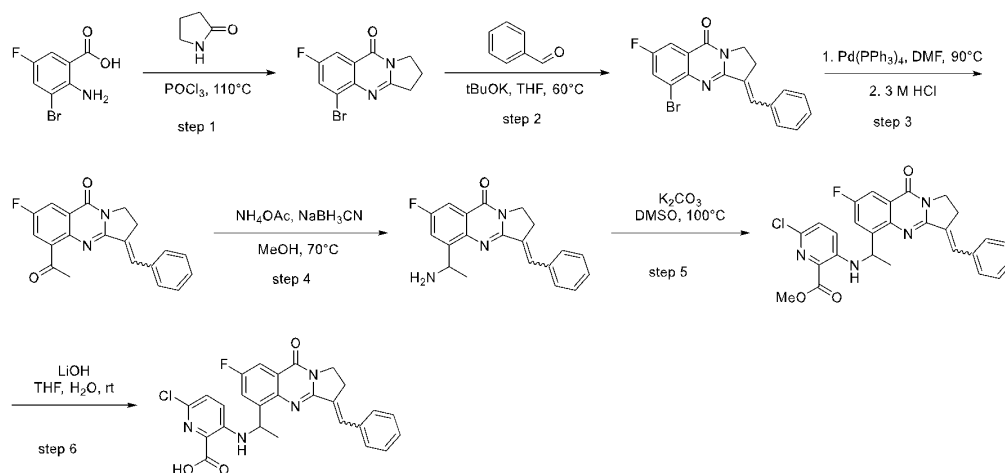
extracted with water (2×50 mL). The aqueous phase was basified with sat. NaHCO_3 to pH = 8 and extracted with DCM (2×100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to give 12-((R)-1-aminoethyl)-10-fluoro-1,2,3,4,4a,5-hexahydro-7H-pyrido[1,2-d]pyrido[1',2':1,2]pyrimido[5,4-b][1,4]oxazin-7-one (40 mg, 66% yield) as a yellow oil. LC-MS: m/z 319.1 $[\text{M}+\text{H}]^+$.

Step 9:

The mixture of 12-((R)-1-aminoethyl)-10-fluoro-1,2,3,4,4a,5-hexahydro-7H-pyrido[1,2-d]pyrido[1',2':1,2]pyrimido[5,4-b][1,4]oxazin-7-one (30 mg, 94 μmol), 6-chloro-3-fluoro-pyridine-2-carboxylate (26.8 mg, 141 μmol) and K_2CO_3 (26 mg, 188 μmol) in DMSO (3 mL) was stirred at 100 °C with microwave irradiation for 1 hour. The mixture was diluted with water (20 mL), and extracted with EA (50 mL). The organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo* to give methyl 6-chloro-3-[[[(1R)-1-(14-fluoro-11-oxo-9-oxa-2,12,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(10),13,15,17-tetraen-16-yl)ethyl]amino]pyridine-2-carboxylate (20 mg, 43% yield) as a yellow oil. LC-MS: m/z 488.1 $[\text{M}+\text{H}]^+$.

Step 10:

The mixture of methyl 6-chloro-3-[[[(1R)-1-(14-fluoro-11-oxo-9-oxa-2,12,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(10),13,15,17-tetraen-16-yl)ethyl]amino]pyridine-2-carboxylate (20 mg, 41 μmol) and LiOH (9.8 mg, 410 μmol) in mixed solvents of THF and water (6 mL, 5:1) was stirred at 25 °C for 2 hours. Upon completion, the mixture was acidified to pH = 6 with sat. NH_4Cl , and then extracted with DCM (2×50 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified with prep-HPLC to give 6-chloro-3-[[[(1R)-1-(14-fluoro-11-oxo-9-oxa-2,12,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(10),13,15,17-tetraen-16-yl)ethyl]amino]pyridine-2-carboxylic acid (2 mg, 10% yield) as a white solid. LC-MS: m/z 474.1 $[\text{M}+\text{H}]^+$.

Example 40**Step 1:**

To a stirred mixture of pyrrolidin-2-one (3.4 g, 40 mmol), 2-amino-3-bromo-5-fluoro-benzoic acid (4.7 g, 20 mmol) at 0°C was dropwise added POCl_3 (30 mL) and the resulting mixture was stirred at 105°C for 16 hours. Upon completion, the mixture was concentrated *in vacuo* and then poured into ice water. The mixture was basified with conc. NaOH aqueous solution and extracted with DCM (3×80 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 0-50% EA in DCM to give 5-bromo-7-fluoro-2,3-dihydro-1H-pyrrolo[2,1-b]quinazolin-9-one (4.3 g, 76% yield) as a yellow solid. LC-MS: m/z 282.9 $[\text{M}+\text{H}]^+$.

Step 2:

The mixture of 5-bromo-7-fluoro-2,3-dihydro-1H-pyrrolo[2,1-b]quinazolin-9-one (1 g, 3.5 mmol), benzaldehyde (1.1 g, 10.6 mmol), KOtBu (396 mg, 3.5 mmol) in THF (20 mL) was stirred at 70°C for 1 hour. Upon completion, the mixture was diluted with water and extracted with EA (3×80 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 0-50% EA in DCM to give 3-benzylidene-5-bromo-7-fluoro-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (600 mg, 46% yield) as a yellow solid. LC-MS: m/z 371.0 $[\text{M}+\text{H}]^+$.

Step 3:

The mixture of 3-benzylidene-5-bromo-7-fluoro-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (600 mg, 1.6 mmol), tributyl(1-ethoxyvinyl)stannane (1.2 g, 3.2 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (187 mg, 161 μmol) in DMF (10 mL) was stirred at 100°C with microwave irradiation for 1 hour. Upon completion, the mixture was treated 3 M HCl (2 mL) to hydrolyze the ether intermediate to ketone. Upon completion, the mixture was basified with sat. NaHCO_3 , diluted with EA (80 mL) and washed with water (3×40 mL). The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 0- 80% EA

in DCM to give 5-acetyl-3-benzylidene-7-fluoro-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (263 mg, 49% yield) as a yellow solid. LC-MS: m/z 335.1 $[M+H]^+$.

Step 4:

The mixture of 5-acetyl-3-benzylidene-7-fluoro-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (220 mg, 658 μ mol), NH_4OAc (254 mg, 3.3 mmol) and $NaBH_3CN$ (207 mg, 3.3 mmol) in MeOH (5 mL) was stirred at 70 °C for 1 hour. Upon completion, the mixture was quenched with water (20 mL) and extracted with DCM (3×30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo* to afford crude product 5-(1-aminoethyl)-3-benzylidene-7-fluoro-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (200 mg), which was used in the next step without further purification. LC-MS: m/z 336.1 $[M+H]^+$.

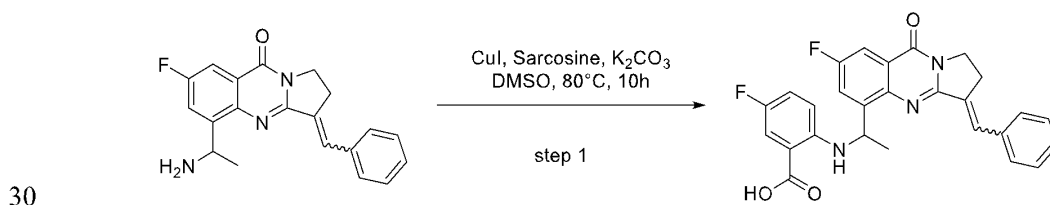
Step 5:

The mixture of methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (68 mg, 358 μ mol), 5-(1-aminoethyl)-3-benzylidene-7-fluoro-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (60 mg, 179 μ mol) and K_2CO_3 (49 mg, 358 μ mol) in DMSO (2 mL) was stirred at 100 °C with microwave irradiation for 3 hours. Upon completion, the mixture was diluted with EA (30 mL) and washed with water (3×15 mL). The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 0-50% EA in DCM to give methyl 3-((1-(3-benzylidene-7-fluoro-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethyl)amino)-6-chloropyridine-2-carboxylate (26 mg, 29% yield). LC-MS: m/z 505.1 $[M+H]^+$.

Step 6:

The mixture of methyl 3-((1-(3-benzylidene-7-fluoro-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethyl)amino)-6-chloropyridine-2-carboxylate (10 mg, 19.8 μ mol) and LiOH (2.37 mg, 99.02 μ mol) in mixed solvents of water and THF (2 mL, 1:2) was stirred at rt for 2 hours. Upon completion, the mixture was acidified with 1 M HCl and then solvent was removed *in vacuo*. The residue was purified by prep-HPLC to give the desired product 3-((1-(3-benzylidene-7-fluoro-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethyl)amino)-6-chloropyridine-2-carboxylic acid (1 mg, 10% yield) as a white solid. LC-MS: m/z 491.1 $[M+H]^+$.

Example 41

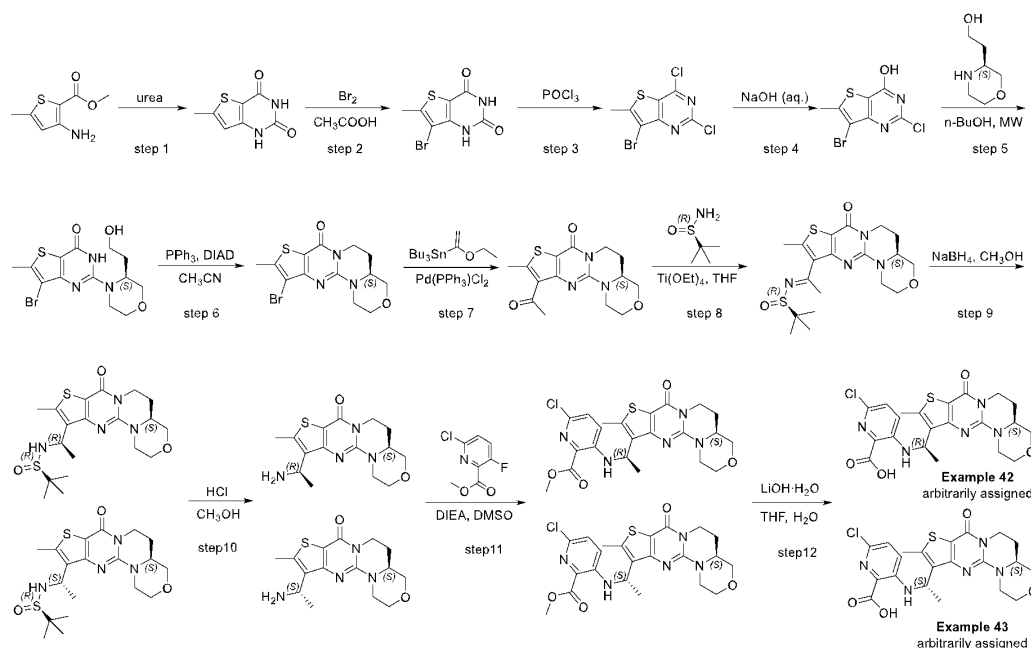


Step 1:

The mixture of CuI (56.8 mg, 298 μ mol) and sarcosine (53 mg, 596 μ mol) in DMSO (2 mL) was stirred at rt for 15 min. Then 4-fluoro-2-iodo-benzoic acid (238 mg, 895 μ mol), 5-(1-

aminoethyl)-3-benzylidene-7-fluoro-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (100 mg, 298 μmol) and K_2CO_3 (124 mg, 895 μmol) was added and the resulting mixture was stirred at 80 °C for 10 hours. Then the mixture was acidified with 1 M HCl and extracted with DCM (3 $\times$ 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by prep-HPLC to afford 2-((1-(3-benzylidene-7-fluoro-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethyl)amino)-5-fluorobenzoic acid (3.5 mg, 3% yield) as a yellow solid. LC-MS: m/z 474.1 $[\text{M}+\text{H}]^+$.

Example 42 and 43



Step 1:

A mixture of methyl 3-amino-5-methylthiophene-2-carboxylate (4 g, 23.4 mmol) and urea (1.4 g, 23.4 mmol) was stirred at 180 °C for 3 hours. The mixture was cooled to rt and diluted with water (200 mL), stirred and filtered to afford 6-methyl-1H-thieno[3,2-d]pyrimidine-2,4-dione (4.2 g, 98% yield) as a white solid. LC-MS: m/z 183.1 $[\text{M}+\text{H}]^+$.

Step 2:

To a stirred solution of 6-methyl-1H-thieno[3,2-d]pyrimidine-2,4-dione (4.2 g, 23 mmol) in AcOH (30 mL) was added Br_2 (18.4 g, 115.3 mmol) under N_2 . The mixture was stirred at 60 °C for 10 hours. The mixture was cooled to rt and concentrated *in vacuo* to give the crude product, which was diluted with water (100 mL), basified with 10% NaHCO_3 (aq.) to pH~9, extracted with DCM (300 mL $\times$ 2). The combined organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel to afford 7-bromo-6-methyl-1H-thieno[3,2-d]pyrimidine-2,4-dione (4.5 g, 75% yield) as a yellow solid. LC-MS: m/z 261.1 $[\text{M}+\text{H}]^+$.

Step 3:

To a stirred solution of 7-bromo-6-methyl-1H-thieno[3,2-d]pyrimidine-2,4-dione (4.5 g, 17.2 mmol) in phosphorus oxychloride (30 mL) was stirred at 120 °C for 16 hours. The mixture was concentrated to afford crude product. The crude was dissolved in CH₃CN (15 mL) and then poured into water (230 mL) slowly. The mixture was filtered and the filter cake was washed with water (50 mL). Then the filter cake was dried under vacuum to afford 7-bromo-2,4-dichloro-6-methyl-thieno[3,2-d]pyrimidine (3 g, 58% yield) as a yellow solid. LC-MS: m/z 297.1 [M+H]⁺.

Step 4:

A mixture of 7-bromo-2,4-dichloro-6-methyl-thieno[3,2-d]pyrimidine (3.4 g, 11.5 mmol) in H₂O (20 mL) and 4 N NaOH (10 mL, aq.) was stirred at 110 °C for 15 hours. The mixture was adjusted to pH 5 with 10% HCl (aq.). The mixture was diluted with water (30 mL) and extracted with CH₂Cl₂ (60 mL × 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to afford 7-bromo-2-chloro-6-methyl-3H-thieno[3,2-d]pyrimidin-4-one (1.2 g, 37% yield) as a yellow solid. LC-MS: m/z 279.1 [M+H]⁺.

Step 5:

To a solution of 2-[(3S)-morpholin-3-yl]ethanol (337 mg, 2.6 mmol) and triethylamine (217 mg, 2.2 mmol) in n-BuOH (10 mL) was added 7-bromo-2-chloro-6-methyl-3H-thieno[3,2-d]pyrimidin-4-one (600 mg, 2.2 mmol). The mixture was stirred at 180 °C for 16 hours.

The mixture was concentrated to afford crude product. The crude was purified by column chromatography on silica gel to afford 7-bromo-2-[(3S)-3-(2-hydroxyethyl)morpholin-4-yl]-6-methyl-3H-thieno[3,2-d]pyrimidin-4-one (250 mg, 31% yield) as a yellow solid. LC-MS: m/z 374.1 [M+H]⁺.

Step 6:

To a stirred solution of 7-bromo-2-[(3S)-3-(2-hydroxyethyl)morpholin-4-yl]-6-methyl-3H-thieno[3,2-d]pyrimidin-4-one (250 mg, 668 μmol), triphenylphosphane (350 mg, 1.3 mmol) in acetonitrile (4 mL) was added DIAD (270 mg, 1.3 mmol) at 0 °C under N₂. The mixture was stirred at 65 °C for 5 hours. The mixture was concentrated to afford crude product. The crude was purified by column chromatography on silica gel to afford (7S)-15-bromo-14-methyl-5-oxa-13-thia-2,10,17-triazatetracyclo[8.7.0.0.2,7.0.12,16]heptadeca-1(17),12(16),14-trien-11-one (120 mg, 50% yield) as a yellow solid. LC-MS: m/z 356.1 [M+H]⁺.

Step 7:

To a stirred mixture of (7S)-15-bromo-14-methyl-5-oxa-13-thia-2,10,17-triazatetracyclo[8.7.0.0.2,7.0.12,16]heptadeca-1(17),12(16),14-trien-11-one (120 mg, 336.9 μmol) and tributyl(1-ethoxyvinyl)stannane (182 mg, 505.3 μmol) in dioxane (4 mL) was added dichloropalladium;triphenylphosphane (47 mg, 67.4 μmol) under N₂. The mixture was stirred at 100 °C for 4 hours. The mixture was cooled to rt. Then 4 M HCl (1 mL, aq.) was added to the mixture, the mixture was stirred at 20 °C for 0.5 h. The mixture was diluted with water (100 mL),

basified with saturated NaHCO_3 (aq.) to pH~9, extracted with DCM (300 mL $\times$ 2). The combined organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel to afford (7S)-15-acetyl-14-methyl-5-oxa-13-thia-2,10,17-triazatetracyclo[8.7.0.02,7.012,16]heptadeca-1(17),12(16),14-trien-11-one (100 mg, 92%
 5 yield) as a yellow solid. LC-MS: m/z 320.1 $[\text{M}+\text{H}]^+$.

Step 8:

A mixture of (7S)-15-acetyl-14-methyl-5-oxa-13-thia-2,10,17-triazatetracyclo[8.7.0.02,7.012,16]heptadeca-1(17),12(16),14-trien-11-one (80 mg, 250.5 μmol) and (R)-2-methylpropane-2-sulfinamide (30 mg, 250.5 μmol) in $\text{Ti}(\text{OEt})_4$ (4 mL) and THF (4
 10 mL) was stirred at 80 $^\circ\text{C}$ for 4 hours. The mixture was cooled to 20 $^\circ\text{C}$, diluted with DCM (500 mL) and water (80 mL), filtered and the filtrate was separated, the combined organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo*, the residue was purified by flash column chromatography on silica gel to afford (R)-2-methyl-N-((E)-1-((S)-10-methyl-8-oxo-1,2,4,4a,5,6-hexahydro-8H-thieno[3",2":4',5']pyrimido[2',1':2,3]pyrimido[6,1-c][1,4]oxazin-11-yl)ethylidene)propane-2-
 15 sulfinamide (60 mg, 57% yield) as a yellow solid. LC-MS: m/z 423.1 $[\text{M}+\text{H}]^+$.

Step 9:

To a solution of (R)-2-methyl-N-((E)-1-((S)-10-methyl-8-oxo-1,2,4,4a,5,6-hexahydro-8H-thieno[3",2":4',5']pyrimido[2',1':2,3]pyrimido[6,1-c][1,4]oxazin-11-yl)ethylidene)propane-2-sulfinamide (60 mg, 142 μmol) in MeOH (2 mL) was added NaBH_4 (8 mg, 213 μmol),
 20 trichlorocerium (17 mg, 71 μmol). The mixture was stirred at rt for 30 minutes. The mixture was quenched with water (50 mL) and extracted with DCM (40 mL $\times$ 2). The combined organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo*, the residue was purified by flash column chromatography on silica gel to afford a mixture of (R)-2-methyl-N-((R)-1-((S)-10-methyl-8-oxo-1,2,4,4a,5,6-hexahydro-8H-thieno[3",2":4',5']pyrimido[2',1':2,3]pyrimido[6,1-c][1,4]oxazin-11-yl)ethyl)propane-2-sulfinamide and (R)-2-methyl-N-((S)-1-((S)-10-methyl-8-oxo-1,2,4,4a,5,6-hexahydro-8H-thieno[3",2":4',5']pyrimido[2',1':2,3]pyrimido[6,1-c][1,4]oxazin-11-yl)ethyl)propane-2-sulfinamide (30 mg, 50% yield) as a yellow solid. LC-MS: m/z 425.1 $[\text{M}+\text{H}]^+$.

Step 10:

To a stirred solution of (R)-2-methyl-N-((R)-1-((S)-10-methyl-8-oxo-1,2,4,4a,5,6-hexahydro-8H-thieno[3",2":4',5']pyrimido[2',1':2,3]pyrimido[6,1-c][1,4]oxazin-11-yl)ethyl)propane-2-sulfinamide and (R)-2-methyl-N-((S)-1-((S)-10-methyl-8-oxo-1,2,4,4a,5,6-hexahydro-8H-thieno[3",2":4',5']pyrimido[2',1':2,3]pyrimido[6,1-c][1,4]oxazin-11-yl)ethyl)propane-2-sulfinamide (30 mg, 71 μmol) in EtOH (2 mL) was added HCl (4 M in ethanol, 0.5 mL). The mixture was stirred
 30 at rt for 2 hours. The mixture was adjusted pH to 8 with 10% K_2CO_3 (aq.) and extracted with DCM (50 mL $\times$ 2). The combined organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo* to afford a mixture of (S)-11-((R)-1-aminoethyl)-10-methyl-1,2,4,4a,5,6-hexahydro-8H-thieno[3",2":4',5']pyrimido[2',1':2,3]pyrimido[6,1-c][1,4]oxazin-8-one and (S)-11-((S)-1-aminoethyl)-

10-methyl-1,2,4,4a,5,6-hexahydro-8H-thieno[3",2":4',5']pyrimido[2',1':2,3]pyrimido[6,1-c][1,4]oxazin-8-one (20 mg, 88% yield) as yellow oil which was used to the next step directly without further purification. LC-MS: m/z 321.1 $[M+H]^+$.

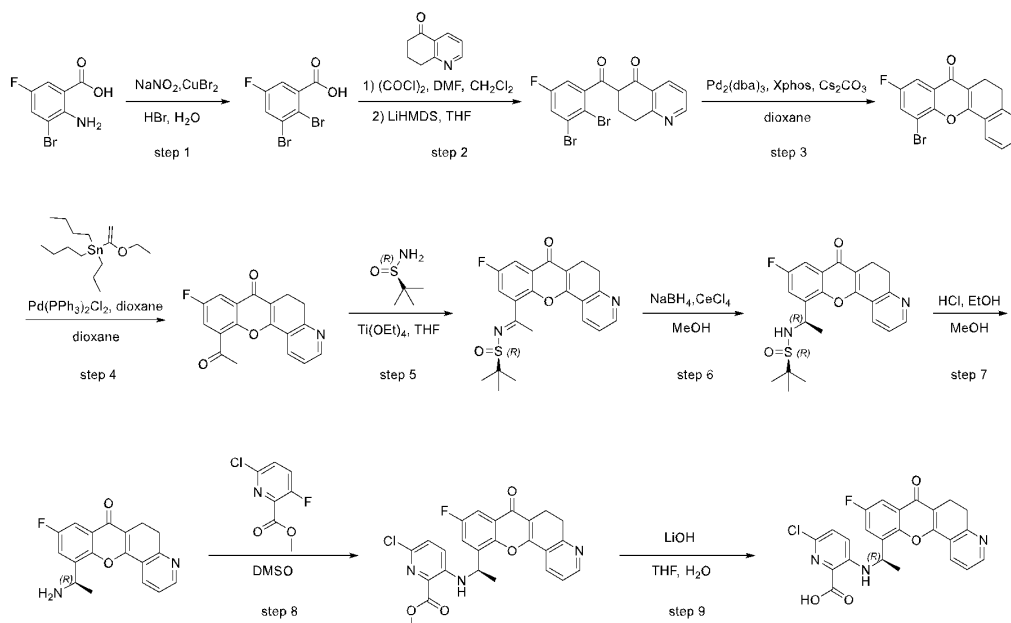
Step 11:

- 5 To a solution of (S)-11-((R)-1-aminoethyl)-10-methyl-1,2,4,4a,5,6-hexahydro-8H-thieno[3",2":4',5']pyrimido[2',1':2,3]pyrimido[6,1-c][1,4]oxazin-8-one and (S)-11-((S)-1-aminoethyl)-10-methyl-1,2,4,4a,5,6-hexahydro-8H-thieno[3",2":4',5']pyrimido[2',1':2,3]pyrimido[6,1-c][1,4]oxazin-8-one (20 mg, 62.4 μ mol) and methyl 6-chloro-3-fluoropicolinate (15 mg, 80 μ mol) in DMSO (1.5 mL) were added K_2CO_3 (9 mg, 62 μ mol). The mixture was stirred at 100 °C for 1 hour
- 10 under N_2 atmosphere before it was cooled to rt. The mixture was added H_2O (10 mL), adjusted pH to 2 with 1 N HCl (aq.) and extracted with EtOAc (50 mL $\times$ 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by prep-HPLC to give a mixture of methyl 6-chloro-3-(((R)-1-((S)-10-methyl-8-oxo-1,2,4,4a,5,6-hexahydro-8H-thieno[3",2":4',5']pyrimido[2',1':2,3]pyrimido[6,1-c][1,4]oxazin-11-
- 15 yl)ethyl)amino)picolinate and methyl 6-chloro-3-(((S)-1-((S)-10-methyl-8-oxo-1,2,4,4a,5,6-hexahydro-8H-thieno[3",2":4',5']pyrimido[2',1':2,3]pyrimido[6,1-c][1,4]oxazin-11-yl)ethyl)amino)picolinate (20 mg, 65% yield) as a white solid. LC-MS: m/z 490.1 $[M+H]^+$.

Step 12:

- To a solution of methyl 6-chloro-3-(((R)-1-((S)-10-methyl-8-oxo-1,2,4,4a,5,6-hexahydro-8H-thieno[3",2":4',5']pyrimido[2',1':2,3]pyrimido[6,1-c][1,4]oxazin-11-yl)ethyl)amino)picolinate and methyl 6-chloro-3-(((S)-1-((S)-10-methyl-8-oxo-1,2,4,4a,5,6-hexahydro-8H-thieno[3",2":4',5']pyrimido[2',1':2,3]pyrimido[6,1-c][1,4]oxazin-11-yl)ethyl)amino)picolinate (20 mg, 40.8 μ mol) in MeOH (1 mL), H_2O (1 mL) was added $LiOH \cdot H_2O$ (3 mg, 102 μ mol). The mixture was stirred at rt for 2 hours. The mixture was added H_2O (10 mL) and adjusted pH to 2 with 1 N HCl (aq.)
- 25 and extracted with DCM (50 mL $\times$ 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by prep-HPLC to give 6-chloro-3-(((R)-1-((S)-10-methyl-8-oxo-1,2,4,4a,5,6-hexahydro-8H-thieno[3",2":4',5']pyrimido[2',1':2,3]pyrimido[6,1-c][1,4]oxazin-11-yl)ethyl)amino)picolinic acid (**Example 42**, 2.1 mg, 11% yield) as a white solid and 6-chloro-3-(((S)-1-((S)-10-methyl-8-oxo-1,2,4,4a,5,6-hexahydro-8H-thieno[3",2":4',5']pyrimido[2',1':2,3]pyrimido[6,1-c][1,4]oxazin-11-yl)ethyl)amino)picolinic acid (**Example 43**, 2.6 mg, 13.4% yield) as a white solid. Both of LC-MS: m/z 476.1 $[M+H]^+$.
- 30

Example 49



Step 1:

To a solution of 2-amino-3-bromo-5-fluoro-benzoic acid (10 g, 42.7 mmol) and NaNO_2 (5.9 g, 85.5 mmol) in HBr (48 wt. % in water) (172.9 g, 2.1 mol) was added CuBr_2 (14.3 g, 64.1 mmol) slowly at 0 °C. Then the mixture was stirred at 25 °C for 4 hours before it was adjusted pH to 8 with 10% aqueous K_2CO_3 . The mixture was diluted with water (100 mL) and extracted with DCM (300 mL). The organic layer was washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give 2,3-dibromo-5-fluoro-benzoic acid (6 g, 47% yield) as a yellow solid.

Step 2:

To a solution of 2,3-dibromo-5-fluoro-benzoic acid (5 g, 16.8 mmol) and oxalyl dichloride (2.8 g, 21.8 mmol) in DCM (100 mL) was added DMF (122.7 mg, 1.7 mmol). The mixture was stirred at 25 °C for 0.5 hour before it was concentrated under reduced pressure to afford crude product, which was used to the next step directly without further purification. To a solution of 7,8-dihydro-6H-quinolin-5-one (3 g, 20.1 mmol) in THF (10 mL) was added a solution of LiHMDS (4.2 g, 25.2 mmol) in THF (10 mL) at 0 °C under N_2 atmosphere. The mixture was stirred at 0 °C for 1 hour before 2,3-dibromo-5-fluorobenzoyl chloride was added into the mixture. The mixture was quenched with aqueous HCl (1 N, 20 mL), diluted with water (100 mL) and then extracted with CH_2Cl_2 (200 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford crude product. The crude product was purified by column chromatography silica gel to afford 6-(2,3-dibromo-5-fluoro-benzoyl)-7,8-dihydro-6H-quinolin-5-one (2 g, 28% yield) as a yellow solid. LCMS: m/z 426.1 $[\text{M}+\text{H}]^+$.

Step 3:

To a solution of 6-(2,3-dibromo-5-fluoro-benzoyl)-7,8-dihydro-6H-quinolin-5-one (2 g, 4.7 mmol) and $\text{Pd}_2(\text{dba})_3$ (430.9 mg, 0.5 mmol) in dioxane (50 mL) were added Xphos (448.1 mg, 0.9 mmol) and Cs_2CO_3 (3.1 g, 9.4 mmol). The mixture was stirred at 100 °C under for 6 hours under N_2 atmosphere before it was cooled to room temperature. The mixture was concentrated under reduced pressure to afford a residue, then it was diluted with DCM (200 mL) and water (100 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford crude product, which was purified by silica gel chromatography to afford 11-bromo-9-fluoro-5,6-dihydro-7H-chromeno[2,3-f]quinolin-7-one (1 g, 62% yield) as a yellow solid. LCMS: m/z 346.1 $[\text{M}+\text{H}]^+$.

Step 4:

- 10 To a solution of 11-bromo-9-fluoro-5,6-dihydro-7H-chromeno[2,3-f]quinolin-7-one (1 g, 2.9 mmol) and bis(triphenylphosphine)palladium(II) chloride (210.6 mg, 0.3 mmol) in dioxane (20 mL) was added tributyl(1-ethoxyvinyl)stannane (1.4 g, 3.8 mmol). The mixture was stirred at 100 °C for 16 hours under N_2 atmosphere before it was cooled to rt. The mixture was diluted with DCM (50 mL) and then quenched with sat. aqueous KF (50 mL). The mixture was stirred at 20 °C under N_2 for 2 hours, then filtered. The filtrate was separated and the organic layer was concentrated *in vacuo*. The residue was dissolved in acetone (30 mL) and 2 N HCl (5 mL) was added. The mixture was stirred at 20 °C under N_2 for 1 hour. Then the mixture was diluted with water (100 mL) and extracted with DCM (200 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford 11-acetyl-9-fluoro-5,6-dihydro-7H-chromeno[2,3-f]quinolin-7-one (500 mg, 56% yield) as a yellow solid. LC-MS: m/z 310.1 $[\text{M}+\text{H}]^+$.

Step 5:

- To a solution of 11-acetyl-9-fluoro-5,6-dihydro-7H-chromeno[2,3-f]quinolin-7-one (500 mg, 1.6 mmol) in titanium ethoxide (6 mL) was added (R)-2-methylpropane-2-sulfinamide (387.2 mg, 3.2 mmol). The mixture was stirred at 70 °C for 16 hours under N_2 before it was cooled to rt. The mixture was diluted with EtOAc (100 mL) and water (50 mL). The mixture was then stirred at 20 °C for 0.5 h, filtered and the organic layer was washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford crude product, which was purified by silica gel chromatography to afford (R,Z)-N-(1-(9-fluoro-7-oxo-5,7-dihydro-6H-chromeno[2,3-f]quinolin-11-yl)ethylidene)-2-methylpropane-2-sulfinamide (400 mg, 61% yield) as a yellow solid. LC-MS: m/z 413.1 $[\text{M}+\text{H}]^+$.

Step 6:

- 30 To a solution of (R,Z)-N-(1-(9-fluoro-7-oxo-5,7-dihydro-6H-chromeno[2,3-f]quinolin-11-yl)ethylidene)-2-methylpropane-2-sulfinamide (400 mg, 970.9 μmol) and trichlorocericium (143.3 mg, 582.5 μmol) in methanol (20 mL) was added NaBH_4 (56.5 mg, 1.5 mmol). The mixture was stirred at 20 °C for 15 minutes. The mixture was diluted with CH_2Cl_2 (100 mL) and water (50 mL). The organic layer was washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford the crude product, which was purified by silica gel chromatography to afford (R)-N-((R)-1-(9-

fluoro-7-oxo-5,7-dihydro-6H-chromeno[2,3-f]quinolin-11-yl)ethyl)-2-methylpropane-2-sulfonamide (300 mg, 78% yield). LC-MS: m/z 415.1 [M+H]⁺.

Step 7:

To a solution of (R)-N-((R)-1-(9-fluoro-7-oxo-5,7-dihydro-6H-chromeno[2,3-f]quinolin-11-yl)ethyl)-2-methylpropane-2-sulfonamide (300 mg, 753.8 μmol) in methanol (10 mL) was added a solution of HCl in EtOH (1.5 mL, 4 N). The mixture was stirred at 25 °C for 10 minutes. The mixture was diluted with CH₂Cl₂ (100 mL) and washed with 10% aq. NaHCO₃. The organic layer was dried over Na₂SO₄, filtered and concentrated to afford (R)-11-(1-aminoethyl)-9-fluoro-5,6-dihydro-7H-chromeno[2,3-f]quinolin-7-one (250 mg, crude) as a gray solid. LC-MS: m/z 311.1 [M+H]⁺.

Step 8:

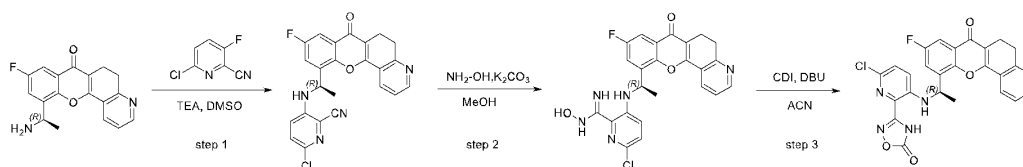
To a solution of methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (9.2 mg, 48.3 μmol) and (R)-11-(1-aminoethyl)-9-fluoro-5,6-dihydro-7H-chromeno[2,3-f]quinolin-7-one (10 mg, 32.2 μmol) in DMSO (1 mL) was added K₂CO₃ (9 mg, 64.5 μmol). The mixture was stirred at 100 °C for 2 hours under N₂ before it was cooled to rt. The mixture was added H₂O (10 mL) and adjusted pH to 2 with HCl (aq., 1 N). The mixture was extracted with EtOAc (50 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by prep-HPLC to give methyl (R)-6-chloro-3-((1-(9-fluoro-7-oxo-5,7-dihydro-6H-chromeno[2,3-f]quinolin-11-yl)ethyl)amino)picolinate (2 mg, 12.9% yield) as a white solid. LC-MS: m/z 479.8 [M+H]⁺.

Step 9:

To a solution of methyl (R)-6-chloro-3-((1-(9-fluoro-7-oxo-5,7-dihydro-6H-chromeno[2,3-f]quinolin-11-yl)ethyl)amino)picolinate (2 mg, 4.2 μmol) in THF (0.5 mL) and H₂O (0.5 mL) was added LiOH·H₂O (0.2 mg, 8.3 μmol). The mixture was stirred at rt for 4 hours. The mixture was added H₂O (10 mL) and adjusted pH to 2 with HCl (aq., 1 N). The mixture was extracted with DCM (50 mL × 3), the organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by prep-HPLC to give (R)-6-chloro-3-((1-(9-fluoro-7-oxo-5,7-dihydro-6H-chromeno[2,3-f]quinolin-11-yl)ethyl)amino)picolinic acid (0.8 mg, 41.2% yield) as a white solid. LC-MS: m/z 465.8 [M+H]⁺.

The following compounds have been prepared in analogy to the representative procedures described for **Example 49**.

ID	Structure	LC-MS: m/z [M+H] ⁺
Example 50		466.1
Example 71		473.8

Example 51**Step 1:**

- 5 To a solution of 11-[(1R)-1-aminoethyl]-9-fluoro-5,6-dihydrochromeno[2,3-f]quinolin-7-one (20 mg, 64.5 μmol) and 6-chloro-3-fluoropyridine-2-carbonitrile (11.1 mg, 70.9 μmol) in DMSO (5 mL) was added TEA (13 mg, 129 μmol). The mixture was stirred at 100 °C for 10 hours under N₂ before it was cooled to rt. The mixture was diluted with EtOAc (50 mL) and water (30 mL). The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford a
- 10 residue, which was purified by silica gel chromatography to give 6-chloro-3-[[[(1R)-1-(9-fluoro-7-oxo-5,6-dihydrochromeno[2,3-f]quinolin-11-yl)ethyl]amino]pyridine-2-carbonitrile (20 mg, 69% yield) as a yellow solid. LC-MS: m/z 447.1 [M+H]⁺.

Step 2:

- To a solution of 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carbonitrile (20 mg, 45.4 μmol) in methanol (10 mL) was added hydroxylamine;hydrochloride (7.9 mg, 113.4 μmol) and K₂CO₃ (9.4 mg, 68.1 μmol). The mixture was stirred at 60 °C for 3 hours under N₂ before it was cooled to rt. The mixture was diluted with DCM (50 mL) and water (20 mL), the organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced
- 20 pressure to afford a residue, which was purified by silica gel chromatography to give 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-

1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]-N-hydroxy-pyridine-2-carboxamide (20 mg, 92% yield) as a yellow solid. LC-MS: m/z 480.1 $[M+H]^+$.

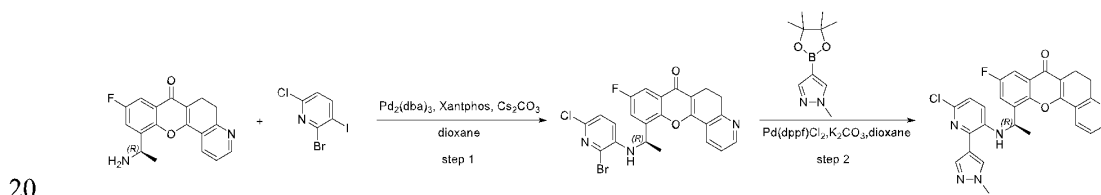
Step 3:

To a solution of 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]-N-hydroxy-pyridine-2-carboxamide (20 mg, 42.2 μ mol) in ACN (5 mL) was added CDI (8.2 mg, 50.6 μ mol) and DBU (16.1 mg, 105.5 μ mol). The mixture was stirred at 100 °C for 12 hours under N₂ before it was cooled to rt. The mixture was diluted with DCM (30 mL) and water (20 mL), the organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford a residue, which was purified by prep-HPLC to give 3-[6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]-2-pyridyl]-4H-1,2,4-oxadiazol-5-one (10 mg, 47% yield) as a white solid. LC-MS: m/z 506.1 $[M+H]^+$.

The following compound has been prepared in analogy to the representative procedures described for Example 51.

ID	Structure	LC-MS: m/z $[M+H]^+$
Example 65		571.7

Example 52



Step 1:

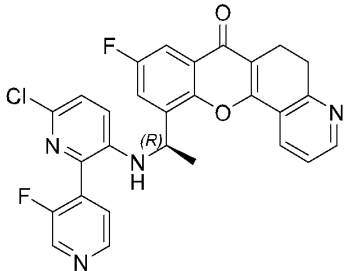
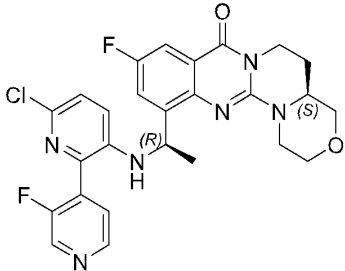
To a solution of (R)-11-(1-aminoethyl)-9-fluoro-5,6-dihydro-7H-chromeno[2,3-f]quinolin-7-one (150 mg, 483.9 μ mol) and 2-bromo-6-chloro-3-iodo-pyridine (200 mg, 629 μ mol) in dioxane (10 mL) was added tris(dibenzylideneacetone)dipalladium(0) (44.3 mg, 48.4 μ mol), (5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (56 mg, 96.8 μ mol) and cesium carbonate (315.3 mg, 967.8 μ mol). The mixture was stirred at 100 °C for 16 hours under N₂ before it was cooled to rt. The

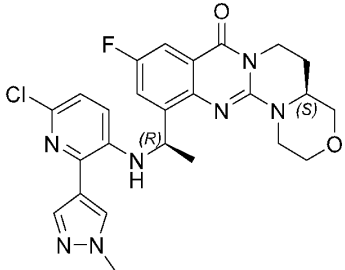
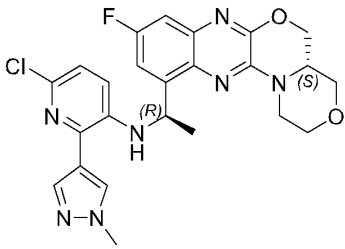
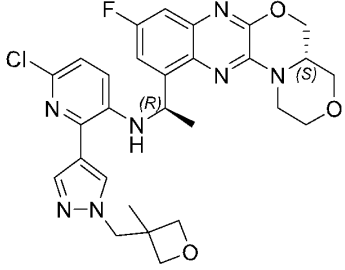
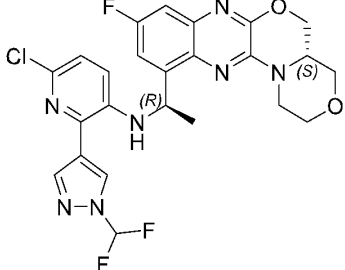
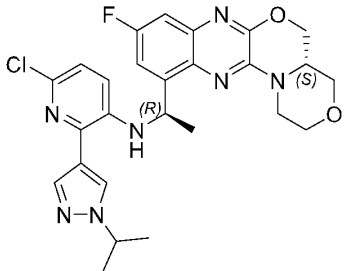
mixture was diluted with DCM and then washed with brine. The organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product. Then the crude was purified by silica gel chromatography to afford (R)-11-(1-((2-bromo-6-chloropyridin-3-yl)amino)ethyl)-9-fluoro-5,6-dihydro-7H-chromeno[2,3-f]quinolin-7-one (100 mg, 32% yield) as a light yellow solid. LC-MS: m/z 500.1 [M+H]⁺.

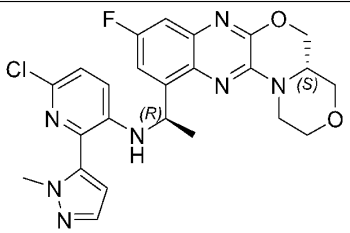
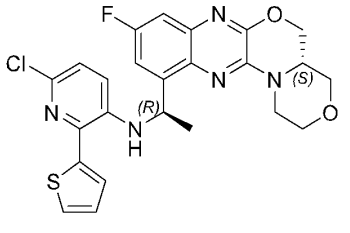
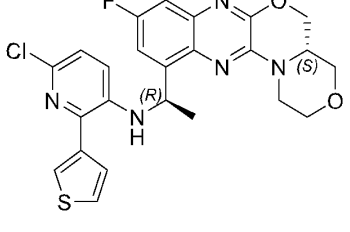
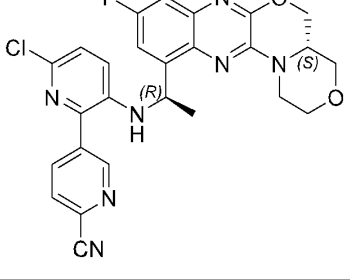
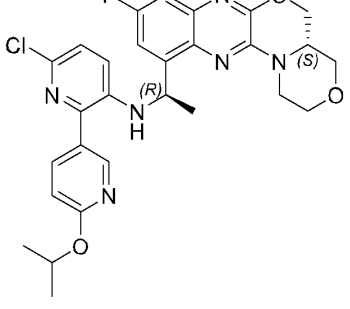
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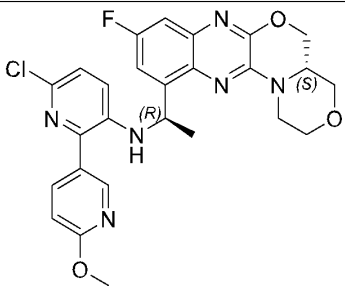
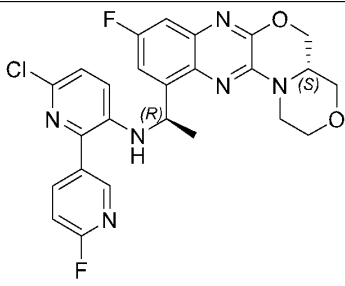
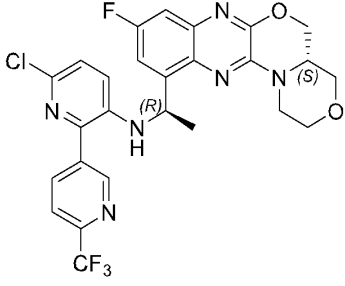
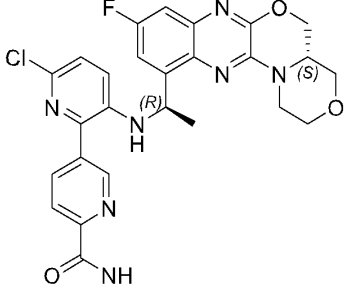
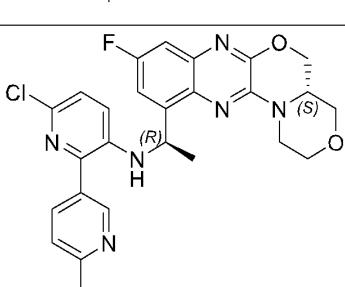
To a solution of (R)-11-(1-((2-bromo-6-chloropyridin-3-yl)amino)ethyl)-9-fluoro-5,6-dihydro-7H-chromeno[2,3-f]quinolin-7-one (20 mg, 40 μmol) and (1-methylpyrazol-4-yl)boronic acid (10.1 mg, 79.9 μmol) in dioxane (10 mL) was added potassium carbonate (11 mg, 79.9 μmol) and cyclopentyl(diphenyl)phosphane;dichloropalladium;iron (5.8 mg, 8 μmol). The mixture was stirred at 100 °C for 10 hours under N₂ before it was cooled to rt. The mixture was concentrated under reduced pressure to afford a residue, which was purified by prep-HPLC to afford (R)-11-(1-((6-chloro-2-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)amino)ethyl)-9-fluoro-5,6-dihydro-7H-chromeno[2,3-f]quinolin-7-one (4 mg, 20% yield) as a white solid. LC-MS: m/z 502.1 [M+H]⁺.

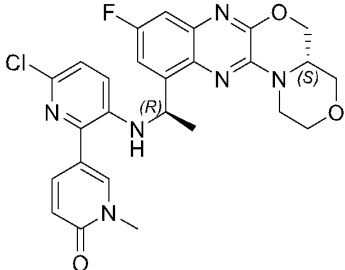
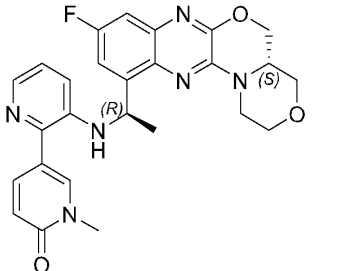
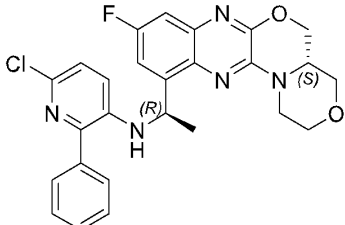
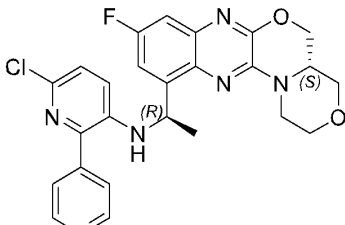
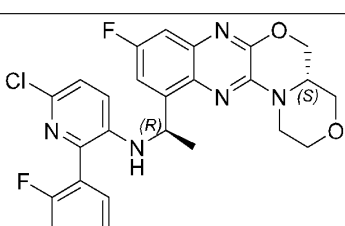
The following compounds have been prepared in analogy to the representative procedures described for **Example 52**.

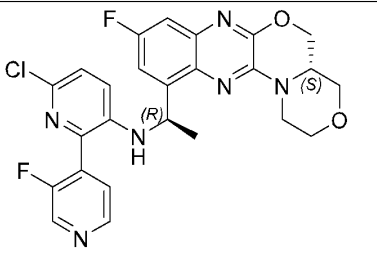
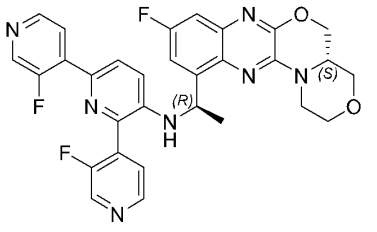
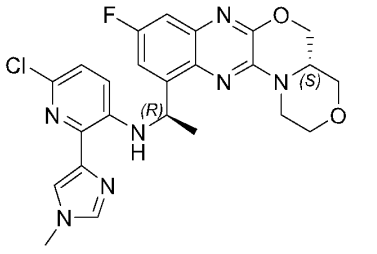
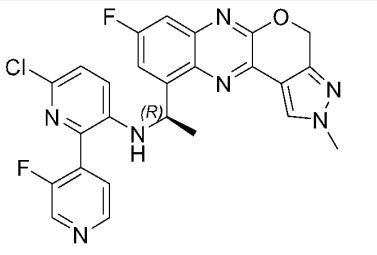
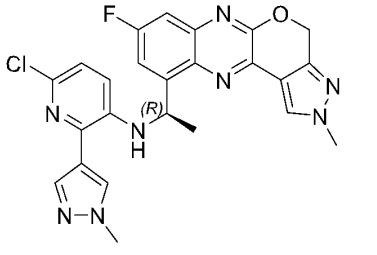
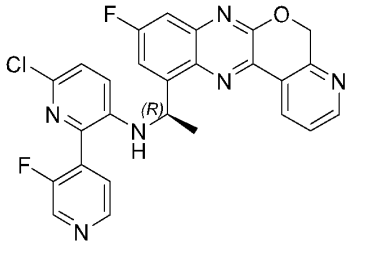
ID	Structure	LC-MS: m/z [M+H] ⁺
Example 53		517.1
Example 63		525.1

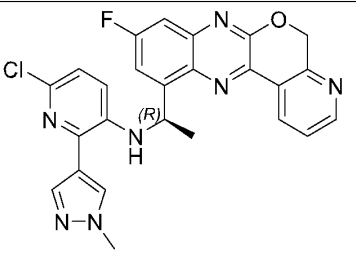
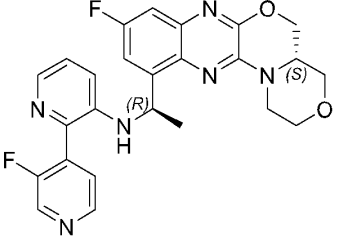
Example 64		510.1
Example 115		496.2
Example 116		566.3
Example 117		532.2
Example 118		524.2

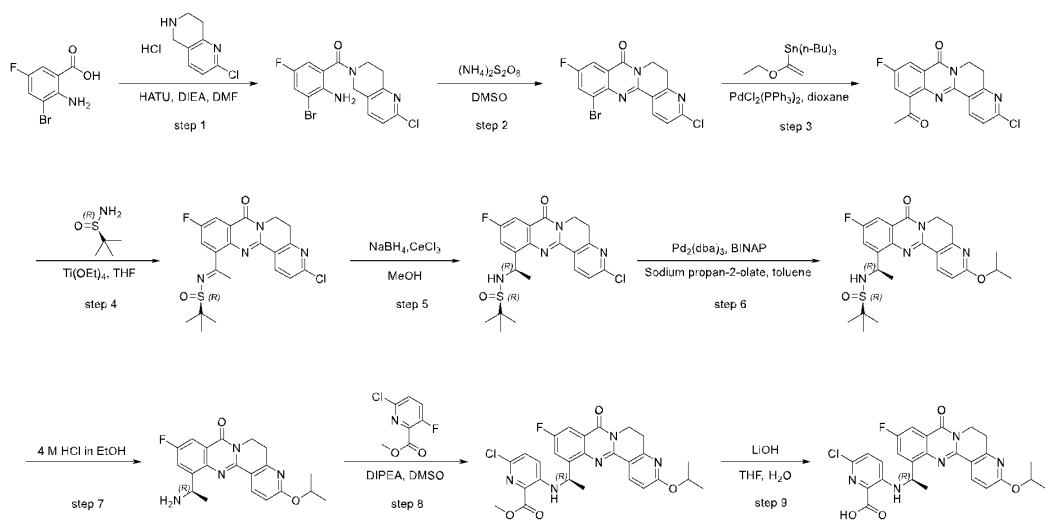
Example 119		496.2
Example 120		498.1
Example 121		498.1
Example 122		517.8
Example 123		550.9

Example 124		522.8
Example 125		511.1
Example 126		560.8
Example 127		549.8
Example 128		542.8

Example 129		522.9
Example 130		488.8
Example 131		491.8
Example 132		493.2
Example 133		509.8

Example 134		510.8
Example 135		571.8
Example 140		495.9
Example 142		505.6
Example 143		490.7
Example 144		502.7

Example 145		487.7
Example 147		476.9

Example 54**Step 1:**

- 5 To a solution of 2-amino-3-bromo-5-fluoro-benzoic acid (7.9 g, 33.8 mmol), 2-chloro-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (8.3 g, 40.5 mmol) in DMF (100 mL) at rt was added HATU (16.7 g, 43.9 mmol) and DIEA (13.1 g, 101.3 mmol). The mixture was stirred at rt for 18 hours. The mixture was poured into ice water (300 mL) and extracted with ethyl acetate (300 mL × 3). The combined organic layer was washed with water (200 mL) and saturated aqueous sodium chloride (200 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by prep-HPLC to afford (2-amino-3-bromo-5-fluoro-phenyl) -(2-chloro-7,8-dihydro-5H-1,6-naphthyridin-6-yl) methanone (10.5 g, 81% yield) as an amorphous solid. LC-MS: m/z 384.0 $[M+H]^+$.

Step 2:

To a solution of (2-amino-3-bromo-5-fluoro-phenyl) -(2-chloro-7,8-dihydro-5H-1,6-naphthyridin-6-yl) methanone (10.5 g, 27.3 mmol) in DMSO (100 mL) was added ammonium persulfate (24.9 g, 109.2 mmol). The mixture was stirred at 60 °C for 18 hours. The mixture was cooled to rt, poured into water (300 mL) and stirred for 0.5 hour. The resulting solid was collected via filtration and washed
5 with water (200 mL) and MTBE (100 mL × 2). The solid was dried *in vacuo* to provide 12-bromo-3-chloro-10-fluoro-5,6-dihydro-1,6-naphthyridino[5,6-b] quinazolin-8-one (3.8 g, 37% yield) as a pale yellow solid. LC-MS: m/z 380.0 [M+H]⁺.

Step 3:

To a mixture of 12-bromo-3-chloro-10-fluoro-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-8-one
10 (3.8 g, 10 mmol) and tributyl(1-ethoxyvinyl)stannane (4.3 g, 12 mmol) in dioxane (100 mL) was added bis(triphenylphosphine)palladium(II) chloride (700.8 mg, 998.4 μmol). The resulting mixture is purged with nitrogen for three times. The mixture was stirred at 100 °C under nitrogen for 16 hours. The reaction mixture was cooled to rt, poured into 1 N HCl (aq.) (60 mL), and stirred for 1 hour. The mixture was neutralized to approximately pH 8 using 10% Na₂CO₃ (aq.). The mixture was diluted
15 with CH₂Cl₂ and MeOH (100 mL, V:V=10:1) and the phases was separated. The water layer was extracted with CH₂Cl₂ and MeOH (60 mL, V:V=10:1) three times and the combined organic layer was dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel to afford 12-acetyl-3-chloro-10-fluoro-5,6-dihydro-1,6-naphthyridino[5,6-b] quinazolin-8-one (2 g, crude) as an earthy yellow solid. LCMS: m/z 344.0.
20 [M+H]⁺.

Step 4:

To a solution of 12-acetyl-3-chloro-10-fluoro-5,6-dihydro-1,6-naphthyridino[5,6-b] quinazolin-8-one (2 g, 5.8 mmol) in THF (20 mL) was added (R)-2-methylpropane-2-sulfinamide (1.4 g, 11.6 mmol) followed by titanium ethoxide (13.3 g, 58.2 mmol). The mixture was stirred at 80 °C for 18
25 hours. The mixture was cooled to 5 °C, quenched with ice water (20 mL) and diluted with EtOAc (30 mL). The mixture was stirred vigorously for 0.5 hour, filtered through a pad of Celite which was washed with EtOAc (30 mL) and separated. The layer was extracted with EtOAc (50 mL × 2) and the combined organic layer was washed with water (50 mL) and saturated NaCl (50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford (R,E)-N-(1-(3-chloro-10-fluoro-8-oxo-
30 5,8-dihydro-6H-[1,6]naphthyridino[5,6-b]quinazolin-12-yl)ethylidene)-2-methylpropane-2-sulfinamide (1.5 g, crude) as an off-white solid. LC-MS: m/z 447.1 [M+H]⁺.

Step 5:

To a stirred solution of (R,E)-N-(1-(3-chloro-10-fluoro-8-oxo-5,8-dihydro-6H-[1,6]naphthyridino[5,6-b]quinazolin-12-yl)ethylidene)-2-methylpropane-2-sulfinamide (1.5 g, 3.4 mmol) in MeOH (15 mL)
35 was added sodium borohydride (127 mg, 3.4 mmol) at rt. The mixture was stirred at rt for 5 minutes. The mixture was quenched with saturated NH₄Cl (aq.) (30 mL) and filtered. The filter cake was washed with EtOAc (50 mL × 2) and the aqueous layer was extracted with EtOAc (40 mL × 2).

The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel to afford a mixture, which was purified by prep-TLC to give (R)-N-[(1R)-1-(3-chloro-10-fluoro-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-12-yl)ethyl]-2-methyl-propane-2-sulfonamide (378 mg, 25% yield) as a white solid. LC-MS: m/z 449.1 [M+H]⁺.

Step 6:

To a microwave tube containing (R)-N-[(1R)-1-(3-chloro-10-fluoro-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-12-yl)ethyl]-2-methyl-propane-2-sulfonamide (60 mg, 133.6 μmol), sodium propan-2-olate (32.9 mg, 400.9 μmol, 20% in THF) and toluene (3 mL) was added Pd₂(dba)₃ (12.2 mg, 13.4 μmol), BINAP (12.5 mg, 20 μmol). The solution was degassed by N₂ gas balloon. The tube was then sealed and heated to 100 °C for 1.5 hours. After the reaction was completed, cooled to rt and filtered through a pad of celite, which was washed with EtOAc (10 mL × 2). The combined solution was concentrated *in vacuo* to obtain a yellowish solid. The product was purified by flash column chromatography on silica gel to afford (R)-N-[(1R)-1-(10-fluoro-3-isopropoxy-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-12-yl)ethyl]-2-methyl-propane-2-sulfonamide (30 mg, 47% yield) as a white solid. LCMS: m/z 473.2 [M+H]⁺.

Step 7:

To a stirred solution (R)-N-[(1R)-1-(10-fluoro-3-isopropoxy-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-12-yl)ethyl]-2-methyl-propane-2-sulfonamide (30 mg, 63.5 μmol) in EtOH (2 mL) was added 4 M HCl in EtOH (1 mL) and the reaction mixture was stirred at rt for 20 minutes. The reaction mixture was evaporated to afford 12-[(1R)-1-aminoethyl]-10-fluoro-3-isopropoxy-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-8-one (28 mg, crude) as an amorphous crystalline solid. LC-MS: m/z 369.2 [M+H]⁺.

Step 8:

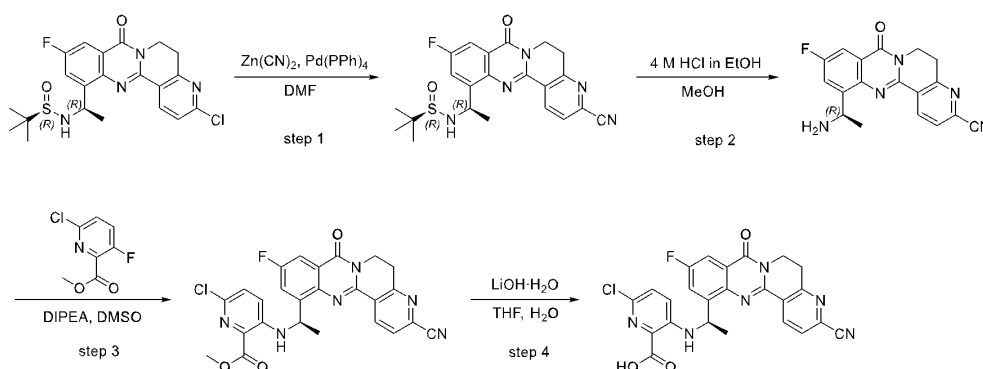
To a solution of 12-[(1R)-1-aminoethyl]-10-fluoro-3-isopropoxy-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-8-one (28 mg, 69.2 μmol) in DMSO (2 mL) was added DIPEA (44.7 mg, 345.8 μmol) followed by methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (17 mg, 89.9 μmol). The mixture was stirred at 100 °C for 15 hours. The mixture was cooled to rt, poured into water (10 mL) and extracted with EtOAc (20 mL × 3). The combined organic layer was washed with water (20 mL) and saturated aqueous sodium chloride (20 mL), dried over sodium sulfate, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel to obtain methyl 6-chloro-3-[[[(1R)-1-(10-fluoro-3-isopropoxy-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-12-yl)ethyl]amino]pyridine-2-carboxylate (25 mg, 67% yield) as brown oil. LC-MS: m/z 538.2 [M+H]⁺.

Step 9:

To a stirred solution of methyl 6-chloro-3-[[[(1R)-1-(10-fluoro-3-isopropoxy-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-12-yl)ethyl]amino]pyridine-2-carboxylate (25 mg, 46.5 μmol) in THF (3 mL) and water (2 mL) was added LiOH·H₂O (3.3 mg, 139.4 μmol). The mixture was

then stirred at rt for 2 hours. The mixture was cooled and diluted with water (5 mL), adjusted the pH to 2~3 with 2 N HCl and extracted with ethyl acetate (10 mL × 3). The combined organic layer was washed with water (15 mL) and saturated aqueous NaCl (15 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 6-chloro-3-[(1R)-1-(10-fluoro-3-isopropoxy-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-12-yl)ethyl]amino]pyridine-2-carboxylic acid (5.5 mg, 23% yield) as an off-white solid. LC-MS: m/z 524.1 [M+H]⁺.

Example 55



Step 1:

To a microwave tube containing (R)-N-[(1R)-1-(3-chloro-10-fluoro-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-12-yl)ethyl]-2-methyl-propane-2-sulfinamide (60 mg, 133.6 μmol) in DMF (3 mL) were added zinc cyanide (78.5 mg, 668.2 μmol), and tetrakis(triphenylphosphine)palladium(0) (15.4 mg, 13.4 μmol). The solution was degassed by N₂ gas balloon. The tube was then sealed and heated to 120 °C for 3 hours. The mixture was cooled to rt and filtered through a pad of celite, which was washed with EtOAc (10 mL × 3). The combined solution was poured into water (30 mL) and extracted with EtOAc (15 mL × 3). The combined organic layer was washed with water (30 mL) and NaCl (30 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford (R)-N-[(1R)-1-(3-cyano-10-fluoro-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-12-yl)ethyl]-2-methyl-propane-2-sulfinamide (62 mg, crude) as a white solid. LC-MS: m/z 440.2 [M+H]⁺.

Step 2:

To a stirred solution (R)-N-[(1R)-1-(3-cyano-10-fluoro-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-12-yl)ethyl]-2-methyl-propane-2-sulfinamide (62 mg, 141.1 μmol) in MeOH (5 mL) was added 4 M HCl in EtOH (2 mL) and the mixture was stirred at rt for 20 minutes. The mixture was concentrated to afford 12-[(1R)-1-aminoethyl]-10-fluoro-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazoline-3-carbonitrile (52 mg, 99% yield) as an amorphous solid. LC-MS: m/z 336.1 [M+H]⁺.

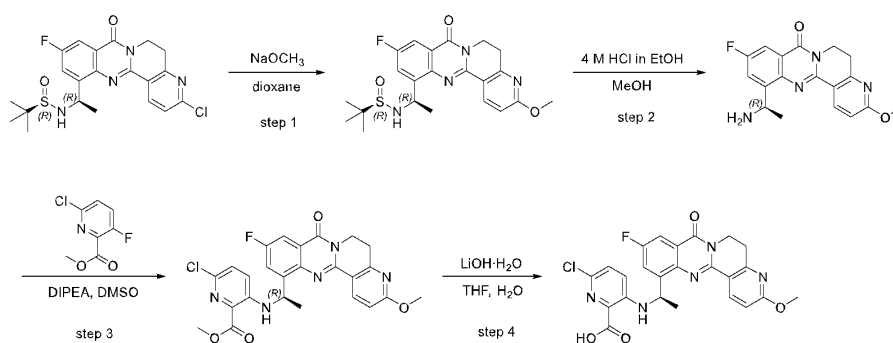
Step 3:

To a solution of 12-[(1R)-1-aminoethyl]-10-fluoro-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazoline-3-carbonitrile (52 mg, 139.9 μmol) in DMSO (3 mL) was added DIPEA (90.4 mg, 699.3 μmol) followed by methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (39.8 mg, 209.8 μmol).

- 5 The mixture was stirred at 100 °C for 15 hours. The reaction mixture was cooled down to room temperature, poured into water (15 mL) and extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layers were washed with water (20 mL) and saturated aqueous sodium chloride (20 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel to obtain methyl 6-chloro-3-[[[(1R)-1-(3-cyano-10-fluoro-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-12-yl)ethyl]amino]pyridine-2-carboxylate (40 mg, 57% yield) as a brown oil. LCMS: (ESI⁺) m/z 505.1 [M+H]⁺.

Step 4:

To a stirred solution of methyl 6-chloro-3-[[[(1R)-1-(3-cyano-10-fluoro-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-12-yl)ethyl]amino]pyridine-2-carboxylate (40 mg, 79.2 μmol) in THF (3 mL) and water (2 mL) was added LiOH·H₂O (5.7 mg, 237.7 μmol). The mixture was then stirred at rt for 2 hours. The mixture was cooled and diluted with water (5 mL), adjusted the pH to 2~3 with 2 N HCl and extracted with EtOAc (20 mL $\times$ 3). The combined organic layer was washed with water (15 mL) and NaCl (15 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 6-chloro-3-[[[(1R)-1-(3-cyano-10-fluoro-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-12-yl)ethyl]amino]pyridine-2-carboxylic acid (8 mg, 21% yield) as a white solid. LC-MS: m/z 491.1 [M+H]⁺.

Example 56**Step 1:**

- 25 To a microwave tube containing (R)-N-[(1R)-1-(3-chloro-10-fluoro-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-12-yl)ethyl]-2-methylpropane-2-sulfonamide (50 mg, 111.4 μmol) in dioxane (3 mL) was added CH₃ONa (18 mg, 334.1 μmol). The tube was then sealed and heated to 110 °C for 3 hours. The reaction was cooled to rt and filtered through a pad of celite, which
30 was washed with EtOAc (20 mL $\times$ 3). The combined solution was concentrated *in vacuo* to obtain a

yellowish solid. The product was purified by flash column chromatography on silica gel to afford (R)-N-[(1R)-1-(10-fluoro-3-methoxy-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-12-yl)ethyl]-2-methyl-propane-2-sulfinamide (35 mg, 71% yield) as brown oil. LC-MS: m/z 445.2 $[M+H]^+$.

Step 2:

5 To a stirred solution (R)-N-[(1R)-1-(10-fluoro-3-methoxy-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-12-yl)ethyl]-2-methyl-propane-2-sulfinamide (35 mg, 78.7 μmol) in EtOH (3 mL) was added 4 M HCl in EtOH (1.5 mL) and the reaction mixture was stirred at rt for 20 minutes. The reaction mixture was evaporated to afford 12-[(1R)-1-aminoethyl]-10-fluoro-3-methoxy-5,6-dihydro-1,6-naphthyridino[5,6-b] quinazolin-8-one (25 mg, 84% yield) as an amorphous solid. LC-MS: m/z
10 341.1 $[M+H]^+$.

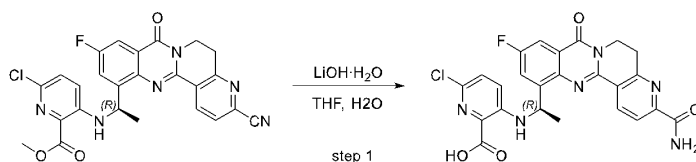
Step 3:

To a solution of 12-[(1R)-1-aminoethyl]-10-fluoro-3-methoxy-5,6-dihydro-1,6-naphthyridino[5,6-b]quinazolin-8-one (25 mg, 66.4 μmol) in DMSO (2 mL) was added DIPEA (42.9 mg, 331.7 μmol) followed by methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (18.9 mg, 99.5 μmol). The
15 mixture was stirred at 100 °C for 15 hours. The mixture was cooled to rt, poured into water (10 mL) and extracted with EtOAc (20 mL $\times$ 3). The combined organic layer was washed with water (20 mL) and NaCl (20 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel to give methyl 6-chloro-3-[[[(1R)-1-(10-fluoro-3-methoxy-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b] quinazolin-12-yl) ethyl] amino] pyridine-2-
20 carboxylate (25 mg, crude) as brown oil. LC-MS: m/z 510.1 $[M+H]^+$.

Step 4:

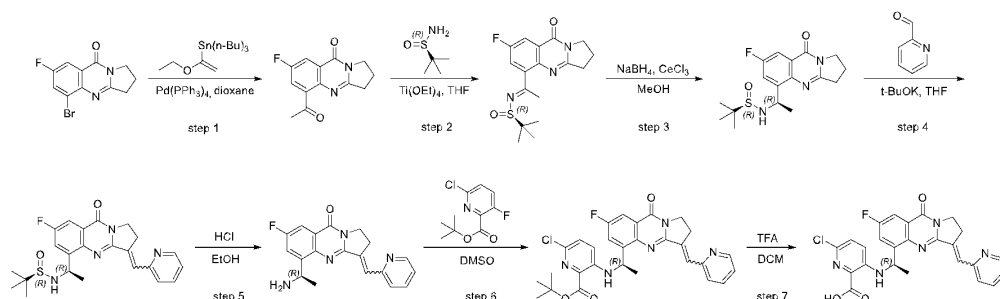
To a stirred solution of methyl 6-chloro-3-[[[(1R)-1-(10-fluoro-3-methoxy-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b] quinazolin-12-yl) ethyl] amino] pyridine-2-carboxylate (25 mg, 49.0 μmol) in THF (3 mL) and water (2 mL) was added $\text{LiOH} \cdot \text{H}_2\text{O}$ (3.5 mg, 147.1 μmol). The mixture was
25 then stirred at rt for 2 hours. The mixture was cooled and diluted with water (5 mL), adjusted the pH to 2~3 with 2 N HCl and extracted with EtOAc (10 mL $\times$ 3). The combined organic layer was washed with water (15 mL) and NaCl (15 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 6-chloro-3-[[[(1R)-1-(10-fluoro-3-methoxy-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b] quinazolin-12-yl) ethyl] amino] pyridine-2-carboxylic acid (5.6 mg,
30 23% yield) as an off-white solid. LC-MS: m/z 496.1 $[M+H]^+$.

Example 57



Step 1:

To a stirred solution of methyl 6-chloro-3-[[[(1R)-1-(3-cyano-10-fluoro-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b] quinazolin-12-yl) ethyl] amino] pyridine-2-carboxylate (20 mg, 39.6 μmol) in THF (3 mL) and water (3 mL) was added LiOH·H₂O (4.7 mg, 198.1 μmol). The mixture was stirred at rt for 3 hours, then heated to 50 °C for 1 hour. The mixture was cooled and diluted with water (5 mL), adjusted the pH to 2~3 with 2 N HCl and extracted with EtOAc (20 mL × 3). The combined organic layer was washed with water (15 mL) and NaCl (15 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 3-[[[(1R)-1-(3-carbamoyl-10-fluoro-8-oxo-5,6-dihydro-1,6-naphthyridino[5,6-b] quinazolin-12-yl) ethyl] amino]-6-chloro-pyridine-2-carboxylic acid (8.6 mg, 43% yield) as a white solid. LC-MS: m/z 509.1 [M+H]⁺.

Example 58**Step 1:**

To a mixture of 5-bromo-7-fluoro-2,3-dihydro-1H-pyrrolo[2,1-b]quinazolin-9-one (3.7 g, 13 mmol) and tributyl(1-ethoxyvinyl)stannane (6.1 g, 16.8 mmol) in dioxane (60 mL) was added tetrakis(triphenylphosphine)palladium(0) (1.5 g, 1.3 mmol). The resulting mixture is purged with nitrogen for three times. The reaction mixture is stirred at 100 °C under nitrogen for 36 hours. The reaction mixture was cooled to rt, poured into 1 N HCl (aq.) (60 mL) and stirred for 1 hour. The mixture is neutralized to pH~8 using 10% K₂CO₃ (aq.). The residue was diluted by CH₂Cl₂ and MeOH (80 mL, V:V = 10:1) and the phases were separated. The water layer was extracted with CH₂Cl₂ and MeOH (80 mL, V:V = 10:1) three times. The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel to afford 5-acetyl-7-fluoro-2,3-dihydro-1H-pyrrolo[2,1-b]quinazolin-9-one (5 g, crude) as a pale yellow solid. LC-MS: m/z 247.1 [M+H]⁺.

Step 2:

To a solution of 5-acetyl-7-fluoro-2,3-dihydro-1H-pyrrolo[2,1-b]quinazolin-9-one (5 g, 20.3 mmol) in THF (50 mL) was added (R)-2-methylpropane-2-sulfonamide (4.9 g, 40.6 mmol) followed by titanium ethoxide (23.2 g, 101.5 mmol). The mixture was stirred at 80 °C for 18 hours. The reaction mixture was cooled to 5 °C, quenched with ice water (50 mL) and diluted with EtOAc (50 mL). The reaction mixture was stirred vigorously for 0.5 hour, filtered through a pad of Celite which

was washed with EtOAc (30 mL) and separated. The aqueous layer was extracted with EtOAc (50 mL × 2). The combined organic layer was washed with water (60 mL) and NaCl (60 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford (R,E)-N-(1-(7-fluoro-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide (6 g, crude) as brown oil. LC-MS: m/z 350.1 [M+H]⁺.

Step 3:

To a stirred solution of (R,E)-N-(1-(7-fluoro-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide (3.5 g, 10 mmol) in MeOH (25 mL) was added NaBH₄ (492.6 mg, 13 mmol) at rt. The reaction mixture was stirred at rt for 20 minutes. After the reaction was completed, the mixture was quenched with saturated NH₄Cl (aq., 100 mL) and filtered. The filter cake was washed with EtOAc (30 mL × 2) and the aqueous layer was extracted with EtOAc (80 mL × 2). The combined organic phase was washed with brine (60 mL), dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel to yield (R)-N-[(1R)-1-(7-fluoro-9-oxo-2,3-dihydro-1H-pyrrolo[2,1-b]quinazolin-5-yl)ethyl]-2-methylpropane-2-sulfinamide (3 g, 85% yield) as an off-white solid. LC-MS: m/z 352.2 [M+H]⁺.

Step 4:

To a solution of (R)-N-[(1R)-1-(7-fluoro-9-oxo-2,3-dihydro-1H-pyrrolo[2,1-b]quinazolin-5-yl)ethyl]-2-methylpropane-2-sulfinamide (400 mg, 1.1 mmol) in THF (10 mL) was added potassium tert-butoxide (281 mg, 2.5 mmol) followed by pyridine-2-carbaldehyde (134.1 mg, 1.2 mmol). The mixture was stirred at 66 °C for 2 hours. The reaction mixture was cooled to rt, poured into ice water (30 mL) and extracted with EtOAc (30 mL × 2). The combined organic layer was washed with water (30 mL) and NaCl (30 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford (R)-N-[(R)-1-(7-fluoro-9-oxo-3-(pyridin-2-ylmethylene)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethyl]-2-methylpropane-2-sulfinamide (500 mg, 99% yield) as a yellow solid, which was used to the next step directly without further purification. LC-MS: m/z 441.2 [M+H]⁺.

Step 5:

To a stirred solution of (R)-N-[(R)-1-(7-fluoro-9-oxo-3-(pyridin-2-ylmethylene)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethyl]-2-methylpropane-2-sulfinamide (200 mg, 454 μmol) in EtOH (5 mL) was added 4 M HCl in EtOH (1.5 mL) and the reaction mixture was stirred at rt for 15 minutes. The reaction mixture was evaporated to afford the crude product and then basified with saturated sodium carbonate solution (10 mL), extracted with CH₂Cl₂ and MeOH (20 mL × 6, V:V=10:1). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give (R)-5-(1-aminoethyl)-7-fluoro-3-(pyridin-2-ylmethylene)-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (100 mg, 65% yield) as an amorphous solid. LC-MS: m/z 337.1 [M+H]⁺.

Step 6:

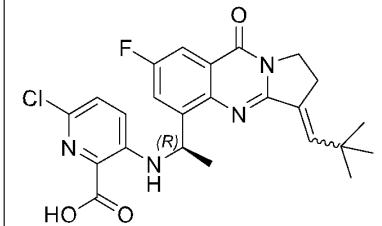
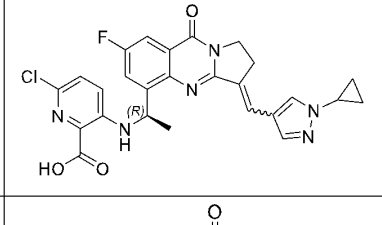
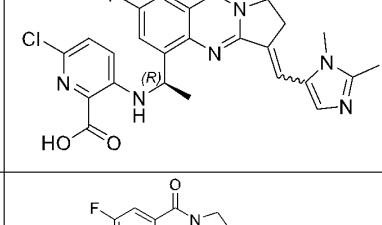
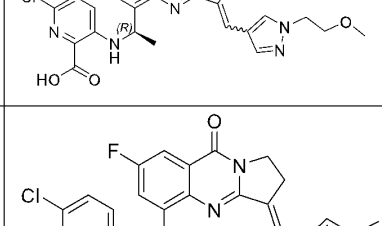
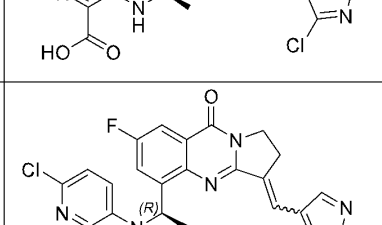
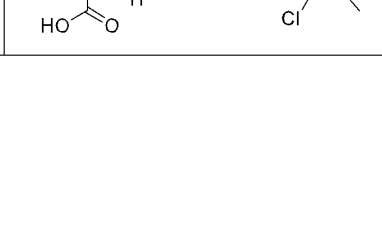
To a microwave tube containing (R)-5-(1-aminoethyl)-7-fluoro-3-(pyridin-2-ylmethylene)-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (30 mg, 89.2 μmol) in DMSO (2 mL) was added tert-butyl 6-chloro-3-fluoro-pyridine-2-carboxylate (41.3 mg, 178.4 μmol). The tube was then sealed and reacted in a microwave reactor at 120 °C for 2 hours. After the reaction was completed, cooled to rt, poured into water (15 mL) and extracted with EtOAc (30 mL $\times$ 3). The combined organic layer was washed with water (30 mL) and NaCl (30 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel to afford tert-butyl (R)-6-chloro-3-((1-(7-fluoro-9-oxo-3-(pyridin-2-ylmethylene)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethyl)amino)picolinate (10 mg, 20% yield) as a pale yellow solid. LC-MS: m/z 548.2 $[\text{M}+\text{H}]^+$.

Step 7:

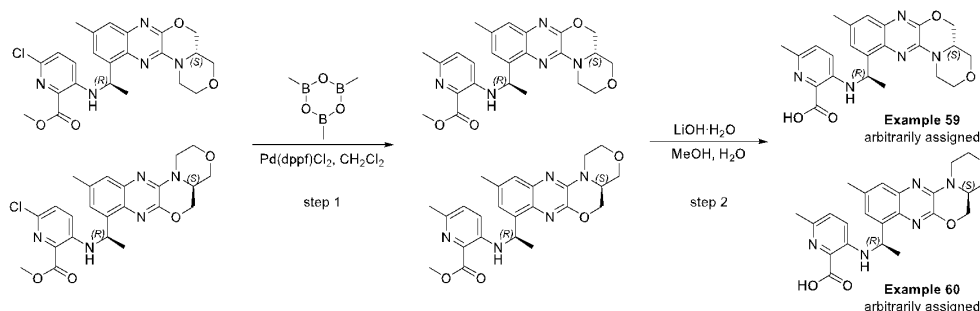
To a stirred solution of tert-butyl (R)-6-chloro-3-((1-(7-fluoro-9-oxo-3-(pyridin-2-ylmethylene)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethyl)amino)picolinate (10 mg, 18.2 μmol) in DCM (3 mL) was added TFA (1 mL) at 0 °C. The reaction mixture was stirred at rt for 12 hours. After the reaction was completed, the mixture was concentrated *in vacuo*. The crude product was purified by prep-HPLC to afford (R)-6-chloro-3-((1-(7-fluoro-9-oxo-3-(pyridin-2-ylmethylene)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethyl)amino)picolinic acid (0.5 mg, 6% yield) as an off-white solid. LC-MS: m/z 492.1 $[\text{M}+\text{H}]^+$.

The following compounds have been prepared in analogy to the representative procedures described for **Example 58**.

ID	Structure	LC-MS: m/z $[\text{M}+\text{H}]^+$
Example 169		495.1
Example 170		495.1

Example 171		471.1
Example 172		521.1
Example 173		509.1
Example 174		539.1
Example 175		529.0
Example 176		529.0

Example 59 and 60



Step 1:

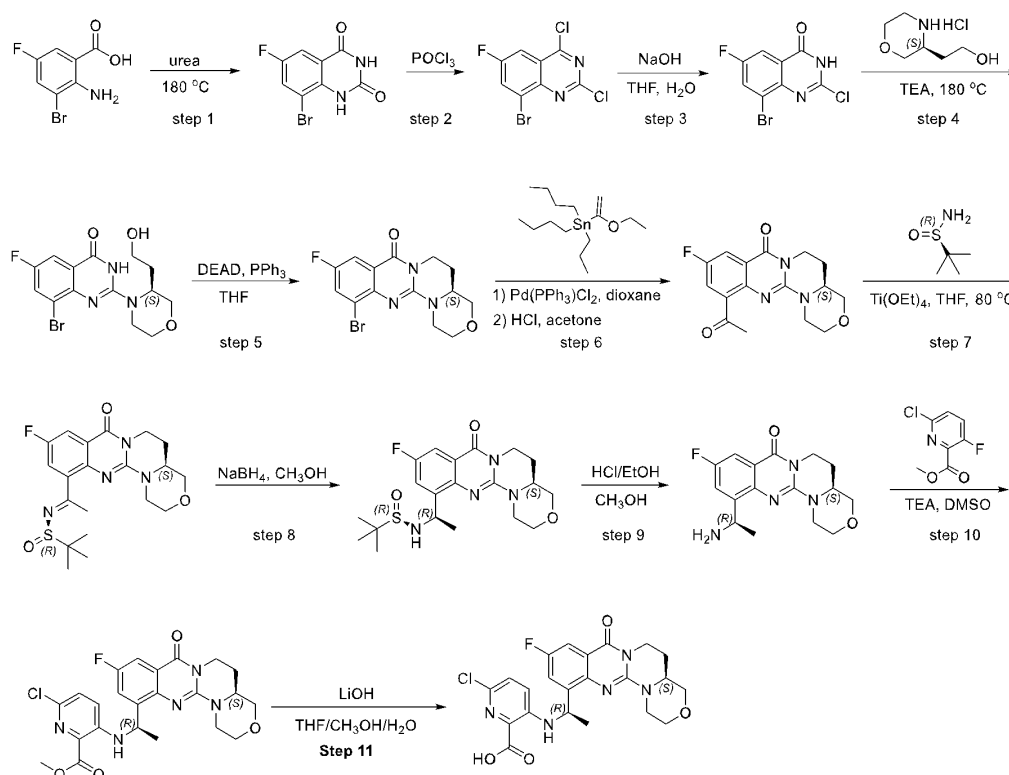
To a stirred mixture of methyl 6-chloro-3-[[[(1R)-1-[(7S)-14-methyl-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0.2,7.0]octadeca-1(18),10,12,14,16-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylate and methyl 6-chloro-3-[[[(1R)-1-[(7S)-15-methyl-9-oxo-2,11,18-triazatetracyclo[8.8.0.0.2,7.0]octadeca-1(18),10,12,14,16-pentaen-13-yl]ethyl]amino]pyridine-2-carboxylate (50 mg, 106.4 μmol) in dioxane (1.5 mL) and H_2O (0.5 mL) was added bis(1-diphenylphosphanyl)cyclopenta-2,4-dien-1-yl)iron;dichloromethane;dichloropalladium (17 mg, 21.3 μmol) and 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (26 mg, 212.8 μmol) under N_2 . The mixture was stirred at 100°C for 1 hour. The mixture was cooled to rt. Then HCl (1 mL, 4 N) was added to the mixture and the mixture was stirred at 20°C for 0.5 hour, extracted with DCM (100 mL $\times$ 2). The combined organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford a mixture of methyl 6-methyl-3-[[[(1R)-1-[(7S)-14-methyl-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0.2,7.0]octadeca-1(18),10,12,14,16-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylate and methyl 6-methyl-3-[[[(1R)-1-[(7S)-15-methyl-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0.2,7.0]octadeca-1(18),10,12,14,16-pentaen-13-yl]ethyl]amino]pyridine-2-carboxylate (20 mg, 42% yield) as a yellow solid. LC-MS: m/z 450.2 $[\text{M}+\text{H}]^+$.

Step 2:

To a stirred mixture of methyl 6-methyl-3-[[[(1R)-1-[(7S)-14-methyl-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0.2,7.0]octadeca-1(18),10,12,14,16-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylate and methyl 6-methyl-3-[[[(1R)-1-[(7S)-15-methyl-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0.2,7.0]octadeca-1(18),10,12,14,16-pentaen-13-yl]ethyl]amino]pyridine-2-carboxylate (20 mg, 44.5 μmol) in MeOH (1 mL) and H_2O (1 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (2 mg, 89 μmol). The mixture was stirred at rt for 2 hours. The mixture was added H_2O (10 mL) and adjusted pH to 2 with 1 N HCl (aq.). The mixture was extracted with DCM (50 mL $\times$ 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by prep-HPLC to give 6-methyl-3-[[[(1R)-1-[(7S)-14-methyl-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0.2,7.0]octadeca-1(18),10,12,14,16-pentaen-16-

yl]ethyl]amino]pyridine-2-carboxylic acid (**Example 59**, 7.5 mg, 38.7% yield) as a white solid (LC-MS: m/z 436.2 $[M+H]^+$) and 6-methyl-3-(((R)-1-((S)-10-methyl-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-8-yl)ethyl)amino)picolinic acid (**Example 60**, 4.4 mg, 22.7% yield) as a white solid. LC-MS: m/z 436.2 $[M+H]^+$.

5

Example 61**Step 1:**

A mixture of 2-amino-3-bromo-5-fluorobenzoic acid (8 g, 34.2 mmol) and urea (2.1 g, 34.2 mmol) was stirred at 180 °C for 5 hours. The mixture was cooled to 100 °C and water (100 mL) was added. The mixture was filtered and the filter cake was washed with water (50 mL). The filter cake was dried under vacuum to afford 8-bromo-6-fluoro-1H-quinazoline-2,4-dione (8.5 g, 96% yield) as a yellow solid.

Step 2:

A mixture of 8-bromo-6-fluoro-1H-quinazoline-2,4-dione (8.5 g, 32.8 mmol) in phosphorus oxychloride (131.6 g, 80 mL) was stirred at 130 °C for 16 hours. The mixture was concentrated to afford crude product. The crude was dissolved in CH₃CN (15 mL) and then poured into water (230 mL) slowly. The mixture was filtered and the filter cake was washed with water (50 mL). The filter cake was dried under vacuum to afford 8-bromo-2,4-dichloro-6-fluoro-1H-quinazoline (7 g, 72.1% yield) as a yellow solid.

Step 3:

A mixture of 8-bromo-2,4-dichloro-6-fluoro-quinazoline (400 mg, 1.4 mmol) in THF (8 mL) and 2 N NaOH (aq., 4 mL) was stirred at 20 °C for 1 hour. The mixture was adjusted to pH 5 with 1 N HCl (aq.). The mixture was diluted with water (30 mL) and extracted with CH₂Cl₂ (60 mL × 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to afford 8-bromo-2-chloro-6-fluoro-quinazolin-4-ol (400 mg, crude) as a yellow solid. LC-MS: m/z 277.0 [M+H]⁺.

Step 4:

To a solution of 8-bromo-2-chloro-6-fluoro-quinazolin-4-ol (530 mg, 1.9 mmol) and triethylamine (773.1 mg, 7.6 mmol) in n-BuOH (10 mL) was added 2-[(3S)-morpholin-3-yl]ethanol (350 mg, 2.1 mmol). The mixture was stirred at 180 °C for 16 hours. The mixture was concentrated to afford crude product, which was purified by column chromatography on silica gel to afford 8-bromo-6-fluoro-2-[(3S)-3-(2-hydroxyethyl)morpholin-4-yl]quinazolin-4-ol (360 mg, 51% yield) as a yellow solid. LC-MS: m/z 372.0 [M+H]⁺.

Step 5:

To a solution of 8-bromo-6-fluoro-2-[(3S)-3-(2-hydroxyethyl)morpholin-4-yl]quinazolin-4-ol (360 mg, 967.2 μmol) and triphenylphosphane (507.4 mg, 1.9 mmol) in THF (9 mL) was added a solution of diethyl (E)-1,2-diazenedicarboxylate (391.2 mg, 1.9 mmol) in THF (1 mL) at 0 °C under N₂. The mixture was stirred at 20 °C for 3 hours. The mixture was concentrated to afford crude product which was purified by column chromatography on silica gel to afford (7S)-16-bromo-14-fluoro-5-oxa-2,10,18-triazatetracyclo[8.8.0.02,7.012,17]octadeca-1(18),12(17),13,15-tetraen-11-one (600 mg, crude) as a yellow solid. LC-MS: m/z 354.0 [M+H]⁺.

Step 6:

To a solution of (7S)-16-bromo-14-fluoro-5-oxa-2,10,18-triazatetracyclo[8.8.0.02,7.012,17]octadeca-1(18),12(17),13,15-tetraen-11-one (600 mg, 1.7 mmol) in dioxane (10 mL) was added tributyl(1-ethoxyvinyl)stannane (917.7 mg, 2.5 mmol) and dichloropalladium;triphenylphosphane (237.8 mg, 338.8 μmol). The mixture was degassed with a stream of N₂ for three times and then stirred at 100 °C for 16 hours. The mixture was quenched with saturated KF solution (50 mL) and extracted with CH₂Cl₂ (150 mL × 2). The combined extracts were washed with brine (50 mL) and dried over anhydrous Na₂SO₄. Solvents were evaporated and the crude was dissolved in acetone (10 mL). 2 N HCl (aq., 3 mL) was added and the solution was then stirred at 20 °C for 20 minutes. The mixture was diluted with CH₂Cl₂ (150 mL) and washed with 10% NaHCO₃ (aq. 50 mL), dried over Na₂SO₄, filtered and concentrated to afford crude product which was purified by column chromatography on silica gel to afford (7S)-16-acetyl-14-fluoro-5-oxa-2,10,18-triazatetracyclo[8.8.0.02,7.012,17]octadeca-1(18),12(17),13,15-tetraen-11-one (450 mg, crude) as a light yellow solid.

Step 7:

To a solution of (7S)-16-acetyl-14-fluoro-5-oxa-2,10,18-triazatetracyclo[8.8.0.02,7.012,17]octadeca-1(18),12(17),13,15-tetraen-11-one (450 mg, 1.4 mmol) in titanium ethoxide (8 mL) and THF (8 mL) was added (R)-2-methylpropane-2-sulfinamide (515.6 mg, 4.2 mmol). The mixture was stirred at 5 80 °C for 16 hours under N₂. The mixture was diluted with EtOAc (200 mL) and then water (50 mL) was added. The mixture was stirred at 20 °C for 0.5 hour. The mixture was filtered and the organic layer was washed with brine (50 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product which was purified by column chromatography on silica gel eluting to afford (R)-N-((E)-1-((S)-10-fluoro-8-oxo-1,2,4,4a,5,6-hexahydro-8H-
10 [1,4]oxazino[4',3':3,4]pyrimido[2,1-b]quinazolin-12-yl)ethylidene)-2-methylpropane-2-sulfinamide (480 mg, 80.5% yield) as light yellow oil. LC-MS: m/z 421.3 [M+H]⁺.

Step 8:

To a solution of (R)-N-((E)-1-((S)-10-fluoro-8-oxo-1,2,4,4a,5,6-hexahydro-8H-
[1,4]oxazino[4',3':3,4]pyrimido[2,1-b]quinazolin-12-yl)ethylidene)-2-methylpropane-2-sulfinamide
15 (480 mg, 1.1 mmol) and trichlorocerium (112.5 mg, 456.6 μmol) in methanol (10 mL) was added sodiumboranuide (95 mg, 2.5 mmol). The mixture was stirred at 20 °C for 10 minutes. The mixture was diluted with CH₂Cl₂ (70 mL) and then washed with brine (30 mL × 2). The organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product which was purified by column chromatography on silica gel to afford (R)-N-[(1R)-1-[(7S)-14-fluoro-11-oxo-5-oxa-2,10,18-
20 triazatetracyclo[8.8.0.02,7.012,17]octadeca-1(18),12(17),13,15-tetraen-16-yl]ethyl]-2-methylpropane-2-sulfinamide (260 mg, 54% yield) as a light yellow solid. LC-MS: m/z 423.2 [M+H]⁺.

Step 9:

To a solution of (R)-N-[(1R)-1-[(7S)-14-fluoro-11-oxo-5-oxa-2,10,18-
triazatetracyclo[8.8.0.02,7.012,17]octadeca-1(18),12(17),13,15-tetraen-16-yl]ethyl]-2-methyl-
25 propane-2-sulfinamide (55 mg, 130.1 μmol) in methanol (8 mL) was added a solution of 4 N HCl in EtOH (1.5 mL). The mixture was stirred at 20 °C for 5 minutes. The mixture was diluted with CH₂Cl₂ (100 mL) and then washed with 10% NaHCO₃ (aq., 15 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated to afford (7S)-16-[(1R)-1-aminoethyl]-14-fluoro-5-oxa-2,10,18-
triazatetracyclo[8.8.0.02,7.012,17]octadeca-1(18),12(17),13,15-tetraen-11-one (60 mg, crude) as a
30 white solid. The crude was used directly without further purification. LC-MS: m/z 319.1 [M+H]⁺.

Step 10:

To a solution of (7S)-16-[(1R)-1-aminoethyl]-14-fluoro-5-oxa-2,10,18-
triazatetracyclo[8.8.0.02,7.012,17]octadeca-1(18),12(17),13,15-tetraen-11-one (60 mg, 188.5 μmol) and triethylamine (76.3 mg, 753.9 μmol) in DMSO (3 mL) was added methyl 6-chloro-3-fluoro-
35 pyridine-2-carboxylate (35.7 mg, 188.5 μmol). The mixture was stirred at 100 °C for 16 hours. The mixture was diluted with EtOAc (100 mL) and washed with aq.NaCl (30 mL × 3). The organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by

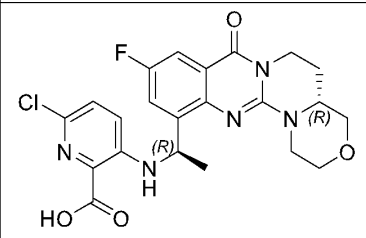
column chromatography on silica gel to afford methyl 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-11-oxo-5-oxa-2,10,18-triazatetracyclo[8.8.0.02,7.012,17]octadeca-1(18),12(17),13,15-tetraen-16-yl]ethyl]amino]pyridine-2-carboxylate (50 mg, 54% yield) as a white solid. LC-MS: m/z 488.1 $[M+H]^+$.

5 Step 11:

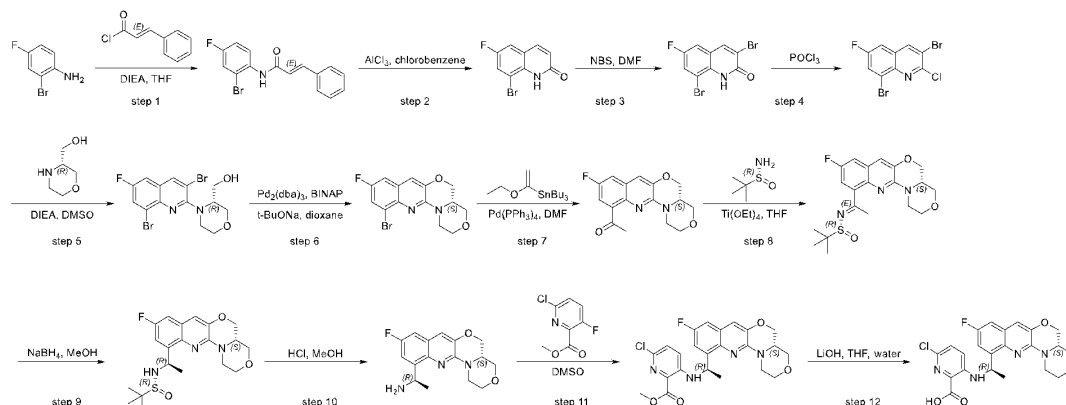
To a solution of methyl 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-11-oxo-5-oxa-2,10,18-triazatetracyclo[8.8.0.02,7.012,17]octadeca-1(18),12(17),13,15-tetraen-16-yl]ethyl]amino]pyridine-2-carboxylate (50 mg, 102.5 μmol) in THF (4 mL), methanol (1 mL) and water (1 mL) was added lithium;hydroxide;hydrate (21.5 mg, 512.4 μmol). The mixture was stirred at 20 °C for 20 minutes.

- 10 The mixture was adjusted to pH 5 with aq. NaHCO_3 , diluted with brine (20 mL) and then extracted with CH_2Cl_2 (60 mL $\times$ 2). The combined organic layer was dried over Na_2SO_4 , filtered and concentrated to afford crude product. The crude was purified by prep-HPLC to afford 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-11-oxo-5-oxa-2,10,18-triazatetracyclo[8.8.0.02,7.012,17]octadeca-1(18),12(17),13,15-tetraen-16-yl]ethyl]amino]pyridine-2-carboxylic acid (25 mg, 52% yield) as a
- 15 white solid. LC-MS: m/z 474.1 $[M+H]^+$.

The following compound has been prepared in analogy to the representative procedures described for **Example 61**.

ID	Structure	LC-MS: m/z $[M+H]^+$
Example 62		474.1

20 Example 69



Step 1:

To a stirred solution of 2-bromo-4-fluoro-aniline (6 g, 31.6 mmol), (E)-3-phenylprop-2-enoyl chloride (5.3 g, 31.6 mmol) in THF (50 mL) was added DIPEA (12.2 g, 94.7 mmol) at 25 °C. The mixture was stirred at 25 °C under N₂ for 10 hours, diluted with water (50 mL) and extracted with DCM (100 mL).

- 5 The organic layer was washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by silica gel chromatography to give (E)-N-(2-bromo-4-fluoro-phenyl)-3-phenyl-prop-2-enamide (8 g, 79% yield) as a yellow solid. LC-MS: m/z 319.8 [M+H]⁺.

Step 2:

- 10 To a stirred solution of (E)-N-(2-bromo-4-fluoro-phenyl)-3-phenyl-prop-2-enamide (8 g, 25 mmol) in chlorobenzene (40 mL) was added AlCl₃ (11.7 g, 87.5 mmol) in portions at 25 °C. The mixture was stirred at 120 °C under N₂ for 5 hours. The mixture was diluted with water (50 mL), then adjust pH to 7 with saturated aqueous NaHCO₃ and extracted with DCM (300 mL × 2). The organic layer was washed with brine (300 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure.
- 15 The crude was purified by silica gel chromatography to give 8-bromo-6-fluoro-quinolin-2-ol (3 g, 50% yield) as a yellow solid. LC-MS: m/z 241.9 [M+H]⁺.

Step 3:

- To a stirred solution of 8-bromo-6-fluoro-quinolin-2-ol (1.9 g, 7.9 mmol) in DMF (30 mL) was added NBS (2.8 g, 15.7 mmol) at 25 °C. The mixture was stirred at 60 °C under N₂ for 12 hours. The
- 20 mixture was diluted with water (50 mL) and extracted with EtOAc (100 mL × 2). The organic layer was washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 3,8-dibromo-6-fluoro-quinolin-2-ol (1.5 g, 60% yield) as yellow oil. LC-MS: m/z 319.8 [M+H]⁺.

Step 4:

- 25 A solution of 3,8-dibromo-6-fluoro-quinolin-2-ol (1.5 g, 4.7 mmol) in POCl₃ (21.5 g, 140.2 mmol) was stirred at 120 °C under N₂ for 2 hours. The mixture was added to saturated aqueous NaHCO₃ slowly, then extracted with EtOAc (300 mL × 2). The organic layer was washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by silica gel chromatography to give 3,8-dibromo-2-chloro-6-fluoro-quinoline (1.2 g, 76% yield) as a yellow
- 30 solid. LC-MS: m/z 337.9 [M+H]⁺.

Step 5:

- To a stirred solution of 3,8-dibromo-2-chloro-6-fluoro-quinoline (1 g, 3 mmol) and [(3R)-morpholin-3-yl]methanol (690 mg, 5.9 mmol) in DMSO (10 mL) was added DIPEA (1.9 g, 14.7 mmol) at 25 °C. The mixture was stirred at 130 °C under microwave for 4 hours. The mixture was diluted with water
- 35 (20 mL) and extracted with DCM (50 mL × 2). The organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The mixture was purified by

silica gel chromatography to give [(3R)-4-(3,8-dibromo-6-fluoro-2-quinolyl)morpholin-3-yl]methanol (400 mg, 32% yield) as a yellow solid. LC-MS: m/z 418.9 $[M+H]^+$.

Step 6:

To a stirred solution of [(3R)-4-(3,8-dibromo-6-fluoro-2-quinolyl)morpholin-3-yl]methanol (400 mg, 952 μmol) in dioxane (10 mL) was added (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one; palladium (87 mg, 95 μmol), [1-(2-diphenylphosphanyl-1-naphthyl)-2-naphthyl]-diphenyl-phosphane (119 mg, 190 μmol), t-BuONa (275 mg, 2.9 mmol) at 25 °C. The mixture was stirred at 100 °C under N_2 for 10 hours. The mixture was diluted with water (30 mL) and extracted with DCM (50 mL $\times$ 2). The organic layer was washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The mixture was purified by silica gel chromatography to give (S)-11-bromo-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[3,2-b]quinoline (200 mg, 62% yield) as a yellow solid. LC-MS: m/z 339.0 $[M+H]^+$.

Step 7:

To a stirred solution of (S)-11-bromo-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[3,2-b]quinoline (200 mg, 590 μmol) in DMF (10 mL) was added tributyl(1-ethoxyvinyl)stannane (319 mg, 885 μmol), palladium; triphenylphosphane (34 mg, 29 μmol) at 25 °C under N_2 . The mixture was stirred at 100 °C for 4 hours. The mixture was diluted with DCM (50 mL), then quenched with saturated aqueous KF (50 mL). The mixture was stirred at 20 °C for 2 hours, filtered and separated. The organic layer was concentrated under reduced pressure, then dissolved in acetone (30 mL) and 2 N HCl (5 mL) was added. The mixture was stirred at 20 °C for 30 minutes. Then the mixture was diluted with water (50 mL) and extracted with DCM (100 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give (S)-1-(9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[3,2-b]quinolin-11-yl)ethan-1-one (80 mg, 45% yield) as a yellow solid. LC-MS: m/z 303.1 $[M+H]^+$.

Step 8:

To a stirred solution of (S)-1-(9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[3,2-b]quinolin-11-yl)ethan-1-one (80 mg, 265 μmol) in THF (10 mL) was added $Ti(OEt)_4$ (604 mg, 2.7 mmol), (R)-2-methylpropane-2-sulfinamide (128 mg, 1.1 mmol) at 25 °C. The mixture was stirred at 85 °C for 12 hours. The mixture was diluted with EtOAc (50 mL) and water (50 mL) was added. The mixture was filtered, the filtrate was extracted with EtOAc (50 mL $\times$ 2). The organic layer was washed with brine (50 mL), dried over Na_2SO_4 , then concentrated under reduced pressure. The mixture was purified by silica gel chromatography to give (R)-N-((E)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[3,2-b]quinolin-11-yl)ethylidene)-2-methylpropane-2-sulfinamide (100 mg, 93% yield) as a yellow solid. LC-MS: m/z 406.1 $[M+H]^+$.

Step 9:

To a stirred solution of (R)-N-((E)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[3,2-b]quinolin-11-yl)ethylidene)-2-methylpropane-2-sulfonamide (100 mg, 247 μ mol) in methanol (5 mL) was added CeCl_3 (61 mg, 247 μ mol), NaBH_4 (11 mg, 296 μ mol) at 20 °C. The mixture was stirred at 20 °C for 10 minutes. The mixture was diluted with water (50 mL), then extracted with DCM (100 mL). The organic layer was dried over Na_2SO_4 (50 mL), filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give (R)-N-((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[3,2-b]quinolin-11-yl)ethyl)-2-methylpropane-2-sulfonamide (100 mg, 99% yield) as a yellow solid. LC-MS: m/z 408.1 $[\text{M}+\text{H}]^+$.

Step 10:

To a stirred solution of (R)-N-((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[3,2-b]quinolin-11-yl)ethyl)-2-methylpropane-2-sulfonamide (100 mg, 245 μ mol) in methanol (5 mL) was added HCl (600 μ L, 4.0 M in ethanol) at 0 °C. The mixture was stirred at 0 °C for 30 minutes. The pH of the mixture was adjusted to 8 with saturated aqueous NaHCO_3 , then diluted with water (50 mL) and extracted with DCM (100 mL $\times$ 2). The organic layer was washed with brine (100 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give (R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[3,2-b]quinolin-11-yl)ethan-1-amine (70 mg, 94% yield) as yellow oil. LC-MS: m/z 304.1 $[\text{M}+\text{H}]^+$.

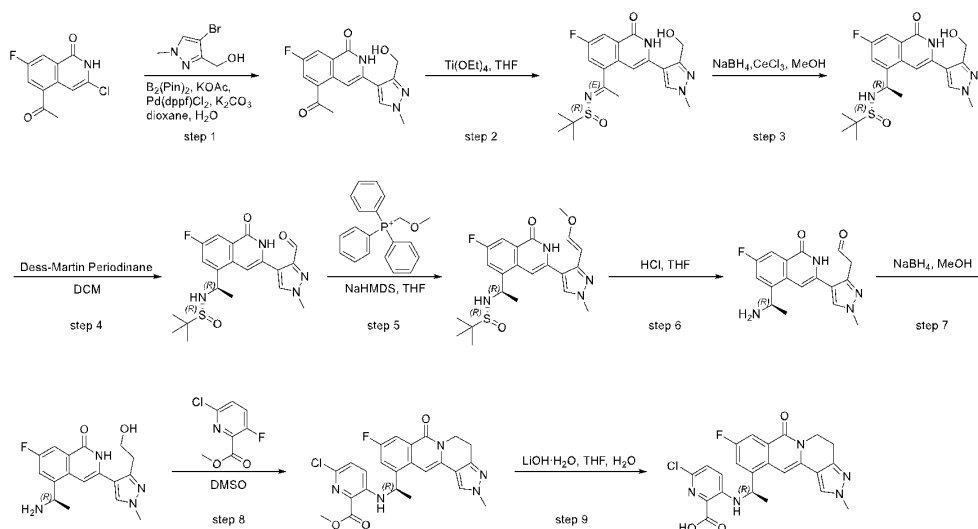
Step 11:

To a stirred solution of (R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[3,2-b]quinolin-11-yl)ethan-1-amine (70 mg, 231 μ mol) in DMSO (5 mL) was added methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (88 mg, 462 μ mol) at 20 °C. The mixture was stirred at 120 °C for 2 hours. The mixture was diluted with water (10 mL), then extracted with EtOAc (50 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The mixture was purified by silica gel chromatography to give methyl 6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[3,2-b]quinolin-11-yl)ethyl)amino)picolinate (40 mg, 37% yield) as yellow oil. LC-MS: m/z 473.1 $[\text{M}+\text{H}]^+$.

Step 12:

To a stirred solution of methyl 6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[3,2-b]quinolin-11-yl)ethyl)amino)picolinate (40 mg, 85 μ mol) in mixed solvents of water and THF (5 mL, 1:3) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (20 mg, 846 μ mol). The mixture was stirred at 20 °C for 2 hours. The pH of the mixture was adjusted to 6 with saturated aqueous NH_4Cl , then extracted with DCM (50 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC to give 6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[3,2-b]quinolin-11-yl)ethyl)amino)picolinic acid (20 mg, 52% yield) as a white solid. LC-MS: m/z 459.1 $[\text{M}+\text{H}]^+$.

Example 72



Step 1:

To a stirred solution of (4-bromo-1-methyl-1H-pyrazol-3-yl)methanol (1.2 g, 6.3 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (3.2 g, 12.6 mmol) in dioxane (30 mL) was added Pd(dppf)Cl₂ (460 mg, 628 μmol), KOAc (1.9 g, 18.9 mmol) at 20 °C. The mixture was stirred at 100 °C under N₂ for 2 hours. Then the mixture was filtered. To the filtrate was added 5-acetyl-3-chloro-7-fluoroisoquinolin-1(2H)-one (805 mg, 3.4 mmol), Pd(dppf)Cl₂ (246 mg, 336 μmol), K₂CO₃ (1.4 g, 10.1 mmol), water (3 mL) at 20 °C. The mixture was stirred at 100 °C under N₂ for 2 hours. The mixture was diluted with water (50 mL) and extracted with DCM (100 mL × 2). The organic layer was washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The mixture was purified by silica gel chromatography to give 5-acetyl-7-fluoro-3-(3-(hydroxymethyl)-1-methyl-1H-pyrazol-4-yl)isoquinolin-1(2H)-one (1.2 g, crude) as yellow oil. LC-MS: m/z 316.1 [M+H]⁺.

Step 2:

To a stirred solution of 5-acetyl-7-fluoro-3-(3-(hydroxymethyl)-1-methyl-1H-pyrazol-4-yl)isoquinolin-1(2H)-one (1.2 g, 3.8 mmol) in THF (30 mL) was added Ti(OEt)₄ (17.4 g, 76.1 mmol), (R)-2-methylpropane-2-sulfinamide (923 mg, 7.6 mmol) at 20 °C. The mixture was stirred at 85 °C for 12 hours. The mixture was diluted with EtOAc (50 mL) and water (50 mL). The mixture was stirred and filtered, the filtrate was extracted with EtOAc (50 mL × 2). The organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The mixture was purified by silica gel chromatography to give (R,E)-N-(1-(7-fluoro-3-(3-(hydroxymethyl)-1-methyl-1H-pyrazol-4-yl)-1-oxo-1,2-dihydroisoquinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide (1.2 g, 75% yield) as a yellow solid. LC-MS: m/z 419.1 [M+H]⁺.

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Step 3:

To a stirred solution of (R,E)-N-(1-(7-fluoro-3-(3-(hydroxymethyl)-1-methyl-1H-pyrazol-4-yl)-1-oxo-1,2-dihydroisoquinolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide (1.2 g, 2.9 mmol) in methanol (15 mL) was added CeCl_3 (707 mg, 2.9 mmol), NaBH_4 (325 mg, 8.6 mmol) at 20 °C. The mixture was stirred at 20 °C for 10 minutes, diluted with water (50 mL), then extracted with DCM (100 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give (R)-N-((R)-1-(7-fluoro-3-(3-(hydroxymethyl)-1-methyl-1H-pyrazol-4-yl)-1-oxo-1,2-dihydroisoquinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (800 mg, 66% yield) as a yellow solid. LC-MS: m/z 421.2 $[\text{M}+\text{H}]^+$.

Step 4:

To a stirred solution of (R)-N-((R)-1-(7-fluoro-3-(3-(hydroxymethyl)-1-methyl-1H-pyrazol-4-yl)-1-oxo-1,2-dihydroisoquinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (850 mg, 2 mmol) in DCM (30 mL) was added Dess-Martin periodinane (1.7 g, 4 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 hour. The mixture was quenched with water (50 mL), then extracted with DCM (100 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give (R)-N-((R)-1-(7-fluoro-3-(3-formyl-1-methyl-1H-pyrazol-4-yl)-1-oxo-1,2-dihydroisoquinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (800 mg, 95% yield) as yellow oil. LC-MS: m/z 419.2 $[\text{M}+\text{H}]^+$.

Step 5:

To a stirred suspension of methoxymethyl(triphenyl)phosphonium;chloride (983 mg, 2.9 mmol) in THF (30 mL) was added sodium;bis(trimethylsilyl)azanide (526 mg, 2.9 mmol, 2 M in THF) at 0 °C. The mixture was stirred at 0 °C for 20 minutes, then (R)-N-((R)-1-(7-fluoro-3-(3-formyl-1-methyl-1H-pyrazol-4-yl)-1-oxo-1,2-dihydroisoquinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (800 mg, 1.9 mmol) was added. The mixture was stirred at 0 - 20 °C for 2 hours, diluted with water (30 mL), then extracted with DCM (50 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give (R)-N-((R)-1-(7-fluoro-3-(3-((E)-2-methoxyvinyl)-1-methyl-1H-pyrazol-4-yl)-1-oxo-1,2-dihydroisoquinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (800 mg, 94% yield) as a yellow solid. LC-MS: m/z 447.2 $[\text{M}+\text{H}]^+$.

Step 6:

To a stirred solution of (R)-N-((R)-1-(7-fluoro-3-(3-((E)-2-methoxyvinyl)-1-methyl-1H-pyrazol-4-yl)-1-oxo-1,2-dihydroisoquinolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (800 mg, 1.8 mmol) in mixed solvents of water and THF (6 mL, 1:5) was added concentrated hydrogen chloride (1 mL) at 20 °C. The mixture was stirred at 50 °C for 10 minutes. The mixture was concentrated under reduced pressure to give (R)-2-(4-(5-(1-aminoethyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)-1-methyl-1H-pyrazol-3-yl)acetaldehyde (800 mg, crude) as yellow oil. LC-MS: m/z 329.1 $[\text{M}+\text{H}]^+$.

Step 7:

To a stirred solution of (R)-2-(4-(5-(1-aminoethyl)-7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)-1-methyl-1H-pyrazol-3-yl)acetaldehyde (800 mg, 2.4 mmol) in methanol (10 mL) was added NaBH₄ (184 mg, 4.9 mmol) at 20 °C. The mixture was stirred at 20 °C for 10 minutes. The mixture was
5 diluted with water (5 mL), then concentrated under reduced pressure. The residue was diluted with DCM (10 mL), filtered and the filter cake was dried *in vacuo*, diluted with MeOH (20 mL) and filtered, the filtrate was dried under reduced pressure to give (R)-5-(1-aminoethyl)-7-fluoro-3-(3-(2-hydroxyethyl)-1-methyl-1H-pyrazol-4-yl)isoquinolin-1(2H)-one (550 mg, 68% yield) as a yellow solid. LC-MS: m/z 331.1 [M+H]⁺.

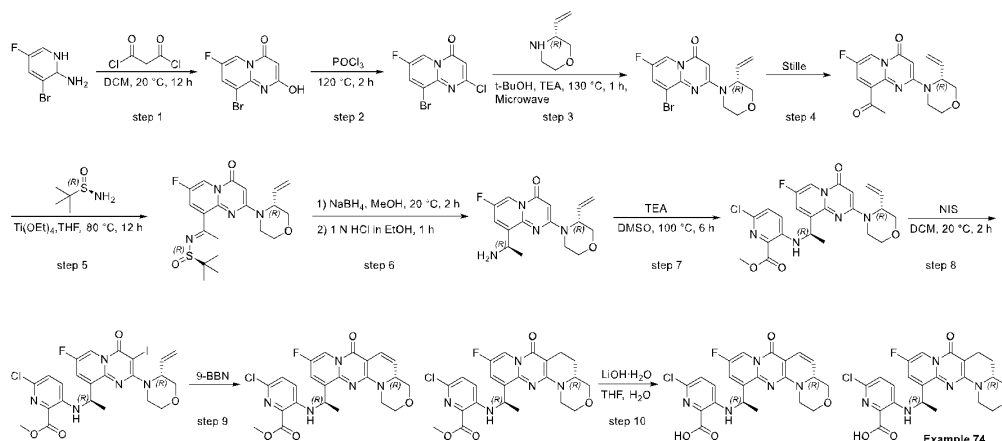
Step 8:

A solution of (R)-5-(1-aminoethyl)-7-fluoro-3-(3-(2-hydroxyethyl)-1-methyl-1H-pyrazol-4-yl)isoquinolin-1(2H)-one (50 mg, 151 μmol) and methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (43 mg, 227 μmol) in DMSO (2 mL) was stirred at 120 °C under microwave for 1 hour. The mixture was diluted with water (20 mL) and extracted with DCM (20 mL × 2). The organic layer was washed with
15 brine (30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The mixture was purified by silica gel chromatography to give methyl (R)-6-chloro-3-((1-(9-fluoro-2-methyl-7-oxo-2,4,5,7-tetrahydropyrazolo[4',3':3,4]pyrido[1,2-b]isoquinolin-11-yl)ethyl)amino)picolinate (10 mg, 14% yield) as yellow oil. LC-MS: m/z 482.2 [M+H]⁺.

Step 9:

To a stirred solution of methyl (R)-6-chloro-3-((1-(9-fluoro-2-methyl-7-oxo-2,4,5,7-tetrahydropyrazolo[4',3':3,4]pyrido[1,2-b]isoquinolin-11-yl)ethyl)amino)picolinate (10 mg, 21 μmol) in mixed solvents of water and THF (8 mL, 1:3) was added LiOH·H₂O (10 mg, 415 μmol) at 20 °C. The mixture was stirred at 20 °C for 2 hours. The pH of the mixture was adjusted to 6 with saturated aqueous NH₄Cl, then extracted with DCM (50 mL). The organic layer was dried over Na₂SO₄, filtered
25 and concentrated under reduced pressure. The residue was purified by prep-HPLC to give (R)-6-chloro-3-((1-(9-fluoro-2-methyl-7-oxo-2,4,5,7-tetrahydropyrazolo[4',3':3,4]pyrido[1,2-b]isoquinolin-11-yl)ethyl)amino)picolinic acid (0.8 mg, 8% yield) as a white solid. LC-MS: m/z 468.1 [M+H]⁺.

Example 74



Step 1:

To a solution of 3-bromo-5-fluoropyridin-2-amine (6.3 g, 33 mmol) in DCM (30 mL) was
 5 added propanedioyl dichloride (5.6 g, 39.6 mmol) at 0 °C. The mixture was stirred at 20 °C for 12 hours. The resulting mixture was quenched by addition of MeOH (20 mL) and concentrated under reduced pressure. The residue was triturated in a solution of petroleum ether and DCM (10:1, 200 mL) and filtered. The filter cake was washed with petroleum ether (10 mL × 3), dried under reduced pressure to give 9-bromo-7-fluoro-2-hydroxy-pyrido[1,2-a]pyrimidin-4-one (7.4 g, 86% yield) as a
 10 yellow solid. LC-MS: m/z 258.8 $[M+H]^+$.

Step 2:

A solution of 9-bromo-7-fluoro-2-hydroxy-pyrido[1,2-a]pyrimidin-4-one (7.4 g 28.6 mmol) in $POCl_3$ (20 mL) was stirred at 120 °C for 2 hours. The resulting mixture was added to water (20 mL) slowly. The mixture was filtered. The filter cake was washed with water (10 mL × 3), dried under reduced
 15 pressure to give 9-bromo-2-chloro-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one (5 g, crude) as a yellow solid.

Step 3:

To a solution of (R)-3-vinylmorpholine hydrochloride (258.8 mg, 1.7 mmol) in t-BuOH (2 mL) was added TEA (729.4 mg, 7.2 mmol). The mixture was stirred at 130 °C for 1 hour. The resulting
 20 mixture was concentrated under reduced pressure. The residue was purified by flash chromatography to give (R)-9-bromo-7-fluoro-2-(3-vinylmorpholino)-4H-pyrido[1,2-a]pyrimidin-4-one (120 mg, crude) as yellow gum.

Step 4:

To a seal tube was added (R)-9-bromo-7-fluoro-2-(3-vinylmorpholino)-4H-pyrido[1,2-a]pyrimidin-4-one (110 mg, 0.3 mmol), tributyl(1-ethoxyvinyl)stannane (139 mg, 0.4
 25 mmol), dichloropalladium;triphenylphosphane (43.8 mg, 0.1 mmol) and dioxane (2 mL). The mixture was backfilled with N_2 and stirred at 90 °C for 12 hours. 1 M HCl (aq.) (5 mL) was added to the

mixture. The mixture was stirred at 20 °C for 1 hour. The resulting mixture was quenched by addition of saturated NaHCO₃ aqueous solution (10 mL) and extracted with EtOAc (20 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to give 9-acetyl-7-fluoro-2-[(3R)-3-vinylmorpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one (80 mg, 80% yield) as yellow oil.

Step 5

To a solution of 9-acetyl-7-fluoro-2-[(3R)-3-vinylmorpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one (75 mg, 0.2 mmol) in THF (5 mL) was added Ti(OEt)₄ (5 mL) and (R)-2-methylpropane-2-sulfinamide (30 mg, 0.25 mmol). The mixture was stirred at 80 °C for 12 hours. The resulting mixture was quenched by addition of water (10 mL) and extracted with EtOAc (30 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give (R)-N-((E)-1-(7-fluoro-3-iodo-4-oxo-2-((R)-3-vinylmorpholino)-4H-pyrido[1,2-a]pyrimidin-9-yl)ethylidene)-2-methylpropane-2-sulfinamide (90 mg, 91% yield) as yellow oil. LC-MS: m/z 421.2 [M+H]⁺.

Step 6:

To a solution of (R)-N-((E)-1-(7-fluoro-3-iodo-4-oxo-2-((R)-3-vinylmorpholino)-4H-pyrido[1,2-a]pyrimidin-9-yl)ethylidene)-2-methylpropane-2-sulfinamide (80 mg, 0.2 mmol) in methanol (1 mL) was added CeCl₃ (23.5 mg, 0.1 mmol) and NaBH₄ (7.2 mg, 0.2 mmol). The mixture was stirred at 20 °C for 1 hour. The resulting mixture was quenched by addition of water (5 mL) and extracted with EtOAc (20 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was added to methanol (2 mL) and then 1 N HCl in EtOH (1 mL) was added to the mixture. The mixture was stirred at 20 °C for 1 hour. The resulting mixture was quenched by addition of saturated NaHCO₃ aqueous solution (5 mL) and extracted with EtOAc (10 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give 9-[(1R)-1-aminoethyl]-7-fluoro-2-[(3R)-3-vinylmorpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one (50 mg, crude) as yellow oil.

Step 7:

To a solution of methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (33 mg, 0.2 mmol) in DMSO (2 mL) was added TEA (47.7 mg, 0.5 mmol) and 9-[(1R)-1-aminoethyl]-7-fluoro-2-[(3R)-3-vinylmorpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one (50 mg, 0.2 mmol). The mixture was stirred at 100 °C for 6 hours. The resulting mixture was quenched by addition of saturated NH₄Cl aqueous solution (5 mL) and extracted with EtOAc (10 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to give methyl 6-chloro-3-[[[(1R)-1-[7-fluoro-4-oxo-2-

[(3R)-3-vinylmorpholin-4-yl]pyrido[1,2-a]pyrimidin-9-yl]ethyl]amino]pyridine-2-carboxylate (30 mg, 39% yield) as yellow oil.

Step 8:

To a solution of methyl 6-chloro-3-[[[(1R)-1-[7-fluoro-4-oxo-2-[(3R)-3-vinylmorpholin-4-yl]pyrido[1,2-a]pyrimidin-9-yl]ethyl]amino]pyridine-2-carboxylate (30 mg, 0.1 mmol) in DCM (1 mL) was added NIS (15 mg, 0.1 mmol). The mixture was stirred at 20 °C for 12 hours. The resulting mixture was quenched by addition of saturated Na₂SO₃ aqueous solution (5 mL) and extracted with EtOAc (10 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to give methyl 6-chloro-3-[[[(1R)-1-[7-fluoro-3-iodo-4-oxo-2-[(3R)-3-vinylmorpholin-4-yl]pyrido[1,2-a]pyrimidin-9-yl]ethyl]amino]pyridine-2-carboxylate (35 mg, 92% yield) as a yellow solid.

Step 9:

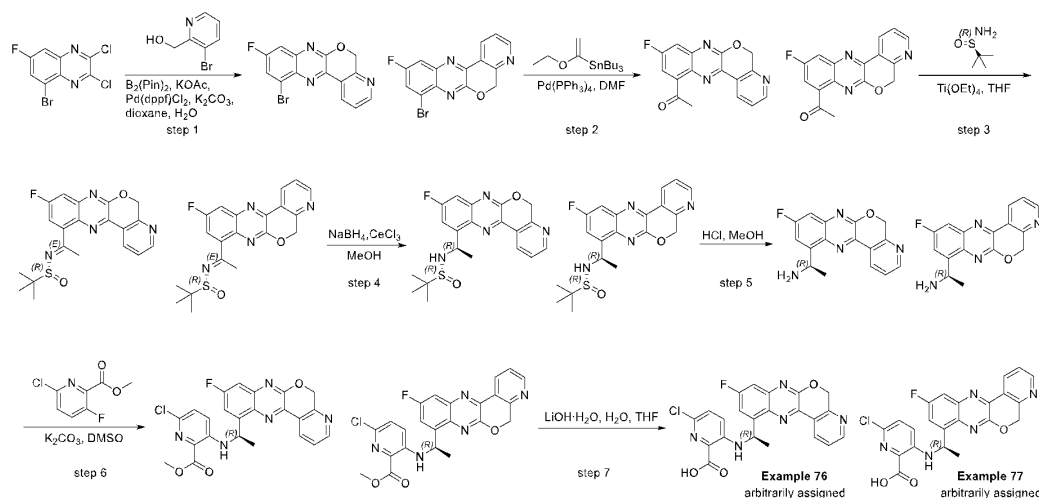
To a solution of methyl 6-chloro-3-[[[(1R)-1-[7-fluoro-3-iodo-4-oxo-2-[(3R)-3-vinylmorpholin-4-yl]pyrido[1,2-a]pyrimidin-9-yl]ethyl]amino]pyridine-2-carboxylate (30 mg, 40 μmol) in THF (5 mL) was added water (1 mL), TEA (14.5 mg, 0.1 mmol) and 9-borabicyclo[3.3.1]nonane (0.1 mmol, 0.2 mL). The mixture was degassed and backfilled with N₂ for 3 times. The mixture was stirred at 60 °C for 6 hours. The resulting mixture was quenched by addition of saturated NH₄Cl aqueous solution (5 mL) and extracted with EtOAc (20 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography to give methyl 6-chloro-3-[[[(1R)-1-[(7R)-14-fluoro-11-oxo-5-oxa-2,12,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(10),8,13,15,17-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylate (3 mg, 12% yield) and methyl 6-chloro-3-[[[(1R)-1-[(7R)-14-fluoro-11-oxo-5-oxa-2,12,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(10),13,15,17-tetraen-16-yl]ethyl]amino]pyridine-2-carboxylate (15 mg, 63% yield) as yellow oil. LC-MS: m/z 488.1 [M+H]⁺.

Step 10:

To a solution of methyl 6-chloro-3-[[[(1R)-1-[(7R)-14-fluoro-11-oxo-5-oxa-2,12,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(10),8,13,15,17-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylate (3 mg, 6.2 μmol) and methyl 6-chloro-3-[[[(1R)-1-[(7R)-14-fluoro-11-oxo-5-oxa-2,12,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(10),13,15,17-tetraen-16-yl]ethyl]amino]pyridine-2-carboxylate (15 mg, 31 μmol) in THF (4 mL) was added LiOH·H₂O (0.2 mg, 40 μmol) and water (1 mL). The mixture was stirred at 40 °C for 1 hour. The resulting mixture was concentrated under reduced pressure.

The residue was purified by prep-HPLC to 6-chloro-3-[[[(1R)-1-[(7R)-14-fluoro-11-oxo-5-oxa-2,12,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(10),13,15,17-tetraen-16-yl]ethyl]amino]pyridine-2-carboxylic acid (**Example 74**, 2 mg, 13% yield) as a white solid. LC-MS: m/z 474.1 [M+H]⁺.

Example 76 and 77



Step 1:

To a stirred solution of (3-bromo-2-pyridyl)methanol (571.8 mg, 3 mmol) in dioxane (10 mL) was added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (772 mg, 3 mmol), Pd(dppf)Cl₂ (222.5 mg, 304 μmol), KOAc (796 mg, 8.1 mmol) at 20 °C. The mixture was stirred at 100 °C for 1 hour, then the mixture was filtered. To the filtrate was added 5-bromo-2,3-dichloro-7-fluoro-quinoxaline (300 mg, 1 mmol), Na₂CO₃ (322 mg, 3 mmol) and water (500 μL). The mixture was stirred at 100 °C for 2 hours, diluted with water (50 mL) and extracted with DCM (100 mL × 2). The organic layer was washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The mixture was purified by silica gel chromatography to give a mixture of 16-bromo-14-fluoro-9-oxa-6,11,18-triazatetracyclo[8.8.0.02,7.012,17]octadeca-1(18),2(7),3,5,10,12(17),13,15-octaene and 13-bromo-15-fluoro-9-oxa-6,11,18-triazatetracyclo[8.8.0.02,7.012,17]octadeca-1(18),2(7),3,5,10,12(17),13,15-octaene (300 mg, 89% yield) as a yellow solid. LC-MS: m/z 331.9 [M+H]⁺.

Step 2:

To a mixture of 16-bromo-14-fluoro-9-oxa-6,11,18-triazatetracyclo[8.8.0.02,7.012,17]octadeca-1(18),2(7),3,5,10,12(17),13,15-octaene and 13-bromo-15-fluoro-9-oxa-6,11,18-triazatetracyclo[8.8.0.02,7.012,17]octadeca-1(18),2(7),3,5,10,12(17),13,15-octaene (200 mg, 602 μmol) in DMF (5 mL) was added Pd(PPh₃)₄ (35 mg, 30 μmol), tributyl(1-ethoxyvinyl)stannane (217 mg, 602 μmol) at 20 °C. The mixture was stirred at 100 °C for 4 hours under N₂. The mixture was diluted with DCM (50 mL), then quenched with saturated aqueous KF (50 mL) and stirred at 20 °C for 2 hours. The mixture was filtered, the filtrate was separated, the organic layer was concentrated under reduced pressure. The residue was dissolved in acetone (30 mL) and 2 N HCl (5 mL). The mixture was stirred at 20 °C for 30 minutes. Then the mixture was diluted with water (50 mL) and extracted with DCM (100 mL), the organic layer was dried over Na₂SO₄, filtered and concentrated

under reduced pressure. The mixture was purified by silica gel chromatography to give a mixture of 1-(9-fluoro-5H-pyrido[3',2':4,5]pyrano[2,3-b]quinoxalin-11-yl)ethan-1-one and 1-(10-fluoro-5H-pyrido[3',2':4,5]pyrano[2,3-b]quinoxalin-8-yl)ethan-1-one (140 mg, 79% yield) as a yellow solid. LC-MS: m/z 296.0 $[M+H]^+$.

5 Step 3:

To a mixture of 1-(9-fluoro-5H-pyrido[3',2':4,5]pyrano[2,3-b]quinoxalin-11-yl)ethan-1-one and 1-(10-fluoro-5H-pyrido[3',2':4,5]pyrano[2,3-b]quinoxalin-8-yl)ethan-1-one (140 mg, 474 μ mol) in THF (10 mL) was added $Ti(OEt)_4$ (1.1 g, 4.7 mmol), (R)-2-methylpropane-2-sulfinamide (115 mg, 948 μ mol) at 20 °C. The mixture was stirred at 85 °C for 12 hours. The mixture was diluted with EtOAc (50 mL) then water (50 mL) was added. The mixture was filtered and the filtrate was extracted with EtOAc (50 mL $\times$ 2). The organic layer was washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The mixture was purified by silica gel chromatography to give a mixture of (R,E)-N-(1-(9-fluoro-5H-pyrido[3',2':4,5]pyrano[2,3-b]quinoxalin-11-yl)ethylidene)-2-methylpropane-2-sulfinamide and (R,E)-N-(1-(10-fluoro-5H-pyrido[3',2':4,5]pyrano[2,3-b]quinoxalin-8-yl)ethylidene)-2-methylpropane-2-sulfinamide (120 mg, 64% yield) as a yellow solid. LC-MS: m/z 399.1 $[M+H]^+$.

Step 4:

To a mixture of (R,E)-N-(1-(9-fluoro-5H-pyrido[3',2':4,5]pyrano[2,3-b]quinoxalin-11-yl)ethylidene)-2-methylpropane-2-sulfinamide and (R,E)-N-(1-(10-fluoro-5H-pyrido[3',2':4,5]pyrano[2,3-b]quinoxalin-8-yl)ethylidene)-2-methylpropane-2-sulfinamide (120 mg, 301 μ mol) in methanol (5 mL) was added $CeCl_3$ (37 mg, 150 μ mol), $NaBH_4$ (28 mg, 753 μ mol) at 20 °C. The mixture was stirred at 20 °C for 10 minutes. The mixture was diluted with water (50 mL), then extracted with DCM (100 mL) and the organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give a mixture of (R)-N-((R)-1-(9-fluoro-5H-pyrido[3',2':4,5]pyrano[2,3-b]quinoxalin-11-yl)ethyl)-2-methylpropane-2-sulfinamide and (R)-N-((R)-1-(10-fluoro-5H-pyrido[3',2':4,5]pyrano[2,3-b]quinoxalin-8-yl)ethyl)-2-methylpropane-2-sulfinamide (100 mg, 83% yield) as a yellow solid. LC-MS: m/z 401.1 $[M+H]^+$.

Step 5:

To a mixture of (R)-N-((R)-1-(9-fluoro-5H-pyrido[3',2':4,5]pyrano[2,3-b]quinoxalin-11-yl)ethyl)-2-methylpropane-2-sulfinamide and (R)-N-((R)-1-(10-fluoro-5H-pyrido[3',2':4,5]pyrano[2,3-b]quinoxalin-8-yl)ethyl)-2-methylpropane-2-sulfinamide (100 mg, 250 μ mol) in methanol (5 mL) was added HCl (600 μ L, 4 M in ethanol) at 0 °C. The mixture was stirred at 0 °C for 30 minutes. The pH of the mixture was adjust to 8 with saturated aqueous $NaHCO_3$. The mixture was diluted with water (50 mL), and extracted with DCM (100 mL). The organic layer was washed with brine (100 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a mixture of (R)-1-(9-fluoro-5H-pyrido[3',2':4,5]pyrano[2,3-b]quinoxalin-11-yl)ethan-1-amine and (R)-1-(10-fluoro-5H-

pyrido[3',2':4,5]pyrano[2,3-b]quinoxalin-8-yl)ethan-1-amine (40 mg, 54% yield) as yellow oil. LC-MS: m/z 297.1 $[M+H]^+$.

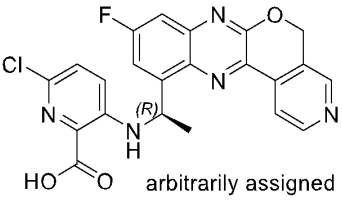
Step 6:

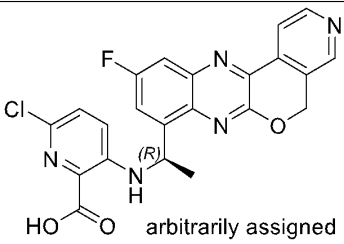
To a stirred solution of (R)-1-(9-fluoro-5H-pyrido[3',2':4,5]pyrano[2,3-b]quinoxalin-11-yl)ethan-1-amine and (R)-1-(10-fluoro-5H-pyrido[3',2':4,5]pyrano[2,3-b]quinoxalin-8-yl)ethan-1-amine (20 mg, 68 μ mol) in DMSO (2 mL) was added methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (13 mg, 68 μ mol), K_2CO_3 (22 mg, 68 μ mol) at 20 °C. The mixture was stirred at 80 °C for 2 hours, diluted with water (10 mL), then extracted with EtOAc (50 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The mixture was purified by silica gel chromatography to give a mixture of methyl (R)-6-chloro-3-((1-(9-fluoro-5H-pyrido[3',2':4,5]pyrano[2,3-b]quinoxalin-11-yl)ethyl)amino)picolinate and methyl (R)-6-chloro-3-((1-(10-fluoro-5H-pyrido[3',2':4,5]pyrano[2,3-b]quinoxalin-8-yl)ethyl)amino)picolinate (20 mg, 64% yield) as yellow oil. LC-MS: m/z 466.1 $[M+H]^+$.

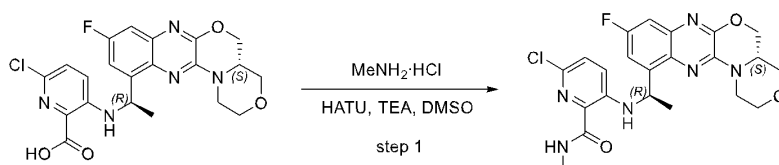
Step 7:

To a mixture of methyl methyl (R)-6-chloro-3-((1-(9-fluoro-5H-pyrido[3',2':4,5]pyrano[2,3-b]quinoxalin-11-yl)ethyl)amino)picolinate and methyl (R)-6-chloro-3-((1-(10-fluoro-5H-pyrido[3',2':4,5]pyrano[2,3-b]quinoxalin-8-yl)ethyl)amino)picolinate (20 mg, 43 μ mol) in mixed solvents of water and THF (8 mL, 1:3) was added $LiOH \cdot H_2O$ (5 mg, 215 μ mol) at 20 °C. The mixture was stirred at 20 °C for 2 hours. The pH of the mixture was adjusted to 6 with saturated aqueous NH_4Cl , then extracted with DCM (50 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC to give (R)-6-chloro-3-((1-(9-fluoro-5H-pyrido[3',2':4,5]pyrano[2,3-b]quinoxalin-11-yl)ethyl)amino)picolinic acid (0.1 mg, 1% yield) as a white solid (**Example 76**, LC-MS: m/z 452.0 $[M+H]^+$) and (R)-6-chloro-3-((1-(10-fluoro-5H-pyrido[3',2':4,5]pyrano[2,3-b]quinoxalin-8-yl)ethyl)amino)picolinic acid (**Example 77**, 1 mg, 10% yield) as a white solid. LC-MS: m/z 452.0 $[M+H]^+$.

The following compounds have been prepared in analogy to the representative procedures described for **Example 76 and 77**.

ID	Structure	LC-MS: m/z $[M+H]^+$
Example 78	 arbitrarily assigned	452.0

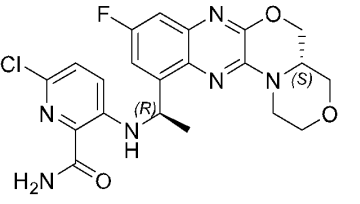
Example 79	 arbitrarily assigned	452.0
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Example 80**Step 1:**

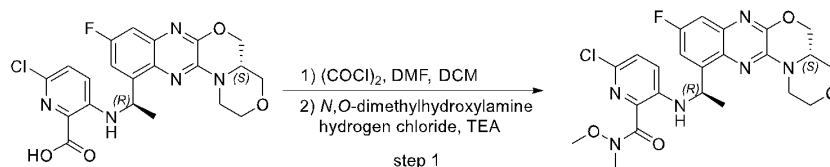
- 5 To a solution of 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylic acid (10 mg, 21.7 μ mol), N,N-diethylethanamine (15.4 mg, 152.2 μ mol) and HATU (16.5 mg, 43.5 μ mol) in DMSO (1 mL) was added methanamine;hydrochloride (7.3 mg, 108.7 μ mol). The mixture was stirred at 20 °C for 1 hour. The mixture was diluted with EtOAc (100 mL) and then
- 10 washed with brine (30 mL $\times$ 3). The organic layer was dried over Na₂SO₄, filtered and concentrated to give crude product. The crude was purified by prep-HPLC to give 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]-N-methyl-pyridine-2-carboxamide (3.4 mg, 33.1% yield) as a white solid. LC-MS: m/z 473.1 [M+H]⁺.

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The following compounds have been prepared in analogy to the representative procedures described for **Example 80**.

ID	Structure	LC-MS: m/z [M+H] ⁺
Example 89		458.8

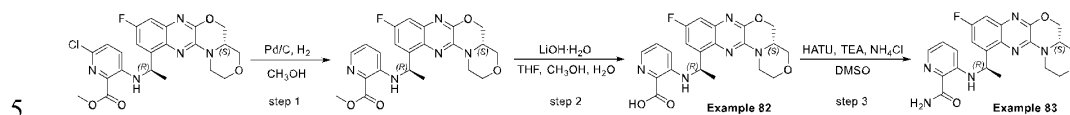
Example 90		549.8
Example 91		516.8
Example 189		508.2

Example 81**Step 1:**

- 5 To a solution of 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylic acid (30 mg, 65.2 μ mol) and N,N-dimethylformamide (476.8 μ g, 6.5 μ mol) in CH_2Cl_2 (2 mL) was added oxalyl dichloride (24.8 mg, 195.7 μ mol). The mixture was stirred at 20 °C for 10 minutes. The mixture was concentrated to give 6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-
- 10 4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)picolinoyl chloride (30 mg, crude) as a yellow solid. To the solution of 6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)picolinoyl chloride (15 mg, 31.4 μ mol) in CH_2Cl_2 (2 mL) was added TEA (15.8 mg, 156.8 μ mol) and N,O-
- 15 dimethylhydroxylamine hydrogen chloride (7.6 mg, 78.5 μ mol). The mixture was stirred at 20 °C for 10 minutes. The mixture was diluted with water (20 mL) and then extracted with CH_2Cl_2 (40 mL $\times$ 2). The combined organic layer was dried over Na_2SO_4 , filtered and concentrated to afford crude product. The crude was purified by prep-HPLC to give 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]-N-

methoxy-N-methyl-pyridine-2-carboxamide (2.9 mg, 18.4% yield) as a white solid. LC-MS: m/z 502.8 $[M+H]^+$.

Example 82 and 83



Step 1:

To a solution of methyl 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylate (34 mg, 71.7 μ mol) in methanol (8 mL) was added palladium (30 mg, 50% purity). The mixture was degassed with a stream of H_2 for three times and then stirred at 20 °C for 3 hours under H_2 atmosphere at 1 atm. The mixture was filtered and the filter cake was washed with CH_3OH (10 mL). The combined filtrate was concentrated to afford crude product. The crude was purified by column chromatography on silica gel to give methyl 3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylate (18 mg, 57.1% yield) as a light yellow solid. LC-MS: m/z 439.9 $[M+H]^+$.

Step 2:

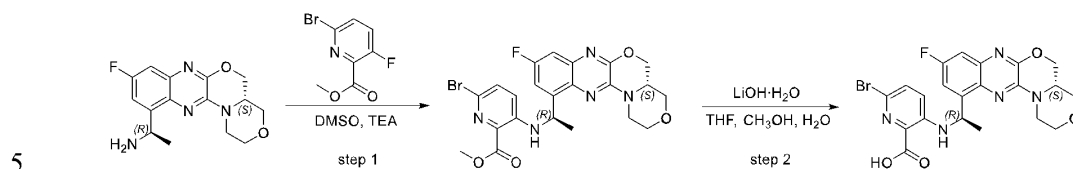
To a solution of methyl 3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylate (18 mg, 40.9 μ mol) in THF (4 mL), methanol (1 mL) and water (1 mL) was added lithium;hydroxide;hydrate (8.6 mg, 204.8 μ mol). The mixture was stirred at 20 °C for 50 minutes. The mixture was adjusted to pH 5 with aq.HCl, diluted with brine (15 mL) and then extracted with EtOAc (30 mL $\times$ 3). The combined organic layer was dried over Na_2SO_4 , filtered and concentrated to give crude product which was purified by prep-HPLC to give 3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylic acid (13 mg, 74.6% yield) as a white solid. LC-MS: m/z 447.8 $[M+Na]^+$.

Step 3:

To a solution of 3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylic acid (9.2 mg, 21.7 μ mol), TEA (15.4 mg, 152.2 μ mol) and HATU (16.5 mg, 43.5 μ mol) in DMSO (1 mL) was added ammonium;chloride (11.6 mg, 217.5 μ mol). The mixture was stirred at 20 °C for 1 hour. The mixture was diluted with EtOAc (100 mL) and then washed with brine (30 mL $\times$ 3). The organic layer was dried over Na_2SO_4 , filtered and concentrated to give crude product. The crude was purified by prep-HPLC to give 3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-

triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carboxamide (2.4 mg, 26% yield) as a white solid. LC-MS: m/z 425.2 $[M+H]^+$.

Example 84



Step 1:

To a solution of (1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethanamine (20 mg, 65.7 μ mol) and TEA (17.3 mg, 170.8 μ mol) in DMSO (1.5 mL) was added methyl 6-bromo-3-fluoropyridine-2-carboxylate (23.1 mg, 98.5 μ mol). The mixture was stirred at 100 °C for 16 hours. The mixture was diluted with EtOAc (50 mL) and then washed with brine (15 mL $\times$ 4). The organic layer was dried over Na₂SO₄, filtered and concentrated to give crude product. The crude was purified by column chromatography on silica gel to give methyl 6-bromo-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylate (20 mg, 58.7% yield) as a yellow solid. LC-MS: m/z 517.8 $[M+H]^+$.

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Step 2:

To a solution of methyl 6-bromo-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylate (20 mg, 38.6 μ mol) in THF (4 mL), water (1 mL) and methanol (1 mL) was added lithium hydroxide hydrate (8.1 mg, 192.9 μ mol). The mixture was stirred at 20 °C for 50 minutes. The mixture was adjusted to pH 5 with aq. HCl, diluted with water (30 mL) and then extracted with EtOAc (50 mL $\times$ 3). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by prep-HPLC to give 6-bromo-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylic acid (16.9 mg, 86.8% yield) as a white solid. LC-MS: m/z 525.7 $[M+Na]^+$.

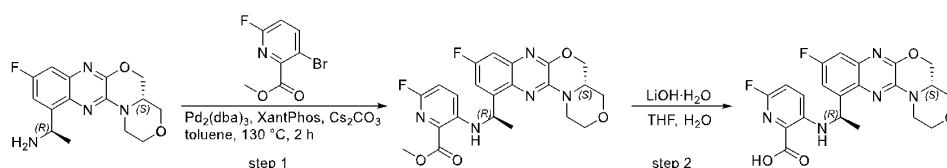
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25

The following compound has been prepared in analogy to the representative procedures described for Example 84.

30

ID	Structure	LC-MS: m/z [M+H] ⁺
Example 85		461.1

Example 86**Step 1:**

- 5 To a solution of (1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethanamine (8 mg, 26.3 μmol) and tris(dibenzylideneacetone)dipalladium(0) (4.8 mg, 5.3 μmol) in toluene (1.5 mL) was added methyl methyl 3-bromo-6-fluoropyridine-2-carboxylate (9.2 mg, 39.4 μmol), (5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (6.1 mg, 10.5 μmol) and dicesium;carbonate (21.4 mg, 65.7 μmol).
- 10 The mixture was degassed with a stream of N₂ for three times and then stirred at 130 °C for 2 hours under N₂. The mixture was diluted with EtOAc (50 mL) and then washed with brine (15 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated to give methyl 6-fluoro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylate (15 mg, crude) as a yellow solid. LC-MS: m/z
- 15 457.9 [M+H]⁺.

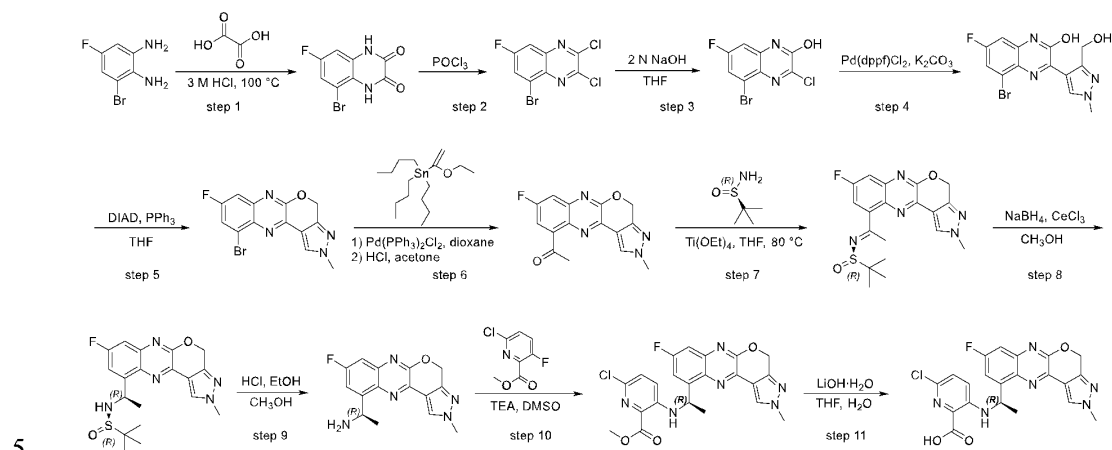
Step 2:

- To a solution of methyl 6-fluoro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylate (15 mg, 32.8 μmol) in THF (2 mL) and water (0.5 mL) was added
- 20 lithium;hydroxide;hydrate (6.8 mg, 163.9 μmol). The mixture was stirred at 20 °C for 16 hours. The mixture was adjusted to pH 5 with aq.HCl, diluted with water (10 mL) and then extracted with EtOAc (30 mL × 3). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by prep-HPLC to give 6-fluoro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-
- 25 yl]ethyl]amino]pyridine-2-carboxylic acid (2.8 mg, 19.3% yield) as a white solid. LC-MS: m/z 444.2 [M+H]⁺.

The following compounds have been prepared in analogy to the representative procedures described for **Example 86**.

ID	Structure	LC-MS: m/z [M+H] ⁺
Example 92		476.8
Example 93		443.2
Example 194		425.2

Example 87



Step 1:

To a solution of 3-bromo-5-fluoro-benzene-1,2-diamine (5 g, 24.4 mmol) in 3 N HCl (60 mL) was added oxalic acid (4.4 g, 48.7 mmol). The mixture was stirred at 100 °C for 8 hours. The mixture was filtered and the filter cake was washed with water (50 mL). The solid was dried under vacuum to give 5-bromo-7-fluoro-1,4-dihydroquinoxaline-2,3-dione (6.2 g, 98.2% yield) as a brown solid.

Step 2:

A solution of 5-bromo-7-fluoro-1,4-dihydroquinoxaline-2,3-dione (6.2 g, 23.9 mmol) in POCl₃ (98.7 g, 643.7 mmol) was stirred at 120 °C for 2 hours. The mixture was concentrated and diluted with CH₃CN (30 mL). The mixture was poured into water (100 mL) and extracted with CH₂Cl₂ (150 mL × 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by column chromatography on silica gel to give 5-bromo-2,3-dichloro-7-fluoro-quinoxaline (5.6 g, 79.1% yield) as a yellow solid.

Step 3:

A solution of 5-bromo-2,3-dichloro-7-fluoro-quinoxaline (2.7 g, 9.1 mmol) in THF (30 mL) and aq.NaOH (2 N, 15 mL) was stirred at 20 °C for 8 hours. The mixture was diluted with water (40 mL) and adjusted to pH 6 with aq.HCl (2 N). The mixture was extracted with CH₂Cl₂ (100 mL × 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to give 5-bromo-3-chloro-7-fluoro-quinoxalin-2-ol (2.6 g, crude) as a yellow solid. LC-MS: m/z 276.6 [M+H]⁺.

Step 4:

To a solution of (4-bromo-1-methyl-pyrazol-3-yl)methanol (2.3 g, 11.7 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (5.9 g, 23.5 mmol) in dioxane (28 mL) was added Pd(dppf)Cl₂ (1.7 g, 2.4 mmol) and K₂CO₃ (2.3 g, 23.6 mmol). The mixture was degassed with a stream of N₂ for three times and then stirred at 100 °C for 1.5 hours. The mixture was concentrated to give [1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl]methanol (2.9 g, crude). To a mixture of [1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-3-yl]methanol (2.9 g, 12.2 mmol) in dioxane (28 mL) was added Pd(dppf)Cl₂ (593.3 mg, 810.8 μmol), 5-bromo-3-chloro-7-fluoro-quinoxalin-2-ol (2.6 g, 8.1 mmol), dipotassium carbonate (2.3 g, 17 mmol) and water (5 mL). The mixture was degassed with a stream of N₂ for three times and stirred at 100 °C for 3 hours. The mixture was diluted with water (40 mL) and extracted with CH₂Cl₂ (100 mL × 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to give crude product. The crude was purified by column chromatography on silica gel to give the product as a black solid. Then the solid was purified by triturated eluting with CH₂Cl₂ (15 mL) to give 5-bromo-7-fluoro-3-[3-(hydroxymethyl)-1-methyl-pyrazol-4-yl]quinoxalin-2-ol (275 mg, 9.6% yield) as a yellow solid. LC-MS: m/z 352.7 [M+H]⁺.

Step 5:

To a solution of 5-bromo-7-fluoro-3-[3-(hydroxymethyl)-1-methyl-pyrazol-4-yl]quinoxalin-2-ol (35 mg, 99.1 μmol) and triphenylphosphane (38.9 mg, 148.6 μmol) in THF (6 mL) was added DIAD (30.1 mg, 148.6 μmol). The mixture was stirred at 20 °C for 20 minutes. The combined solution was concentrated to afford crude product. The crude was purified by column chromatography on silica gel to afford the product as a white solid. Then the solid was purified by triturated eluting with CH₂Cl₂ (15 mL) to afford 7-bromo-5-fluoro-13-methyl-17-oxa-2,9,13,14-

tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-1,3(8),4,6,9,11,14-heptaene (65 mg, 28% yield) as a white solid.

Step 6:

To a solution of 7-bromo-5-fluoro-13-methyl-17-oxa-2,9,13,14-

- 5 tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-1,3(8),4,6,9,11,14-heptaene (65 mg, 193.9 μ mol) in dioxane (5 mL) was added tributyl(1-ethoxyvinyl)stannane (140.1 mg, 387.9 μ mol) and dichloropalladium;triphenylphosphane (27.2 mg, 38.8 μ mol). The mixture was degassed with a stream of N₂ for three times and then stirred at 100 °C for 16 hours. The mixture was quenched with KF solution (15 mL) and extracted with CH₂Cl₂ (50 mL $\times$ 2). The combined organic layer was dried
10 over Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by column chromatography on silica gel to afford 7-(1-ethoxyvinyl)-5-fluoro-13-methyl-17-oxa-2,9,13,14-tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-1,3(8),4,6,9,11,14-heptaene (60 mg, 94.8% yield) as a yellow solid. LC-MS: m/z 326.8 [M+H]⁺.

To a solution of 7-(1-ethoxyvinyl)-5-fluoro-13-methyl-17-oxa-2,9,13,14-

- 15 tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-1,3(8),4,6,9,11,14-heptaene (60 mg, 183.8 μ mol) in acetone (8 mL) was added aq.HCl (4 mL, 2 N). The mixture was stirred at 20 °C for 20 minutes. The mixture was diluted with CH₂Cl₂ (80 mL) and washed with aq.NaHCO₃ (30 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by column chromatography on silica gel to afford 1-(5-fluoro-13-methyl-17-oxa-2,9,13,14-
20 tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-1,3(8),4,6,9,11,14-heptaen-7-yl)ethanone (53 mg, 96.6% yield) as a yellow solid. LC-MS: m/z 298.8 [M+H]⁺.

Step 7:

To a solution of 1-(5-fluoro-13-methyl-17-oxa-2,9,13,14-tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-1,3(8),4,6,9,11,14-heptaen-7-yl)ethanone (53 mg, 177.7 μ mol) in titanium ethoxide (4 mL) and THF

- 25 (4 mL) was added (R)-2-methylpropane-2-sulfinamide (64.6 mg, 533.1 μ mol). The mixture was stirred at 80 °C for 16 hours under N₂. The mixture was diluted with EtOAc (120 mL) and then water (18 mL) was added. The mixture was stirred at 20 °C for 0.5 hour. The mixture was filtered and the organic layer was washed with brine (20 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by column chromatography on silica gel
30 to afford (R,E)-N-(1-(8-fluoro-2-methyl-2,4-dihydropyrazolo[4',3':4,5]pyrano[2,3-b]quinoxalin-10-yl)ethylidene)-2-methylpropane-2-sulfinamide (110 mg, crude) as a yellow solid. LC-MS: m/z 401.8 [M+H]⁺.

Step 8:

To a solution of (R,E)-N-(1-(8-fluoro-2-methyl-2,4-dihydropyrazolo[4',3':4,5]pyrano[2,3-

- 35 b]quinoxalin-10-yl)ethylidene)-2-methylpropane-2-sulfinamide (110 mg, 274 μ mol) and trichlorocerium (27 mg, 109.6 μ mol) in methanol (8 mL) was added sodium;boranuide (20.7 mg, 548 μ mol). The mixture was stirred at 20 °C for 10 minutes. The mixture was diluted with CH₂Cl₂ (90

mL) and then washed with brine (30 mL × 2). The organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by column chromatography on silica gel to afford (R)-N-[(1R)-1-(5-fluoro-13-methyl-17-oxa-2,9,13,14-

5 tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-1,3(8),4,6,9,11,14-heptaen-7-yl)ethyl]-2-methyl-propane-2-sulfinamide (80 mg, 72.4% yield) as a white solid. LC-MS: m/z 403.8 [M+H]⁺.

Step 9:

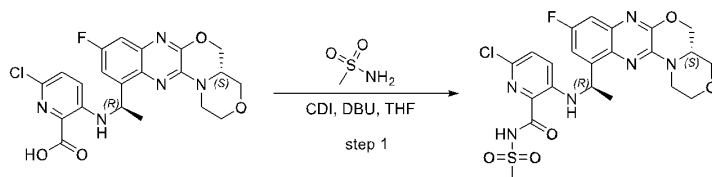
To a solution of (R)-N-[(1R)-1-(5-fluoro-13-methyl-17-oxa-2,9,13,14-tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-1,3(8),4,6,9,11,14-heptaen-7-yl)ethyl]-2-methyl-propane-2-sulfinamide (80 mg, 198.3 μmol) in methanol (8 mL) was added a solution of HCl in EtOH (1 mL, 10 4 N). The mixture was stirred at 20 °C for 5 minutes. The mixture was diluted with water (15 mL), adjusted pH to 7 with aq.NaHCO₃ and then extracted with CH₂Cl₂ (60 mL × 3). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to give (1R)-1-(5-fluoro-13-methyl-17-oxa-2,9,13,14-tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-1,3(8),4,6,9,11,14-heptaen-7-yl)ethanamine (65 mg, crude) as a white solid. The crude was used directly without further 15 purification. LC-MS: m/z 299.8 [M+H]⁺.

Step 10:

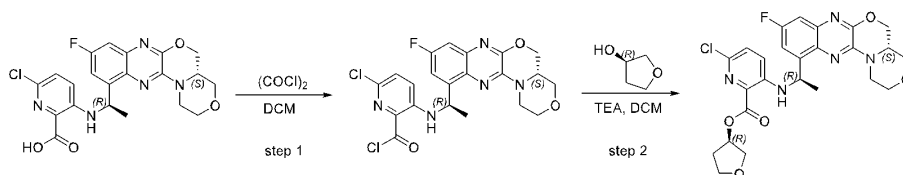
To a solution of (1R)-1-(5-fluoro-13-methyl-17-oxa-2,9,13,14-tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-1,3(8),4,6,9,11,14-heptaen-7-yl)ethanamine (20 mg, 66.8 μmol) and TEA (20.3 mg, 200 μmol) in DMSO (1.5 mL) was added methyl 6-chloro-3-fluoro-20 pyridine-2-carboxylate (19 mg, 100 μmol). The mixture was stirred at 100 °C for 16 hours. The mixture was diluted with EtOAc (50 mL) and then washed with brine (20 mL × 3). The organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by column chromatography on silica gel to afford methyl 6-chloro-3-[[[(1R)-1-(5-fluoro-13-methyl-17-oxa-2,9,13,14-tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-1,3(8),4,6,9,11,14-heptaen-7-yl)ethyl]amino]pyridine-2-carboxylate (10 mg, 31.9% yield) as a yellow solid. LC-MS: m/z 468.7 25 [M+H]⁺.

Step 11:

To a solution of methyl 6-chloro-3-[[[(1R)-1-(5-fluoro-13-methyl-17-oxa-2,9,13,14-tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-1,3(8),4,6,9,11,14-heptaen-7-yl)ethyl]amino]pyridine-2-carboxylate (10 mg, 21.3 μmol) in THF (2 mL) and water (0.5 mL) was added 30 lithium;hydroxide;hydrate (4.4 mg, 106.6 μmol). The mixture was stirred at 20 °C for 6 hours. The mixture was adjusted to pH 5 with aq.HCl, diluted with water (10 mL) and then extracted with EtOAc (30 mL × 3). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by prep-HPLC to afford 6-chloro-3-[[[(1R)-1-(5-fluoro-13-methyl-17-oxa-2,9,13,14-tetrazatetracyclo[8.7.0.0^{3,8}.0^{11,15}]heptadeca-1,3(8),4,6,9,11,14-heptaen-7-yl)ethyl]amino]pyridine-2-carboxylic acid (1.9 mg, 19.6% yield) as a white solid. LC-MS: m/z 454.7 35 [M+H]⁺.

Example 88**Step 1:**

To a solution of 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylic acid (10 mg, 21.2 μ mol) in THF (10 mL) was added CDI (7 mg, 43.1 μ mol). The mixture was stirred at 60 °C for 1 hour. Then DBU (13.2 mg, 87 μ mol) and methanesulfonamide (2.5 mg, 26.1 μ mol) were added to the mixture. The resulting mixture was quenched by addition of saturated NH₄Cl aqueous solution (5 mL) and extracted with EtOAc (20 mL $\times$ 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]-N-methylsulfonyl-pyridine-2-carboxamide (2.2 mg, 18.8% yield) as a yellow solid. LC-MS: m/z 536.8 [M+H]⁺.

Example 101**Step 1:**

To a stirred solution of 6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)picolinic acid (300 mg, 653.6 μ mol) in DCM (10 mL) was added oxalyl dichloride (164.7 mg, 1.3 mmol). The mixture was stirred at 25 °C for 1 hour before it was concentrated under reduced pressure to give 6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)picolinoyl chloride (350 mg, crude) which was used directly in the next step without further purification.

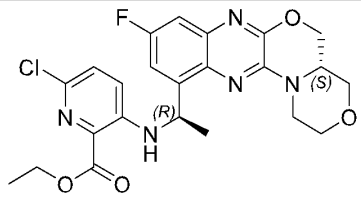
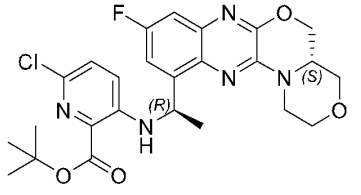
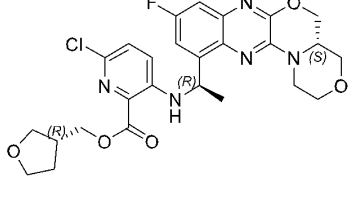
Step 2:

To a solution of (3R)-tetrahydrofuran-3-ol (3.6 mg, 41.8 μ mol), TEA (6.3 mg, 62.7 μ mol) in DCM (4 mL) was added a solution of 6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)picolinoyl chloride (10 mg, 20.9 μ mol) in DCM (4 mL). The mixture was stirred at 25 °C for 2 hours before it was concentrated

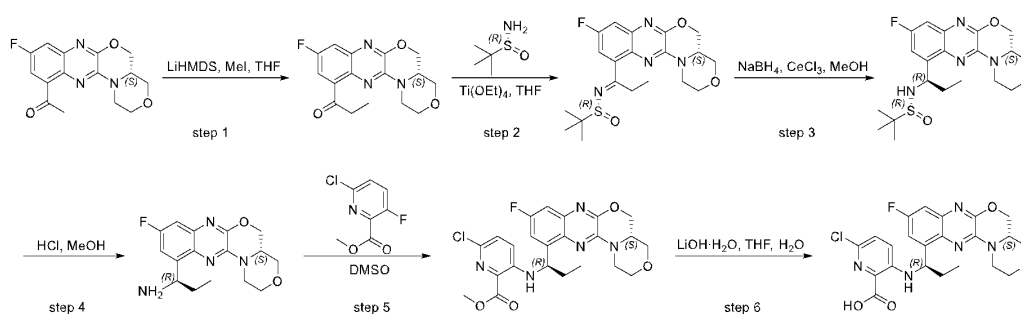
under reduced pressure to afford a residue, which was purified by prep-HPLC to afford (R)-tetrahydrofuran-3-yl 6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)picolinate (3.9 mg, 35% yield) as a white solid. LC-MS: m/z 530.1[M+H]⁺.

5

The following compounds have been prepared in analogy to the representative procedures described for **Example 101**.

ID	Structure	LC-MS: m/z [M+H] ⁺
Example 102		488.1
Example 103		516.1
Example 104		544.1

Example 105



10

Step 1:

To a stirred solution of (S)-1-((9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethan-1-one (50 mg, 165 μ mol) in THF (5 mL) was added LiHMDS (41 mg, 247 μ mol, 2 M in THF) at -78 °C. The mixture was stirred at -

78 °C for 30 minutes, then iodomethane (28 mg, 198 μ mol) was added dropwise. The mixture was

stirred at 15 °C under N₂ for 2 hours, diluted with water (50 mL) and extracted with DCM (50 mL × 2). The organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give (S)-1-(9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)propan-1-one (50 mg, 96% yield) as a yellow solid. LC-MS: m/z 318.1 [M+H]⁺.

Step 2:

To a stirred solution of (S)-1-(9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)propan-1-one (80 mg, 252 μmol) in THF (5 mL) was added Ti(OEt)₄ (1.2 g, 5 mmol), (R)-2-methylpropane-2-sulfinamide (61 mg, 504 μmol) at 20 °C. The mixture was stirred at 85 °C for 12 hours. The mixture was diluted with EtOAc (50 mL) then water (50 mL) was added. The mixture was filtered and the filtrate was extracted with EtOAc (50 mL × 2). The organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give (R)-N-((E)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)propylidene)-2-methylpropane-2-sulfinamide (100 mg, 94% yield) as a yellow solid. LC-MS: m/z 421.2 [M+H]⁺.

Step 3:

To a stirred solution of (R)-N-((E)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)propylidene)-2-methylpropane-2-sulfinamide (100 mg, 238 μmol) in methanol (2 mL) was added CeCl₃ (59 mg, 237 μmol), NaBH₄ (18 mg, 476 μmol) at 20 °C. The mixture was stirred at 20 °C for 10 minutes, diluted with water (20 mL) and extracted with DCM (50 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give (R)-N-((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)propyl)-2-methylpropane-2-sulfinamide (60 mg, 60% yield) as a yellow solid. LC-MS: m/z 423.2 [M+H]⁺.

Step 4:

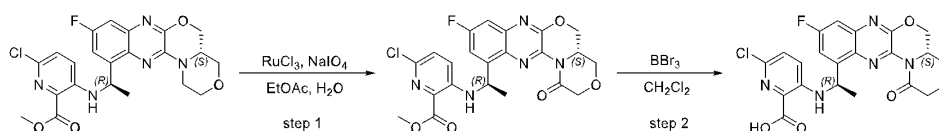
To a stirred solution of (R)-N-((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)propyl)-2-methylpropane-2-sulfinamide (60 mg, 142 μmol) in methanol (5 mL) was added HCl (300 μL, 4.0 M in ethanol) at 0 °C. The mixture was stirred at 0 °C for 30 minutes. The pH of the mixture was adjusted to 8 with saturated aqueous NaHCO₃. The mixture was diluted with water (30 mL), and extracted with DCM (30 mL × 2). The organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give (R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)propan-1-amine (40 mg, 88% yield) as yellow oil. LC-MS: m/z 319.1 [M+H]⁺.

Step 5:

To a stirred solution of (R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)propan-1-amine (40 mg, 126 μ mol) in DMSO (2 mL) was added methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (36 mg, 188 μ mol) at 20 °C. The mixture was stirred at 120 °C under microwave for 2 hours. The mixture was diluted with water (30 mL), then extracted with EtOAc (50 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give methyl 6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)propyl)amino)picolinate (20 mg, 33% yield) as a yellow solid. LC-MS: m/z 488.2 [M+H]⁺.

Step 6:

To a stirred solution of methyl 6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)propyl)amino)picolinate (20 mg, 41 μ mol) in mixed solvents of water and THF (8 mL, 1:3) was added LiOH·H₂O (10 mg, 410 μ mol) at 20 °C. The mixture was stirred at 20 °C for 2 hours. The pH of the mixture was adjusted to 6 with saturated aqueous NH₄Cl, then extracted with DCM (50 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC to give 6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)propyl)amino)picolinic acid (6 mg, 31% yield) as a white solid. LC-MS: m/z 474.1 [M+H]⁺.

Example 106**Step 1:**

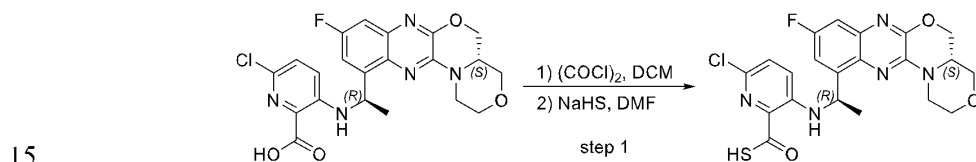
To a solution of trichlororuthenium (19.3 mg, 92.8 μ mol) and methyl 6-chloro-3-[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.02,7.012,17]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylate (110 mg, 232.1 μ mol) in EtOAc (6 mL) and water (6 mL) was added sodium periodate (114.2 mg, 533.8 μ mol). The mixture was stirred at 20 °C for 3 hours. The mixture was diluted with water (50 mL) and extracted with EtOAc (70 mL $\times$ 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by column chromatography on silica gel to afford methyl 6-chloro-3-[(1R)-1-[(7S)-14-fluoro-3-oxo-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.02,7.012,17]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylate (15 mg, 13.3% yield) as a yellow solid. LC-MS: m/z 487.7 [M+H]⁺.

Step 2:

To a solution of methyl 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-3-oxo-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0.2,7.0]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylate (12 mg, 24.6 μmol) in CH_2Cl_2 (3 mL) was added

5 tribromoborane (123.2 mg, 491.9 μmol). The mixture was stirred at 20 °C for 3 hours. The mixture was quenched with water (20 mL) and then the mixture was adjusted to pH 5 with aq. NaHCO_3 . The mixture was extracted with CH_2Cl_2 (70 mL $\times$ 2). The combined organic layer was dried over Na_2SO_4 , filtered and concentrated to afford crude product. The crude was purified prep-HPLC to afford 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-3-oxo-5,9-dioxo-2,11,18-

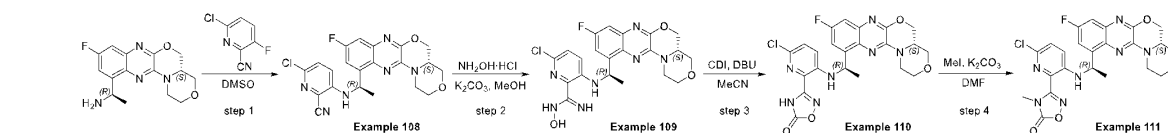
10 triazatetracyclo[8.8.0.0.2,7.0]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylic acid (2.7 mg, 23.2% yield) as a white solid. LC-MS: m/z 473.7 $[\text{M}+\text{H}]^+$.

Example 107**Step 1:**

To a stirred solution of 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0.2,7.0]octadeca-1(18),10,12,14,16-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylic acid (20 mg, 43.5 μmol) and oxalyl dichloride (8 mg, 65.2 μmol) in DCM (1 mL) was

20 added DMF (two drops). The mixture was stirred at 25 °C for 0.5 hour. Then NaSH (24.8 mg, 434.9 μmol) was added to the above mixture. The reaction mixture was stirred at 25 °C for 2 hours. The mixture was extracted with EtOAc (50 mL $\times$ 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by prep-HPLC to give 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-

25 triazatetracyclo[8.8.0.0.2,7.0]octadeca-1(18),10,12,14,16-pentaen-16-yl]ethyl]amino]pyridine-2-carbothioic S-acid (15 mg, 72% yield) as a white solid. LC-MS: m/z 475.8 $[\text{M}+\text{H}]^+$.

Example 108, 109, 110 and 111

Step 1:

To a stirred solution of (R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethan-1-amine (500 mg, 1.6 mmol) in DMSO (10 mL) was added 6-chloro-3-fluoro-pyridine-2-carbonitrile (283 mg, 1.8 mmol) at 20 °C.

- 5 The mixture was stirred at 120 °C under N₂ for 1 hour. The mixture was diluted with water (50 mL) and extracted with EtOAc (100 mL × 2). The organic layer was washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)picolinonitrile (600 mg, 83%
10 yield) as a yellow solid. LC-MS: m/z 440.9 [M+H]⁺.

Step 2:

To a stirred solution of 6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)picolinonitrile (300 mg, 680 μmol) in methanol (10 mL) was added hydroxylaminutese;hydrochloride (118 mg, 1.7 mmol), K₂CO₃
15 (141 mg, 1 mmol) at 20 °C. The mixture was stirred at 60 °C under N₂ for 3 hours. The mixture was diluted with water (50 mL) and extracted with DCM (100 mL × 2). The organic layer was washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)-N-
20 hydroxypicolinimidamide (300 mg, 93% yield) as a yellow solid. LC-MS: m/z 474.1 [M+H]⁺.

Step 3:

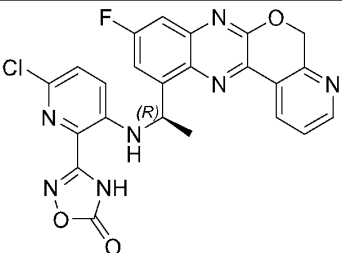
To a stirred solution of 6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)-N-hydroxypicolinimidamide (20 mg, 42 μmol) in ACN (2 mL) was added CDI (8 mg, 51 μmol), DBU (16 mg, 106 μmol) at 20 °C.
25 The mixture was stirred at 100 °C under N₂ for 12 hours. The mixture was diluted with water (50 mL) and extracted with DCM (100 mL × 2). The organic layer was washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The mixture was purified by prep-HPLC to give 3-(6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)pyridin-2-yl)-1,2,4-oxadiazol-
30 5(4H)-one (6 mg, 28% yield) as a white solid. LC-MS: m/z 499.8 [M+H]⁺.

Step 4:

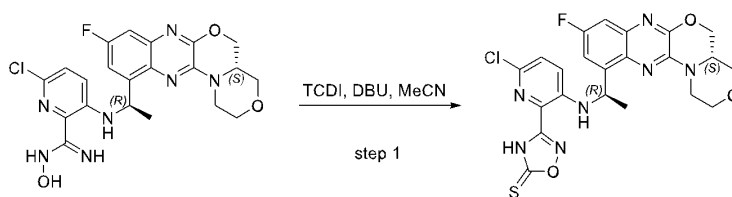
To a stirred solution of 3-(6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)pyridin-2-yl)-1,2,4-oxadiazol-
5(4H)-one (5 mg, 10 μmol) in DMF (1 mL) was added K₂CO₃ (6 mg, 40 μmol), iodomethane (2 mg,
35 11 μmol) at 0 °C. The mixture was stirred at 20 °C for 2 hours. The mixture was diluted with water (10 mL) and extracted with EtOAc (50 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The mixture was purified by prep-HPLC to give 3-(6-chloro-3-

((*(R)*)-1-((*(S)*)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)pyridin-2-yl)-4-methyl-1,2,4-oxadiazol-5(4H)-one (1 mg, 19% yield) as a white solid. LC-MS: m/z 514.2 $[M+H]^+$.

- 5 The following compound has been prepared in analogy to the representative procedures described for **Example 110**.

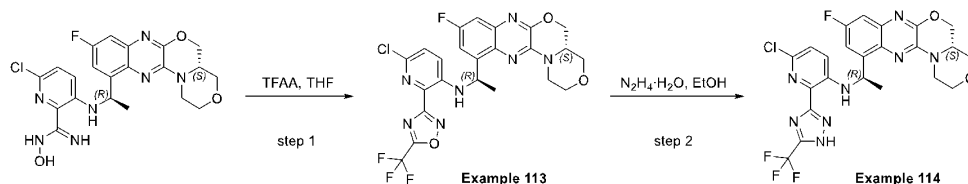
ID	Structure	LC-MS: m/z $[M+H]^+$
Example 146		491.6

Example 112



10 Step 1:

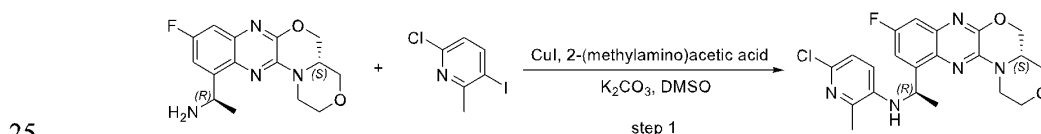
- To a stirred solution of 6-chloro-3-(((*(R)*)-1-((*(S)*)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)-N-hydroxypicolinimidamide (20 mg, 42 μ mol) in ACN (2 mL) was added DBU (16 mg, 105.5 μ mol), di(imidazol-1-yl)methanethione (TCDI, 9 mg, 51 μ mol) at 20 °C. The mixture was stirred at 100 °C under N_2 for 12
- 15 hours. The mixture was diluted with water (50 mL) and extracted with DCM (100 mL $\times$ 2). The organic layer was washed with brine (100 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The mixture was purified by prep-HPLC to give 3-(6-chloro-3-(((*(R)*)-1-((*(S)*)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)pyridin-2-yl)-1,2,4-oxadiazole-5(4H)-thione (0.4 mg, 2% yield) as a white solid. LC-
- 20 MS: m/z 516.1 $[M+H]^+$.

Example 113 and 114**Step 1:**

To a stirred solution of 6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)-N-hydroxycolinimidamide (100 mg, 211 μ mol) in THF (10 mL) was added TFAA (89 mg, 422 μ mol) at 20 °C. The mixture was stirred at 20 °C under N₂ for 12 hours. The mixture was diluted with water (50 mL) and extracted with DCM (100 mL $\times$ 2). The organic layer was washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The mixture was purified by silica gel chromatography to give 6-chloro-N-((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)-2-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-3-amine (100 mg, 86% yield) as a yellow solid. LC-MS: m/z 552.1 [M+H]⁺.

Step 2:

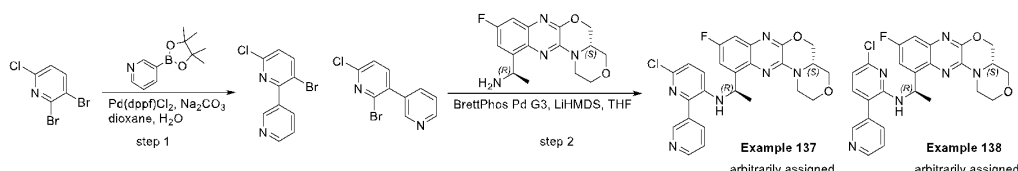
To a stirred solution of 6-chloro-N-((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)-2-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)pyridin-3-amine (20 mg, 36 μ mol) in ethanol (3 mL) was added hydrazine hydrate (9 mg, 181 μ mol). The mixture was stirred at 20 °C for 6 hours. The mixture was diluted with water (10 mL), then extracted with EtOAc (50 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The mixture was purified by prep-HPLC to give 6-chloro-N-((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)-2-(5-(trifluoromethyl)-1H-1,2,4-triazol-3-yl)pyridin-3-amine (2 mg, 8% yield) as a white solid. LC-MS: m/z 551.2 [M+H]⁺.

Example 136**Step 1:**

To a solution of 6-chloro-3-iodo-2-methylpyridine (25 mg, 98.6 μ mol) and (1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0.2,7.0.12,17]octadeca-1(18),10,12,14,16-pentaen-16-yl]ethanamine (20 mg, 65.7 μ mol), 2-(methylamino)acetic acid (3 mg, 32.9 μ mol) in DMSO (2 mL) was added K₂CO₃ (23 mg, 164.3 μ mol) and CuI (6.3 mg, 32.9 μ mol). The mixture was stirred at 100 °C for 1 hour under N₂ before it was cooled to rt. The mixture was added H₂O (10 mL) and

adjusted pH to 2 with HCl (aq, 1 N). The mixture was extracted with EtOAc (50 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by prep-HPLC to give 6-chloro-N-[(1R)-1-[(7S)-14-fluoro-5,9-dioxa-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12,14,16-pentaen-16-yl]ethyl]-2-methyl-pyridin-3-amine (5 mg, 17.7% yield) as a white solid. LC-MS: m/z 429.9 [M+H]⁺.

Example 137 and 138



Step 1:

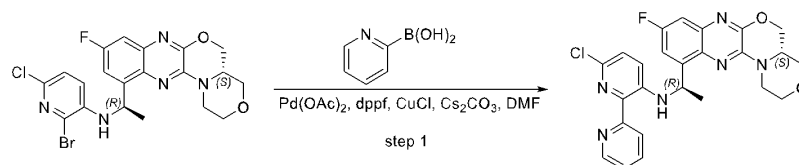
To a solution of 2,3-dibromo-6-chloro-pyridine (200 mg, 737.1 μmol) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (196.5 mg, 958.2 μmol) in dioxane (6 mL) and water (0.8 mL) was added Pd(dppf)Cl₂ (107.8 mg, 147.4 μmol) and Na₂CO₃ (234.4 mg, 2.2 mmol). The mixture was degassed with a stream of N₂ for three times and then stirred at 95 °C for 1.5 hours. The mixture was diluted with CH₂Cl₂ (60 mL) and washed with brine (35 mL × 2). The organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by column chromatography on silica gel to afford a mixture of 3-bromo-6-chloro-2-(3-pyridyl)pyridine and 2-bromo-6-chloro-3,3'-bipyridine (65 mg, 32.7% yield) as a white solid. LC-MS: m/z 268.8 [M+H]⁺.

Step 2:

To a solution of 3-bromo-6-chloro-2-(3-pyridyl)pyridine and 2-bromo-6-chloro-3,3'-bipyridine (15 mg, 55.6 μmol) and (1R)-1-[(7S)-14-fluoro-5,9-dioxa-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethanamine (16.9 mg, 55.6 μmol) in dioxane (2 mL) was added [2-(2-aminophenyl)phenyl]-methylsulfonyloxy-palladium;dicyclohexyl-[3,6-dimethoxy-2-(2,4,6-triisopropylphenyl)phenyl]phosphane (10.1 mg, 11.1 μmol), 2-(dicyclohexylphosphino)-3,6-dimethoxy-2'-4'-6'-tri-*i*-propyl-1,1'-biphenyl (11.9 mg, 22.3 μmol) and lithium;bis(trimethylsilyl)azanide (74.5 mg, 445.2 μmol). The mixture was degassed with a stream of N₂ for three times and then stirred at 65 °C for 1 hour. The mixture was diluted with CH₂Cl₂ (60 mL) and washed with aq.NH₄Cl (15 mL), brine (35 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by column chromatography on silica gel to afford crude product. Then the crude was purified by prep-HPLC to afford 6-chloro-N-[(1R)-1-[(7S)-14-fluoro-5,9-dioxa-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]-2-(3-pyridyl)pyridin-3-amine (**Example 137**, 2.2 mg, 8% yield) as a white solid. LC-MS: m/z 492.8 [M+H]⁺. Meanwhile 6-chloro-N-[(1R)-1-[(7S)-14-fluoro-5,9-dioxa-2,11,18-

triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]-3-(3-pyridyl)pyridin-2-amine (**Example 138**, 0.8 mg, 2.9% yield) was obtained as a white solid LC-MS: m/z 492.8 [M+H]⁺.

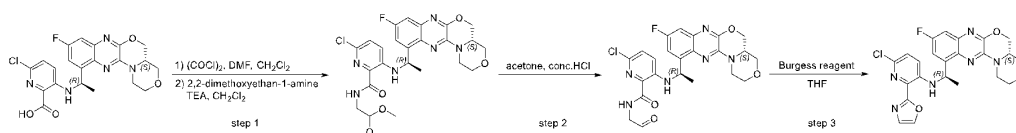
5 Example 139



Step 1:

To a solution of 2-bromo-6-chloro-N-[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]pyridin-3-amine (18 mg, 36.4 μ mol) and 2-pyridylboronic acid (8.9 mg, 72.7 μ mol) in DMF (1 mL) was added diacetoxypalladium (3.3 mg, 14.5 μ mol), cyclopentyl(diphenyl)phosphane;iron (16.1 mg, 29.1 μ mol), cuprous;chloride (3.6 mg, 36.4 μ mol) and dicesium;carbonate (35.6 mg, 109.2 μ mol). The mixture was degassed with a stream of N₂ for three times and then stirred at 100 °C for 1.5 hours. The mixture was diluted with EtOAc (60 mL) and washed with brine (15 mL $\times$ 3). The organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by prep-HPLC to afford 6-chloro-N-[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]-2-(2-pyridyl)pyridin-3-amine (1 mg, 5.6% yield) as a white solid. LC-MS: m/z 492.9 [M+H]⁺.

20 Example 141



Step 1:

To a solution of 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylic acid (15 mg, 32.6 μ mol) in CH₂Cl₂ (2 mL) was added oxalyl dichloride (12.4 mg, 97.8 μ mol) and DMF (2 drops). The mixture was stirred at 20 °C for 10 minutes. The mixture was concentrated to afford crude product and used directly. To this solution of 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylic acid (20 mg, 41.8 μ mol) in CH₂Cl₂ (2 mL) was added TEA (21.2 mg, 209.1 μ mol) and 2,2-dimethoxyethanamine (8.8 mg, 83.6 μ mol). The mixture was stirred at 20 °C for 10 minutes. The mixture was diluted with water (20 mL) and then extracted with

CH₂Cl₂ (40 mL × 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by column chromatography on silica gel to afford 6-chloro-N-(2,2-dimethoxyethyl)-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carboxamide (5 mg, 21.8% yield) as a light yellow solid. LC-MS: m/z 546.8 [M+H]⁺.

Step 2:

To a solution of 6-chloro-N-(2,2-dimethoxyethyl)-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carboxamide (3 mg, 5.5 μ mol) in acetone (4 mL) was added conc.HCl (2 mL). The mixture was stirred at 20 °C for 3 hours. The mixture was adjusted to pH~7 with aq.NaHCO₃ and then extracted with CH₂Cl₂ (30 mL $\times$ 3). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to afford 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]-N-(2-oxoethyl)pyridine-2-carboxamide (2 mg, 72.8% yield) as yellow oil. LC-MS: m/z 500.8 [M+H]⁺.

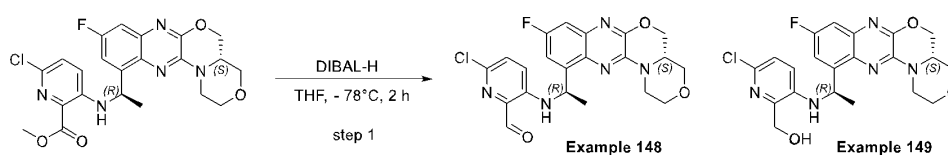
15 **Step 3:**

To a solution of 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]-N-(2-oxoethyl)pyridine-2-carboxamide (2 mg, 4 μ mol) in THF (1.5 mL) was added methoxycarbonyl-(triethylammonio)sulfonyl-azanide (2.8 mg, 11.9 μ mol). The mixture was stirred at 20 °C for 1 hour.

20 The mixture was diluted with CH₂Cl₂ (30 mL) and washed with brine (10 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by prep-HPLC to afford 6-chloro-N-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]-2-oxazol-2-yl]pyridin-3-amine (0.9 mg, 46.7% yield) as a white solid. LC-MS: m/z 483.1 [M+H]⁺.

25

Example 148 and 149

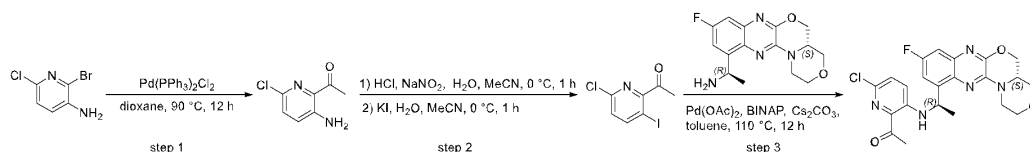


Step 1:

30 To a stirred solution of methyl 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carboxylate (30 mg, 63.3 μ mol) in THF (6 mL) was added DIBAL-H (1 M, 126.3 μ L) at -78°C under N₂. The mixture was stirred at -78 °C for 2 hours. The resulting mixture was quenched by addition of saturated NH₄Cl aqueous solution (15 mL) and extracted with EtOAc (30 mL $\times$ 3). The

combined organic layer was washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford 6-chloro-3-[[1(R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,11}.7.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carbaldehyde (6 mg, 21.4% yield) as a yellow solid. LC-MS: m/z 443.8 [M+H]⁺. Meanwhile, (6-chloro-3-((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)pyridin-2-yl)methanol (10 mg, 35.4% yield) was also obtained as a yellow solid. LC-MS: m/z 445.9 [M+H]⁺.

Example 150



Step 1:

To a sealed tube were added 2-bromo-6-chloro-pyridin-3-amine (200 mg, 964 μmol), dichloropalladium;triphenylphosphane (100 mg, 14.2 μmol), tributyl(1-ethoxyvinyl)stannane (481 mg, 1.3 mmol) and dioxane (2 mL). The mixture was backfilled with N_2 and stirred at 100 $^\circ\text{C}$ for 12 hours. 1 M HCl (aq.) was added to the mixture and the mixture was stirred at 20 $^\circ\text{C}$ for 2 hours. The resulting mixture was quenched by addition of saturated NaHCO_3 aqueous solution (5 mL) and extracted with EtOAc (10 mL $\times$ 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford 1-(3-amino-6-chloro-2-pyridyl)ethanone (120 mg, 73% yield) as yellow gum.

Step 2:

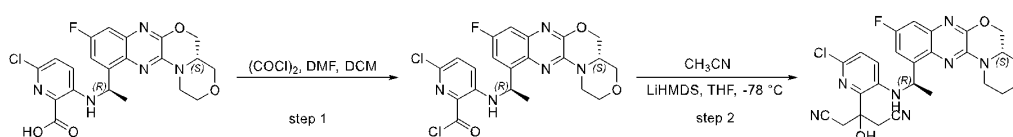
To a solution of 1-(3-amino-6-chloro-2-pyridyl)ethanone (120 mg, 0.7 mmol) in MeCN (5 mL) was added HCl (12 M, 2 mL), NaNO₂ (97.1 mg, 1.4 mmol) and water (5 mL) at 0 °C. The mixture was stirred at 0 °C for 1 hour. KI (291.9 mg, 1.7 mmol) was added to the mixture and stirred at 0 °C for 1 hour. The resulting mixture was quenched by addition of saturated NaHCO₃ aqueous solution (5 mL) and saturated Na₂SO₃ aqueous solution (5 mL). The mixture was extracted with EtOAc (10 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford 1-(6-chloro-3-iodo-2-pyridyl)ethanone (20 mg, 10.1% yield) as a white solid. LC-MS: m/z 281.7 [M+H]⁺.

Step 3:

To a sealed tube were added (1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethanamine (21.6 mg, 71.1 μmol), 1-(6-chloro-3-iodo-2-pyridyl)ethanone (20 mg, 71.1 μmol), Cs_2CO_3 (46.3 mg, 142

μmol), (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one; palladium (13.0 mg, 0.0142 mmol), (5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (16.5 mg, 28.2 μmol) and dioxane (2 mL). The mixture was backfilled with N₂ and stirred at 100 °C for 12 hours. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography to afford crude product. The residue was purified by prep-HPLC to afford 1-[6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]-2-pyridyl]ethanone (2.5 mg, 7.7% yield) as a white solid. LC-MS: m/z 457.9 [M+H]⁺.

10 Example 151



Step 1:

To a solution of DMF (476.8 μg, 6.5 μmol) and 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-

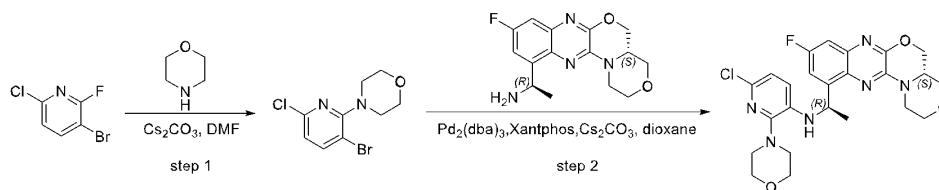
yl]ethyl]amino]pyridine-2-carboxylic acid (30 mg, 65.2 μmol) in CH₂Cl₂ (2 mL) was added oxalyl dichloride (24.8 mg, 195.7 μmol). The mixture was stirred at 20 °C for 10 minutes. The mixture was concentrated to afford 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carbonyl chloride (30 mg, crude) as a yellow solid.

20 Step 2:

To a solution of acetonitrile (5.1 mg, 125.4 μmol) in THF (2 mL) was added LiHMDS (1 N, 125.4 μL) at -78 °C. The mixture was stirred at -78 °C for 30 minutes. Then 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-carbonyl chloride (15 mg, 31.3 μmol) was added and the mixture was

stirred at -78 °C for 10 minutes. The mixture was quenched with aq.NH₄Cl (20 mL) and then extracted with CH₂Cl₂ (40 mL × 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by prep-HPLC to give 3-[6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]-2-pyridyl]-3-hydroxy-pentanedinitrile (1.5 mg,

9.1% yield) as a yellow solid. LC-MS: m/z 524.2 [M+H]⁺.

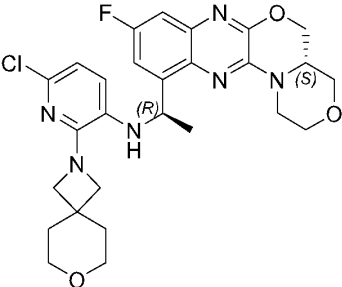
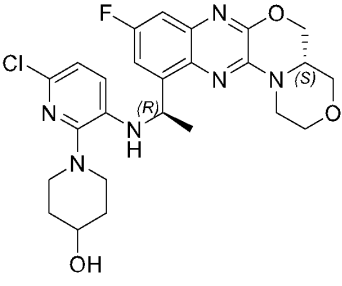
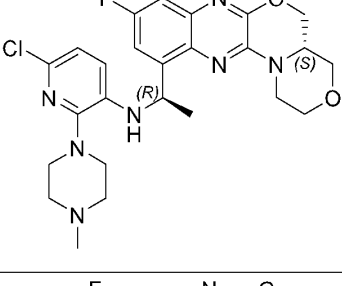
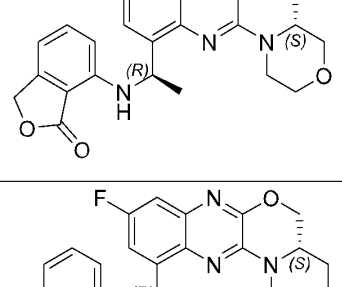
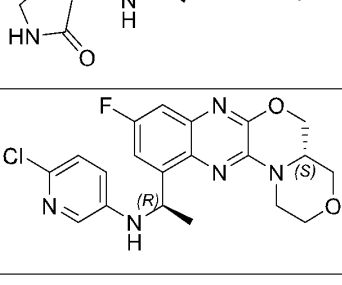
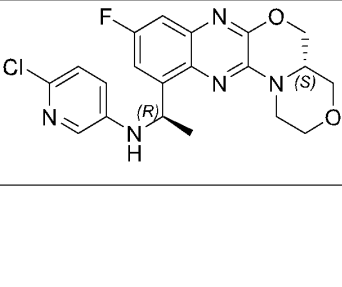
Example 152**Step 1:**

To a stirred solution of 3-bromo-6-chloro-2-fluoropyridine (200 mg, 950.4 μmol) and morpholine (207 mg, 2.4 mmol) in DMF (4 mL) was added Cs_2CO_3 (309.7 mg, 950.4 μmol). The mixture was stirred at 25 °C for 16 hours before it was diluted with EtOAc (100 mL) and water (50 mL). The organic layer was washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford crude product, which was purified by silica gel chromatography to afford 4-(3-bromo-6-chloro-2-pyridyl)morpholine (150 mg, 57% yield) as a white solid. LC-MS: m/z 277.2 $[\text{M}+\text{H}]^+$.

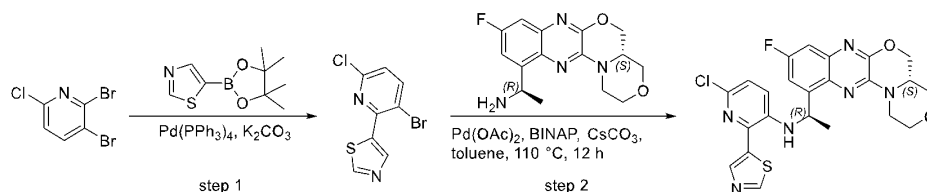
Step 2:

To a solution of 4-(3-bromo-6-chloro-2-pyridyl)morpholine (32.8 mg, 118.3 μmol) and (R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethan-1-amine (30 mg, 98.6 μmol) in dioxane (4 mL) was added (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one; palladium (9 mg, 9.9 μmol), (5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenylphosphane (17.1 mg, 29.6 μmol) and Cs_2CO_3 (64.2 mg, 197.2 μmol). The mixture was stirred at 100 °C for 12 hours under N_2 before it was cooled to rt. The mixture was diluted with water (20 mL) and DCM (30 mL). The organic layer was washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford crude product. The residue was purified by prep-HPLC to give 6-chloro-N-((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)-2-morpholinopyridin-3-amine (12 mg, 24% yield) as a yellow solid. LC-MS: m/z 500.9 $[\text{M}+\text{H}]^+$.

The following compounds have been prepared in analogy to the representative procedures described for **Example 152**.

ID	Structure	LC-MS: m/z [M+H] ⁺
Example 153		540.9
Example 154		514.9
Example 155		513.9
Example 156		436.9
Example 157		435.9
Example 158		415.9

Example 159



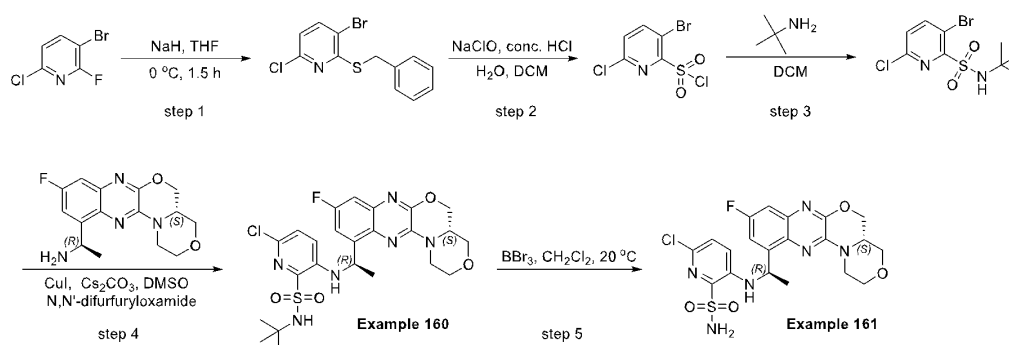
Step 1:

To a solution of 2,3-dibromo-6-chloro-pyridine (50 mg, 0.2 mmol) in dioxane (1 mL) was added Pd(PPh₃)₄ (42.6 mg, 0.4 mmol) and K₂CO₃ (50.9 mg, 0.4 mmol). The mixture was stirred at 100 °C for 12 hours. The resulting mixture was quenched by addition of saturated NH₄Cl aqueous solution (5 mL) and extracted with EtOAc (30 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by TLC to afford 5-(3-bromo-6-chloro-2-pyridyl)thiazole (10 mg, 19.7% yield) as a yellow solid.

Step 2:

To a sealed tube was added (1R)-1-((14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0.2,7.0.12,17]octadeca-1(18),10,12(17),13,15-pentaen-16-yl)ethanamine) (20 mg, 65.7 μmol), 5-(3-bromo-6-chloro-2-pyridyl)thiazole (10 mg, 36.2 μmol), Pd(OAc)₂ (4.2 mg, 7.2 μmol), BINAP (9 mg, 14.5 μmol), Cs₂CO₃ (35.5 mg, 10.9 μmol) and toluene (2 mL). The mixture was backfilled with N₂ and stirred at 110 °C for 12 hours. The resulting mixture was concentrated under reduced pressure. The residue was purified by TLC to afford crude product. The crude was purified by prep-HPLC to afford 6-chloro-N-[(1R)-1-((14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0.2,7.0.12,17]octadeca-1(18),10,12(17),13,15-pentaen-16-yl)ethyl)-2-thiazol-5-yl]pyridin-3-amine (1.5 mg, 4% yield) as a white solid. LC-MS: m/z 498.8 [M+H]⁺.

Example 160 and 161



Step 1:

To a solution of NaH (456.2 mg, 19 mmol) in THF (40 mL) was added phenylmethanethiol (1.4 g, 10.9 mmol). The mixture was stirred at 0 °C for 5 minutes. Then 3-bromo-6-chloro-2-fluoropyridine

(2 g, 9.5 mmol) was added and the mixture was stirred at 20 °C for 1.5 hours. The mixture was quenched with water (50 mL) and extracted with CH₂Cl₂ (60 mL × 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to afford 2-benzylsulfanyl-3-bromo-6-chloro-pyridine (3 g, crude) as a light yellow solid.

5 **Step 2:**

To a solution of 2-benzylsulfanyl-3-bromo-6-chloro-pyridine (3 g, 9.5 mmol) in water (7.5 mL), concentrated hydrochloric acid (12 N, 3.7 mL) and water (7.5 mL) was added NaClO (50.7 g, 47.7 mmol) at 0 °C over 10 minutes. The mixture was stirred at 0 °C for 20 minutes. The mixture was extracted with CH₂Cl₂ (40 mL × 2) and the organic solution containing 3-bromo-6-chloro-pyridine-2-sulfonyl chloride was used directly to next step.

10 **Step 3:**

A solution of 3-bromo-6-chloro-pyridine-2-sulfonyl chloride in CH₂Cl₂ (15 mL) was added 2-methylpropan-2-amine at 0 °C. The mixture was stirred at 20 °C for 20 minutes, diluted with water (20 mL) and extracted with CH₂Cl₂ (30 mL × 3). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by column chromatography on silica gel to afford 3-bromo-N-tert-butyl-6-chloro-pyridine-2-sulfonamide (400 mg, 13% yield over two steps) as a light yellow solid.

15 **Step 4:**

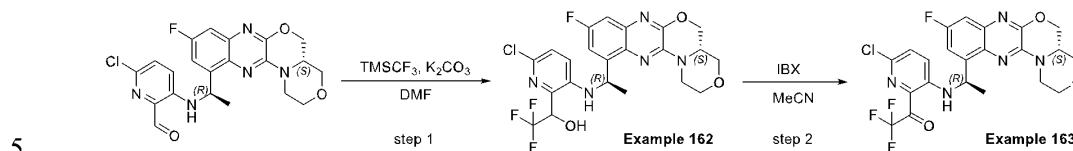
To a solution of (1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethanamine (15 mg, 49.3 μmol) in DMSO (2 mL) was added 3-bromo-N-tert-butyl-6-chloro-pyridine-2-sulfonamide (32.3 mg, 98.5 μmol), Cs₂CO₃ (40.1 mg, 123.2 μmol), N,N'-bis(2-furylmethyl)oxamide (12.2 mg, 49.2 μmol) and CuI (4.6 mg, 24.6 μmol). The mixture was degassed with a stream of N₂ for three times and then stirred at 100 °C for 16 hours. The mixture was diluted with EtOAc (60 mL) and washed with ammonia (30 mL) and brine (35 mL × 2). The organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by column chromatography on silica gel to give N-tert-butyl-6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-sulfonamide (7.1 mg, 26.1% yield) as a white solid. LC-MS: m/z 550.8 [M+H]⁺.

25 **Step 5:**

To a solution of N-tert-butyl-6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]amino]pyridine-2-sulfonamide (13 mg, 23.6 μmol) in CH₂Cl₂ (2 mL) was added BBr₃ (41.3 mg, 165.1 μmol) at 0 °C. The mixture was stirred at 20 °C for 1 hour. The mixture was diluted with CH₂Cl₂ (60 mL) and washed with brine (35 mL × 2). The organic layer was dried over Na₂SO₄, filtered and concentrated to afford crude product. The crude was purified by prep-HPLC to afford 6-chloro-3-[[[(1R)-1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-

yl]ethyl]amino]pyridine-2-sulfonamide (2.2 mg, 18.8% yield) as a light yellow solid. LC-MS: m/z 494.8 $[M+H]^+$.

Example 162 and 163



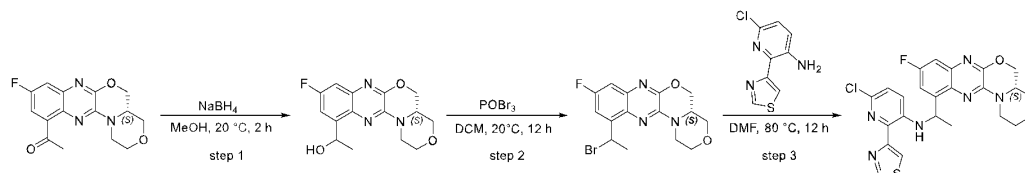
Step 1:

To a solution of 6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)picolinaldehyde (80 mg, 180.2 μ mol) and trimethyl(trifluoromethyl)silane (76.9 mg, 540.7 μ mol) in DMF (5 mL) was added K₂CO₃ (2.5 mg, 18 μ mol). The mixture was stirred at 25 °C for 2 hours before it was quenched with aq.HCl (0.5 mL, 1 N). The mixture was diluted with EtOAc (30 mL) and water (10 mL). The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford crude product, which was purified by prep-HPLC to afford 1-(6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)pyridin-2-yl)-2,2,2-trifluoroethan-1-ol (50 mg, 54% yield) as a light-yellow solid. LC-MS: m/z 513.8 [M+H]⁺.

Step 2:

To a solution of 1-(6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)pyridin-2-yl)-2,2,2-trifluoroethan-1-ol (20 mg, 38.9 μ mol) in MeCN (8 mL) was added IBX (32.7 mg, 116.8 μ mol). The mixture was stirred at 100 $^{\circ}$ C for 2 hours before it was cooled to rt. The mixture was diluted with DCM (30 mL) and water (10 mL). The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford crude product, which was purified by prep-HPLC to afford 1-(6-chloro-3-(((R)-1-((S)-9-fluoro-1,2,4a,5-tetrahydro-4H-[1,4]oxazino[4',3':4,5][1,4]oxazino[2,3-b]quinoxalin-11-yl)ethyl)amino)pyridin-2-yl)-2,2,2-trifluoroethan-1-one (5 mg, 24% yield) as a light-yellow solid. LC-MS: m/z 511.8 [M+H]⁺.

Example 164



30 **Step 1:**

To a solution of 1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethanone (100 mg, 0.3 mmol) in MeOH (2 mL) was added NaBH₄ (20 mg, 0.5 mmol). The mixture was stirred at 20 °C for 2 hours. The resulting mixture was quenched by addition of saturated NH₄Cl aqueous solution (5 mL) and extracted with EtOAc (10 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethanol (100 mg, 99.3% yield) as a black solid.

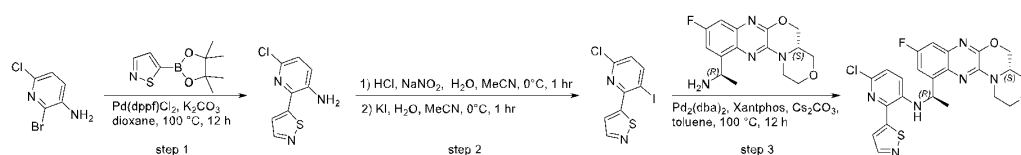
Step 2:

To a solution of 1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethanol (100 mg, 0.3 mmol) in DCM (2 mL) was added POBr₃ (1 mL). The mixture was stirred at 20 °C for 12 hours. The resulting mixture was quenched by addition of saturated NaHCO₃ aqueous solution (5 mL) and extracted with DCM (10 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford (7S)-16-(1-bromoethyl)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaene (50 mg, 41.5% yield) as a yellow solid.

Step 3:

To a solution of 6-chloro-2-thiazol-4-yl-pyridin-3-amine (57.5 mg, 0.3 mmol) in DMF (2 mL) was added (7S)-16-(1-bromoethyl)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaene (50 mg, 0.1 mmol). The mixture was stirred at 80 °C for 12 hours. The residue was purified by prep-HPLC to afford 6-chloro-N-[1-[(7S)-14-fluoro-5,9-dioxo-2,11,18-triazatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl]ethyl]-2-thiazol-4-yl-pyridin-3-amine (18 mg, 26.6% yield) as a white solid. LC-MS: m/z 499.1 [M+H]⁺.

Example 165



Step 1:

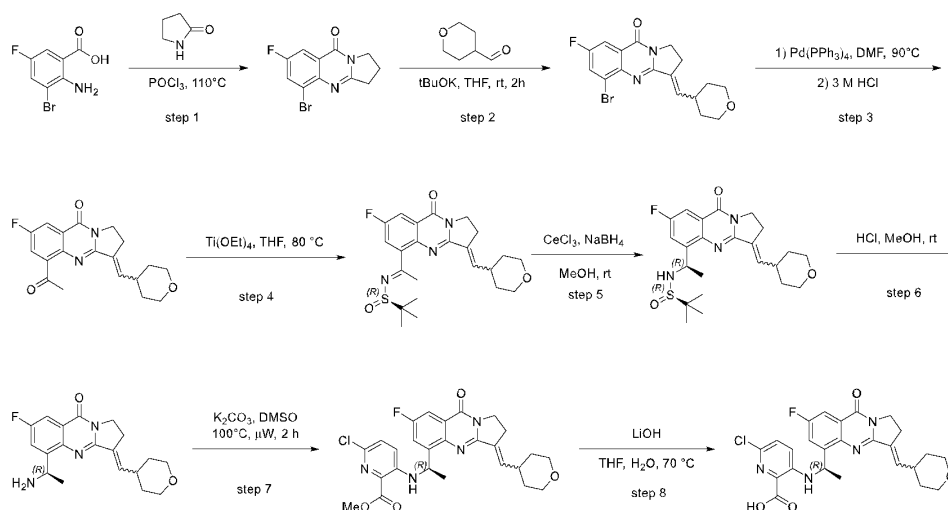
To a solution of 2-bromo-6-chloro-pyridin-3-amine (100 mg, 482 μmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isothiazole (122 mg, 578 μmol) in dioxane (1 mL) was added Pd(dppf)Cl₂ (70.5 mg, 0.1 mmol) and K₂CO₃ (471.2 mg, 1.5 mmol) under N₂. The mixture was stirred at 100 °C for 12 hours. The resulting mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford 6-chloro-2-isothiazol-5-yl-pyridin-3-amine (60 mg, 58.8% yield) as a yellow solid. LC-MS: m/z 212.0 [M+H]⁺.

Step 2:

To a solution of 6-chloro-2-isothiazol-5-yl-pyridin-3-amine (60 mg, 0.3 mmol) in MeCN (1.9 mL) was added 35% HCl (aq.) (1.9 mL) and NaNO₂ (100 mg, 1.5 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 hour. Then KI (240 mg, 1.5 mmol) was added to the resulting mixture and stirred at 0 °C for 1 hour. The resulting mixture was quenched by addition of saturated NaHCO₃ aqueous solution (15 mL) and saturated Na₂SO₃ aqueous solution (15 mL). The mixture was extracted with EtOAc (10 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to afford 5-(6-chloro-3-iodo-2-pyridyl)isothiazole (30 mg, 32.8% yield) as a yellow solid. LC-MS: m/z 322.9 [M+H]⁺.

Step 3:

To a sealed tube was added (1R)-1-(14-fluoro-5,9-dioxo-2-azatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl)ethanamine (20 mg, 66.1 μmol), 5-(6-chloro-3-iodo-2-pyridyl)isothiazole (30 mg, 93 μmol), Cs₂CO₃ (62 mg, 0.2 mmol), Pd₂(dba)₃ (20 mg, 34.8 μmol), Xantphos (40 mg, 69.1 μmol) and toluene (2 mL). The mixture was backfilled with N₂ and stirred at 100 °C for 12 hours. The resulting mixture was concentrated under reduced pressure. The residue was purified by column chromatography to afford 6-chloro-N-[(1R)-1-(14-fluoro-5,9-dioxo-2-azatetracyclo[8.8.0.0^{2,7}.0^{12,17}]octadeca-1(18),10,12(17),13,15-pentaen-16-yl)ethyl]-2-isothiazol-5-yl-pyridin-3-amine (4 mg, 8.7% yield) as a white solid. LC-MS: m/z 499.1 [M+H]⁺.

Example 166**Step 1:**

To a stirred mixture of 2-amino-3-bromo-5-fluorobenzoic acid (10 g, 42.7 mmol) in pyrrolidin-2-one (36.4 g, 427.3 mmol) at 0 °C was dropwise added POCl₃ (65.8 g, 429.1 mmol) and the resulting mixture was stirred at 100 °C for 3 hours. Upon completion, the mixture was concentrated *in vacuo* to

remove excess POCl_3 and the residue was dissolved in ice water (100 mL) and basified with sat. NaHCO_3 . The precipitate was collected by filtration. The filter cake was dried *in vacuo* to give 5-bromo-7-fluoro-2,3-dihydro-1H-pyrrolo[2,1-b]quinazolin-9-one (9 g, 74.4% yield) as a yellow solid. LC-MS: m/z 282.9 $[\text{M}+\text{H}]^+$.

5 **Step 2:**

A mixture of 5-bromo-7-fluoro-2,3-dihydro-1H-pyrrolo[2,1-b]quinazolin-9-one (1.1 g, 4 mmol), tetrahydropyran-4-carbaldehyde (547.9 mg, 4.8 mmol), and t-BuOK (538.6 mg, 4.8 mmol) in THF (20 mL) was stirred at rt for 2 hours. Upon completion, the mixture was quenched with water (20 mL) and extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated *in vacuo* to give crude product 5-bromo-7-fluoro-3-((tetrahydro-2H-pyran-4-yl)methylene)-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (1.52 g) as a yellow solid, which was used in the next step without further purification. LC-MS: 378.9 $[\text{M}+\text{H}]^+$.

Step 3:

A mixture of crude 5-bromo-7-fluoro-3-((tetrahydro-2H-pyran-4-yl)methylene)-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (1.52 g, 4.0 mmol), tributyl(1-ethoxyvinyl)stannane (1.7 g, 4.8 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (463.2 mg, 400.8 μmol) in dioxane (12 mL) was stirred at 100 °C with microwave irradiation for 1 hour. Upon completion, the mixture was treated 3 M HCl to hydrolyze the ether intermediate to ketone. Then the mixture was basified with sat. NaHCO_3 , diluted with EtOAc (80 mL) and washed with water (40 mL $\times$ 3). The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated *in vacuo* to give 5-acetyl-7-fluoro-3-((tetrahydro-2H-pyran-4-yl)methylene)-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (1.8 g, crude) as a yellow solid, which was used in the next step without further purification.

Step 4:

A mixture of crude 5-acetyl-7-fluoro-3-((tetrahydro-2H-pyran-4-yl)methylene)-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (1.8 g, 5.2 mmol), (R)-2-methylpropane-2-sulfinamide (1.3 g, 10.4 mmol) and $\text{Ti}(\text{OEt})_4$ (5 mL) in THF (3 mL) was stirred at 80 °C for 16 hours. Upon completion, the mixture was quenched with water and extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with 0% - 50% EA in DCM) to afford (R)-N-((1E)-1-(7-fluoro-9-oxo-3-((tetrahydro-2H-pyran-4-yl)methylene)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide (1 g, 43.2% yield) as a yellow solid. LC-MS: m/z 446.1 $[\text{M}+\text{H}]^+$.

Step 5:

To a stirred mixture of (R)-N-((1E)-1-(7-fluoro-9-oxo-3-((tetrahydro-2H-pyran-4-yl)methylene)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethylidene)-2-methylpropane-2-sulfinamide (1 g, 2.2 mmol) and CeCl_3 (663.8 mg, 2.7 mmol) in methanol (3 mL) was added NaBH_4 (169.8 mg, 4.5 mmol) in portions and the resulting mixture was stirred at rt for 20 minutes. Upon completion, the

mixture was quenched with water (20 mL) and extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to afford (R)-N-((R)-1-(7-fluoro-9-oxo-3-((tetrahydro-2H-pyran-4-yl)methylene)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (1 g, crude) as a yellow solid. LC-MS: m/z 448.1 [M+H]⁺.

Step 6:

To a stirred solution of (R)-N-((R)-1-(7-fluoro-9-oxo-3-((tetrahydro-2H-pyran-4-yl)methylene)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethyl)-2-methylpropane-2-sulfinamide (1 g, 2.2 mmol) in methanol (3 mL) was dropwise added 4.0 M HCl in 1,4-dioxane (1 mL) and the resulting mixture was stirred at rt for 30 minutes. Upon completion, the mixture was basified with sat. NaHCO₃ and extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to afford (R)-5-(1-aminoethyl)-7-fluoro-3-((tetrahydro-2H-pyran-4-yl)methylene)-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (900 mg, crude) as a yellow solid, which was used in the next step without further purification. LC-MS: m/z 344.1 [M+H]⁺.

Step 7:

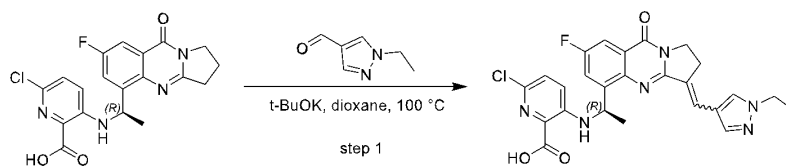
The mixture of (R)-5-(1-aminoethyl)-7-fluoro-3-((tetrahydro-2H-pyran-4-yl)methylene)-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (130 mg, 378.6 μmol), methyl 6-chloro-3-fluoropyridine-2-carboxylate (107.7 mg, 567.9 μmol) and K₂CO₃ (104.6 mg, 757 μmol) in DMSO (2 mL) was stirred at 100 °C with microwave irradiation for 2 hours. Upon completion, the mixture was diluted with EtOAc (30 mL) and washed with water (15 mL × 3). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to give methyl (R)-6-chloro-3-((1-(7-fluoro-9-oxo-3-((tetrahydro-2H-pyran-4-yl)methylene)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethyl)amino)picolinate (194 mg, crude), which was used in the next step without further purification. LC-MS: m/z 513.0 [M+H]⁺.

Step 8:

The mixture of methyl (R)-6-chloro-3-((1-(7-fluoro-9-oxo-3-((tetrahydro-2H-pyran-4-yl)methylene)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethyl)amino)picolinate (194 mg, 378.2 μmol) and LiOH·H₂O (90 mg, 3.8 mmol) in a mixed solvent of water (2 mL) and THF (6 mL) was stirred at 70 °C with microwave irradiation for 20 minutes. Upon completion, the mixture was acidified with 1 M HCl and then solvent was removed *in vacuo*. The residue was purified by prep-HPLC to give (R)-6-chloro-3-((1-(7-fluoro-9-oxo-3-((tetrahydro-2H-pyran-4-yl)methylene)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethyl)amino)picolinic acid (30 mg, 15.9% yield) as a white solid. LC-MS: m/z 499.0 [M+H]⁺.

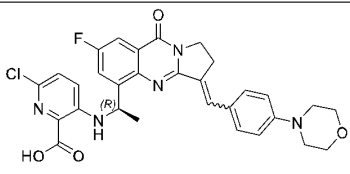
The following compounds have been prepared in analogy to the representative procedures described for **Example 166**.

ID	Structure	LC-MS: m/z [M+H] ⁺
5 Example 167		485.0
10 Example 168		521.1
15 Example 187		523.1

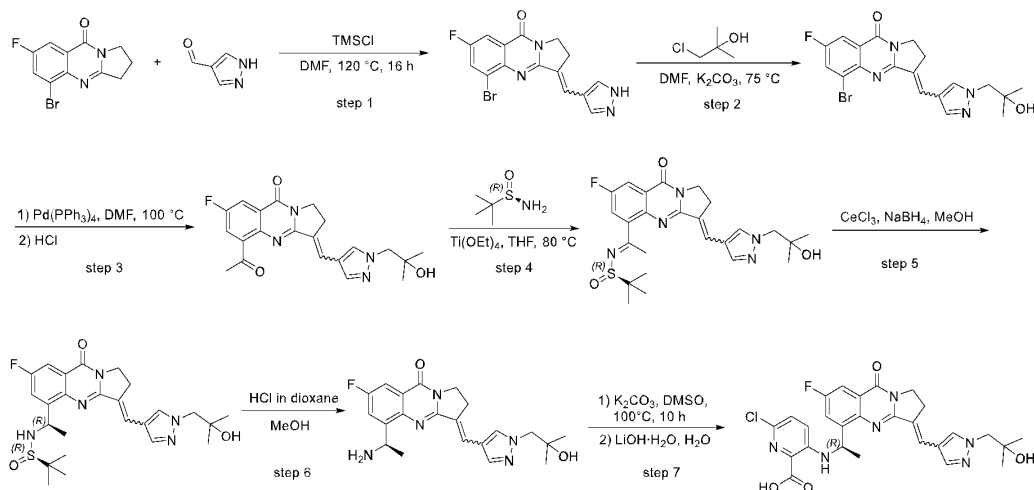
Example 177**Step 1:**

A mixture of 1-ethylpyrazole-4-carbaldehyde (9.3 mg, 74.5 μ mol), 6-chloro-3-[[[(1R)-1-(7-fluoro-9-oxo-2,3-dihydro-1H-pyrrolo[2,1-b]quinazolin-5-yl)ethyl]amino]pyridine-2-carboxylic acid (10 mg, 24.8 μ mol, prepared in analogy to Example 35) and t-BuOK (2.8 mg, 24.8 μ mol) in dioxane (3 mL) was stirred at 100 °C for 30 minutes. Upon completion, the mixture was quenched with 1 M HCl and extracted with DCM. The combined organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by prep-HPLC to give (R)-6-chloro-3-((1-(3-((1-ethyl-1H-pyrazol-4-yl)methylene)-7-fluoro-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethyl)amino)picolinic acid (5 mg, 39.6% yield) as a white solid. LC-MS: m/z 509.1 [M+H]⁺.

The following compound has been prepared in analogy to the representative procedures described for **Example 177**.

ID	Structure	LC-MS: m/z [M+H] ⁺
Example 178		576.1

5

Example 179**Step 1:**

- 10 A mixture of 5-bromo-7-fluoro-2,3-dihydro-1H-pyrrolo[2,1-b]quinazolin-9-one (1.3 g, 4.6 mmol), 1H-pyrazole-4-carbaldehyde (661.9 mg, 6.9 mmol) and TMSCl (5 g, 45.9 mmol) in DMF (20 mL) was stirred at 130 °C for 16 hours. Upon completion, the mixture was concentrated, and the residue was redissolved in EtOAc. The mixture was basified with sat. NaHCO₃. The precipitation was collected by filtration to give 3-((1H-pyrazol-4-yl)methylene)-5-bromo-7-fluoro-2,3-
- 15 dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (2 g, crude) as a yellow solid. LC-MS: m/z 361.0 [M+H]⁺.

Step 2:

- The mixture of 1-chloro-2-methyl-propan-2-ol (300.6 mg, 2.8 mmol), crude 3-((1H-pyrazol-4-yl)methylene)-5-bromo-7-fluoro-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (500 mg, 1.4 mmol) and K₂CO₃ (765.3 mg, 5.5 mmol) in DMF (10 mL) was stirred at 80 °C for 3 hours. Upon completion, the mixture was diluted with EtOAc (100 mL) and washed with water (40 mL × 3). The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with 0-30% MeOH in DCM) to give 5-bromo-7-fluoro-3-((1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)methylene)-2,3-dihydropyrrolo[2,1-b]quinazolin-
- 25 9(1H)-one (350 mg, 58% yield) as a yellow solid. LC-MS: m/z 433.1 [M+H]⁺.

Steps 3-6:

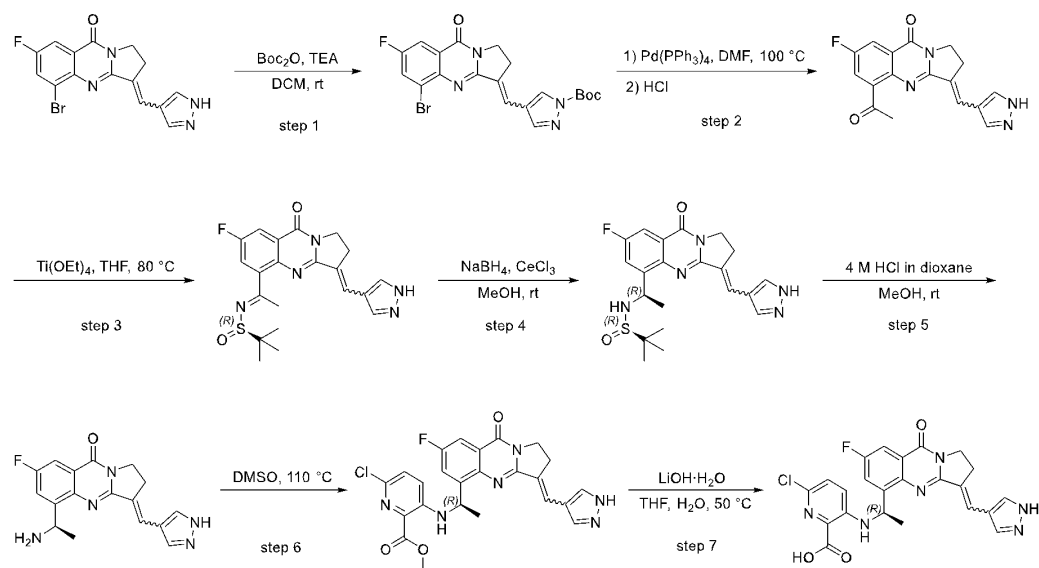
(R)-5-(1-aminoethyl)-7-fluoro-3-((1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)methylene)-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one was synthesized in analogy to the representative procedures (steps 3-6) described for Example 166.

Step 7:

- 5 The mixture of (R)-5-(1-aminoethyl)-7-fluoro-3-((1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)methylene)-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (10 mg, 25 μ mol), methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (9.6 mg, 50 μ mol) and K_2CO_3 (7 mg, 50 μ mol) in DMSO (1.5 mL) was stirred at 100 °C with microwave irradiation for 2 hours. Upon completion, $LiOH \cdot H_2O$ (3 mg, 12.5 μ mol) and water (0.5 mL) was added, and the mixture was stirred at 60 °C with microwave irradiation
- 10 for 30 min. Upon completion, the mixture was acidified with 1 M HCl and then concentrated *in vacuo*. The residue was purified by prep-HPLC to give (R)-6-chloro-3-((1-(7-fluoro-3-((1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)methylene)-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethyl)amino)picolinic acid (0.6 mg, 4% yield) as a white solid. LC-MS: m/z 553.2 $[M+H]^+$.

15

Example 180



Step 1:

- A mixture of 3-((1H-pyrazol-4-yl)methylene)-5-bromo-7-fluoro-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (1 g, 2.8 mmol) and $(Boc)_2O$ (1.2 g, 5.5 mmol) in DCM (20 mL) was stirred at rt for 12 hours. Upon completion, the mixture was concentrated *in vacuo* to give tert-butyl 4-((5-bromo-7-fluoro-9-oxo-1,2-dihydropyrrolo[2,1-b]quinazolin-3(9H)-ylidene)methyl)-1H-pyrazole-1-carboxylate (1.3 g, crude), which was used in the next step without further purification. LC-MS: m/z 461.0 $[M+H]^+$.

- 25 **Step 2:**

A mixture of tert-butyl 4-((5-bromo-7-fluoro-9-oxo-1,2-dihydropyrrolo[2,1-b]quinazolin-3(9H)-ylidene)methyl)-1H-pyrazole-1-carboxylate (1.3 g, 2.8 mmol), tributyl(1-ethoxyvinyl)stannane (2 g, 5.6 mmol) and Pd(PPh₃)₄ (320.7 mg, 277.5 μmol) in DMF (15 mL) was stirred at 100 °C with microwave irradiation for 2 hours. Upon completion, the mixture was treated with 3 M HCl to hydrolyze the ether intermediate to ketone. Then the mixture was basified with sat. NaHCO₃, diluted with EtOAc (100 mL) and washed with water (40 mL × 3). The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with 0% - 30% MeOH in DCM) to give 3-((1H-pyrazol-4-yl)methylene)-5-acetyl-7-fluoro-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (800 mg, 89% yield) as a yellow solid. LC-MS: m/z 325.1 [M+H]⁺.

Steps 3-5:

(R)-3-((1H-pyrazol-4-yl)methylene)-5-(1-aminoethyl)-7-fluoro-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one was synthesized in analogy to the representative procedures (steps 4-6) described for Example 166.

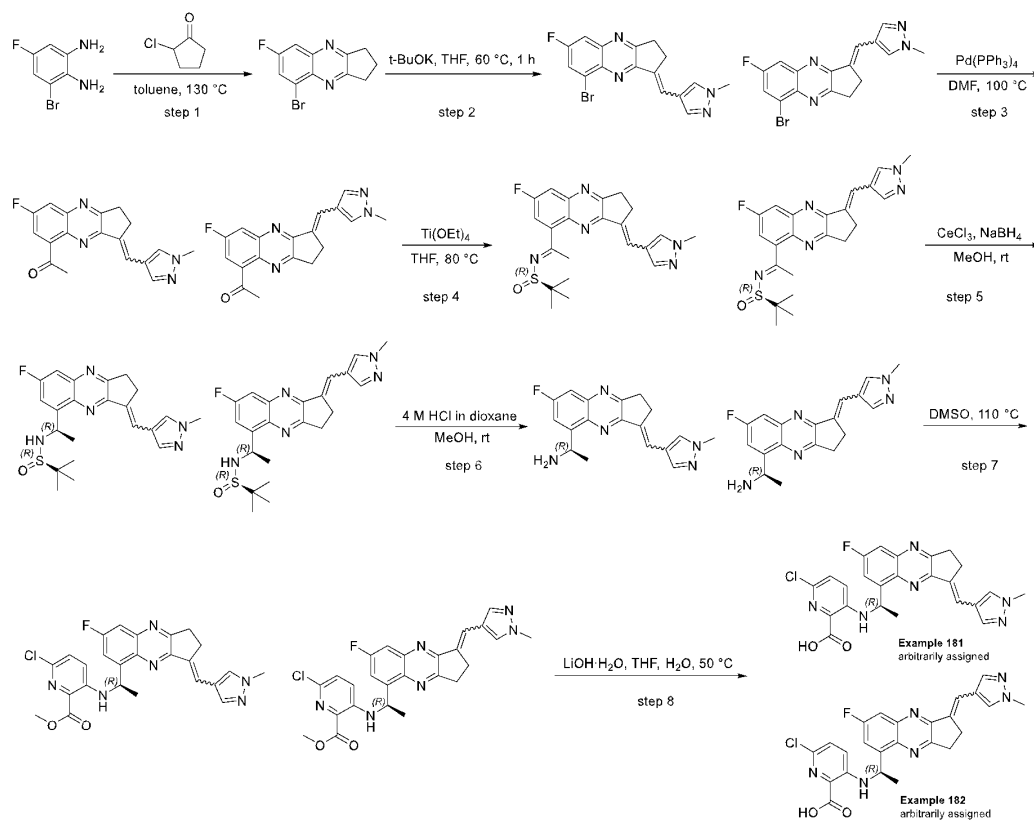
Step 6:

A mixture of methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (35 mg, 184.4 μmol) and (R)-3-((1H-pyrazol-4-yl)methylene)-5-(1-aminoethyl)-7-fluoro-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (30 mg, 92.2 μmol) in DMSO (2 mL) was stirred at 110 °C with microwave irradiation for 2 hours. Upon completion, the mixture was diluted with EtOAc (30 mL) and washed with water (15 mL × 3). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to give methyl (R)-3-((1-(3-((1H-pyrazol-4-yl)methylene)-7-fluoro-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethyl)amino)-6-chloropicolinate (50 mg, crude), which was used in the next step without further purification. LC-MS: m/z 495.1 [M+H]⁺.

Step 7:

The mixture of crude methyl (R)-3-((1-(3-((1H-pyrazol-4-yl)methylene)-7-fluoro-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-5-yl)ethyl)amino)-6-chloropicolinate (50 mg, 0.1 mmol) and LiOH·H₂O (12 mg, 0.5 mmol) in mixed solvent of THF (1 mL) and water (0.5 mL) was stirred at 50 °C with microwave irradiation for 1 hour. Upon completion, the mixture was acidified with 1 M HCl, and the solvent was removed *in vacuo*. The residue was purified by prep-HPLC to give 6-chloro-3-(((1R)-1-((3E)-7-fluoro-9-oxo-3-(1H-pyrazol-4-yl)methylene)-1,2-dihydropyrrolo[2,1-b]quinazolin-5-yl)ethyl)amino]pyridine-2-carboxylic acid (2.2 mg, 5% yield) as a white solid. LC-MS: m/z 481.1 [M+H]⁺.

Example 181 and 182



Step 1:

- 5 A mixture of 3-bromo-5-fluoro-benzene-1,2-diamine (4 g, 19.5 mmol) and 2-chlorocyclopentanone (2.8 g, 23.4 mmol) in toluene (30 mL) was stirred at 130 °C for 4 hours. Upon completion, the mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel to give 8-bromo-6-fluoro-2,3-dihydro-1H-cyclopenta[b]quinoxaline (1.2 g, 23% yield) as a yellow solid. LC-MS: m/z 267.0 $[M+H]^+$.

Step 2:

- 10 A mixture of 8-bromo-6-fluoro-2,3-dihydro-1H-cyclopenta[b]quinoxaline (1.2 g, 4.5 mmol), 1-methylpyrazole-4-carbaldehyde (989.4 mg, 9 mmol) and t-BuOK (1 g, 9 mmol) in THF (15 mL) was stirred at 60 °C for 1 hour. Upon completion, the mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (eluting with 0% - 100% EtOAc in DCM) to give a mixture of 8-bromo-6-fluoro-1-((1-methyl-1H-pyrazol-4-yl)methylene)-2,3-dihydro-1H-cyclopenta[b]quinoxaline and 5-bromo-7-fluoro-1-((1-methyl-1H-pyrazol-4-yl)methylene)-2,3-dihydro-1H-cyclopenta[b]quinoxaline (350 mg, 22% yield) as a yellow solid. LC-MS: m/z 359.0 $[M+H]^+$.

Steps 3-6:

(R)-1-(7-fluoro-3-((1-methyl-1H-pyrazol-4-yl)methylene)-2,3-dihydro-1H-cyclopenta[b]quinoxalin-5-yl)ethan-1-amine and (R)-1-(7-fluoro-1-((1-methyl-1H-pyrazol-4-yl)methylene)-2,3-dihydro-1H-cyclopenta[b]quinoxalin-5-yl)ethan-1-amine were synthesized as a mixture in analogy to the

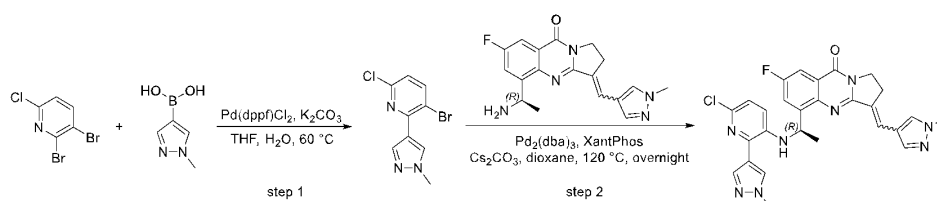
representative procedures (steps 3-6) described for Example 166.

Step 7:

To the mixture of (R)-1-(7-fluoro-3-((1-methyl-1H-pyrazol-4-yl)methylene)-2,3-dihydro-1H-cyclopenta[b]quinoxalin-5-yl)ethan-1-amine and (R)-1-(7-fluoro-1-((1-methyl-1H-pyrazol-4-yl)methylene)-2,3-dihydro-1H-cyclopenta[b]quinoxalin-5-yl)ethan-1-amine (100 mg in total, 0.3 mmol) in DMSO (2 mL) was added methyl 6-chloro-3-fluoropicolinate (114 mg, 0.6 mmol). The resulting mixture was stirred at 110 °C with microwave irradiation for 2 hours. Upon completion, the mixture was diluted with EtOAc (30 mL) and washed with water (15 mL × 3). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to give methyl (R)-6-chloro-3-((1-(7-fluoro-3-((1-methyl-1H-pyrazol-4-yl)methylene)-2,3-dihydro-1H-cyclopenta[b]quinoxalin-5-yl)ethyl)amino)picolinate and methyl (R)-6-chloro-3-((1-(7-fluoro-1-((1-methyl-1H-pyrazol-4-yl)methylene)-2,3-dihydro-1H-cyclopenta[b]quinoxalin-5-yl)ethyl)amino)picolinate as a mixture, which was used in the next step without further purification. LC-MS: m/z 493.2 [M+H]⁺.

Step 8:

To the above generated mixture of methyl (R)-6-chloro-3-((1-(7-fluoro-3-((1-methyl-1H-pyrazol-4-yl)methylene)-2,3-dihydro-1H-cyclopenta[b]quinoxalin-5-yl)ethyl)amino)picolinate and methyl (R)-6-chloro-3-((1-(7-fluoro-1-((1-methyl-1H-pyrazol-4-yl)methylene)-2,3-dihydro-1H-cyclopenta[b]quinoxalin-5-yl)ethyl)amino)picolinate in mixed solvent of THF (1.5 mL) and water (0.5 mL) was added LiOH·H₂O (24 mg, 1 mmol). The resulting mixture was stirred at 50 °C with microwave irradiation for 2 hours. Upon completion, the mixture was acidified with 1 M HCl and then concentrated *in vacuo*. The residue was purified by prep-HPLC to give (R)-6-chloro-3-((1-(7-fluoro-3-((1-methyl-1H-pyrazol-4-yl)methylene)-2,3-dihydro-1H-cyclopenta[b]quinoxalin-5-yl)ethyl)amino)picolinic acid (1.5 mg, 1% yield) as a yellow solid and (R)-6-chloro-3-((1-(7-fluoro-1-((1-methyl-1H-pyrazol-4-yl)methylene)-2,3-dihydro-1H-cyclopenta[b]quinoxalin-5-yl)ethyl)amino)picolinic acid (2.2 mg, 2% yield) as a yellow solid. Both LCMS: m/z 479.1 [M+H]⁺.

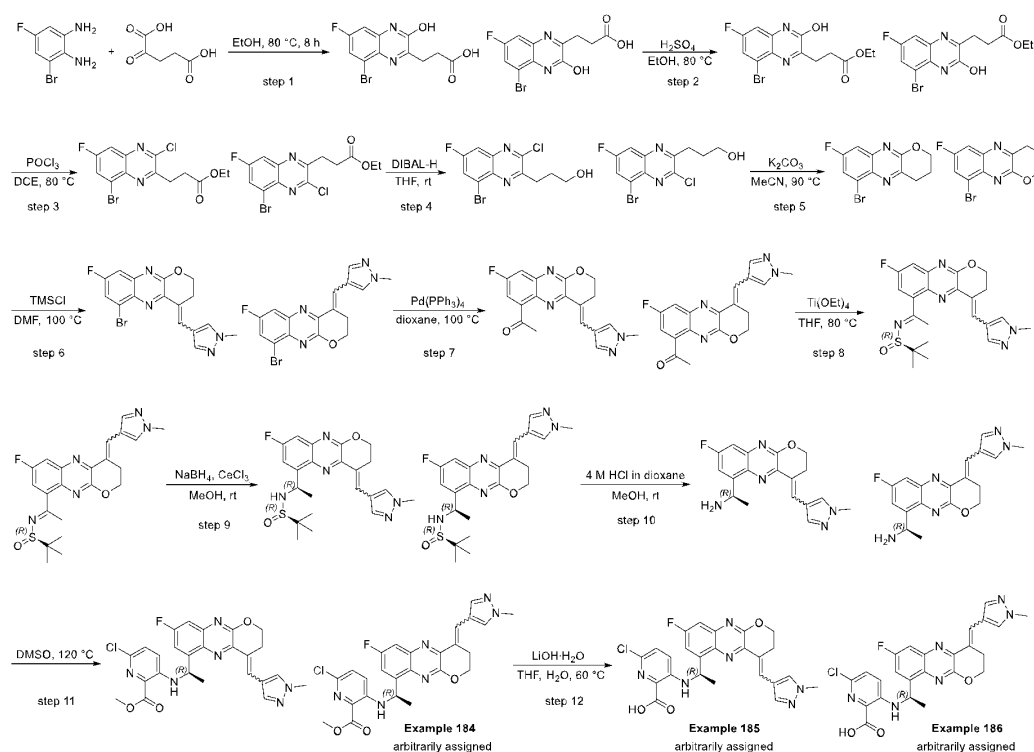
Example 183

Step 1:

A mixture of 2,3-dibromo-6-chloro-pyridine (271.3 mg, 1 mmol), (1-methylpyrazol-4-yl)boronic acid (151.1 mg, 1.2 mmol), Pd(dppf)Cl₂ (73.2 mg, 100 μmol) and K₂CO₃ (276.4 mg, 2 mmol) in mixed solvent of THF (3 mL) and water (0.5 mL) was stirred at 60 °C with microwave irradiation for 2 hours. Upon completion, the mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (eluting with 0% - 50% EtOAc in petroleum ether) to give 3-bromo-6-chloro-2-(1-methylpyrazol-4-yl)pyridine (100 mg, 37% yield) as a yellow solid. LC-MS: m/z 272.0 [M+H]⁺.

Step 2:

- 10 A mixture of 3-bromo-6-chloro-2-(1-methylpyrazol-4-yl)pyridine (16.1 mg, 58.9 μmol), (R)-5-(1-aminoethyl)-7-fluoro-3-((1-methyl-1H-pyrazol-4-yl)methylene)-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (10 mg, 29.5 μmol), Pd₂(dba)₃ (2.7 mg, 3 μmol), Xantphos (1.7 mg, 3 μmol) and Cs₂CO₃ (19.2 mg, 58.9 μmol) in dioxane (1 mL) was stirred at 120 °C for 16 hours. Upon completion, the mixture was concentrated *in vacuo* and the residue was purified by prep-HPLC to give (R)-5-(1-((6-chloro-2-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)amino)ethyl)-7-fluoro-3-((1-methyl-1H-pyrazol-4-yl)methylene)-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (1.5 mg, 10% yield) as a white solid. LC-MS: m/z 531.2 [M+H]⁺.

Example 184, 185 and 186

Step 1:

The mixture of 3-bromo-5-fluoro-benzene-1,2-diamine (4.1 g, 20 mmol) and 2-oxopentanedioic acid (5.8 g, 40 mmol) in EtOH (50 mL) was stirred at 80 °C for 8 hours. 3-(8-bromo-6-fluoro-3-hydroxyquinoxalin-2-yl)propanoic acid and 3-(5-bromo-7-fluoro-3-hydroxyquinoxalin-2-yl)propanoic acid were formed and the mixture was used in the next step without purification. LC-MS: m/z 315.0 [M+H]⁺.

Step 2:

To the reaction mixture of the previous step was added H₂SO₄ (5 mL) and the resulting mixture was stirred at 80 °C for 8 hours. Upon completion, the mixture was concentrated and redissolved in water. The mixture was basified with sat. NaHCO₃ and extracted with EtOAc (100 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to give ethyl 3-(8-bromo-6-fluoro-3-hydroxyquinoxalin-2-yl)propanoate and ethyl 3-(5-bromo-7-fluoro-3-hydroxyquinoxalin-2-yl)propanoate as a mixture, which was used in the next step without further purification. LC-MS: m/z 343.0 [M+H]⁺.

Step 3:

To the mixture generated above in DCE (20 mL) was dropwise added POCl₃ (24.7 g, 160.9 mmol) and the resulting mixture was stirred at 80 °C for 16 hours. Upon completion, the mixture was concentrated *in vacuo*. The residue was diluted with water and basified with sat. NaHCO₃. The mixture was extracted with DCM (100 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with 0% - 50% EtOAc in DCM) to give ethyl 3-(8-bromo-3-chloro-6-fluoroquinoxalin-2-yl)propanoate and ethyl 3-(5-bromo-3-chloro-7-fluoroquinoxalin-2-yl)propanoate as a mixture (1.5 g, 21% yield over 3 steps). LC-MS: m/z 361.0 [M+H]⁺.

Step 4:

To a mixture of ethyl 3-(8-bromo-3-chloro-6-fluoroquinoxalin-2-yl)propanoate and ethyl 3-(5-bromo-3-chloro-7-fluoroquinoxalin-2-yl)propanoate (720 mg in total, 2 mmol) in THF (20 mL) was dropwise added DIBAL-H (3 mL, 1 M in THF, 6 mmol) and the resulting mixture was stirred at rt for 1 hr. Upon completion, the mixture was diluted with THF and quenched with Na₂SO₄·10H₂O. The mixture was stirred at rt for 30 min and then filtered, concentrated *in vacuo* to give 3-(8-bromo-3-chloro-6-fluoroquinoxalin-2-yl)propan-1-ol and 3-(5-bromo-3-chloro-7-fluoroquinoxalin-2-yl)propan-1-ol as a mixture, which was used in the next step without further purification. LC-MS: m/z 319.0 [M+H]⁺.

Step 5:

To the mixture generated above in MeCN (30 mL) was added K₂CO₃ (276.4 mg, 2 mmol) and the resulting mixture was stirred at 90 °C for 16 hours. Upon completion, the mixture was filtered and concentrated. The residue was purified by column chromatography on silica gel (eluting with 0% - 50% EtOAc in DCM) to give 6-bromo-8-fluoro-3,4-dihydro-2H-pyrano[2,3-b]quinoxaline and 9-

bromo-7-fluoro-3,4-dihydro-2H-pyrano[2,3-b]quinoxaline as a mixture (280 mg, 50% yield over 2 steps). LC-MS: m/z 283.0 $[M+H]^+$.

Step 6:

To the above generated mixture of 6-bromo-8-fluoro-3,4-dihydro-2H-pyrano[2,3-b]quinoxaline and
5 9-bromo-7-fluoro-3,4-dihydro-2H-pyrano[2,3-b]quinoxaline (200 mg in total, 0.7 mmol) in DMF (5 mL) was added 1-methylpyrazole-4-carbaldehyde (116.7 mg, 1.1 mmol) and TMSCl (3 mL). The resulting mixture was stirred at 100 °C for 16 hours. Upon completion, the mixture was quenched with sat. NaHCO₃ and extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to give crude product 6-bromo-8-fluoro-4-
10 ((1-methyl-1H-pyrazol-4-yl)methylene)-3,4-dihydro-2H-pyrano[2,3-b]quinoxaline and 9-bromo-7-fluoro-4-((1-methyl-1H-pyrazol-4-yl)methylene)-3,4-dihydro-2H-pyrano[2,3-b]quinoxaline as a mixture, which was used in the next step without further purification. LC-MS: m/z 375.0 $[M+H]^+$.

Steps 7-10:

(R)-1-(8-fluoro-4-((1-methyl-1H-pyrazol-4-yl)methylene)-3,4-dihydro-2H-pyrano[2,3-b]quinoxalin-
15 6-yl)ethan-1-amine and (R)-1-(7-fluoro-4-((1-methyl-1H-pyrazol-4-yl)methylene)-3,4-dihydro-2H-pyrano[2,3-b]quinoxalin-9-yl)ethan-1-amine were prepared as a mixture in analogy to the representative procedures (steps 3-6) described for Example 166.

Step 11:

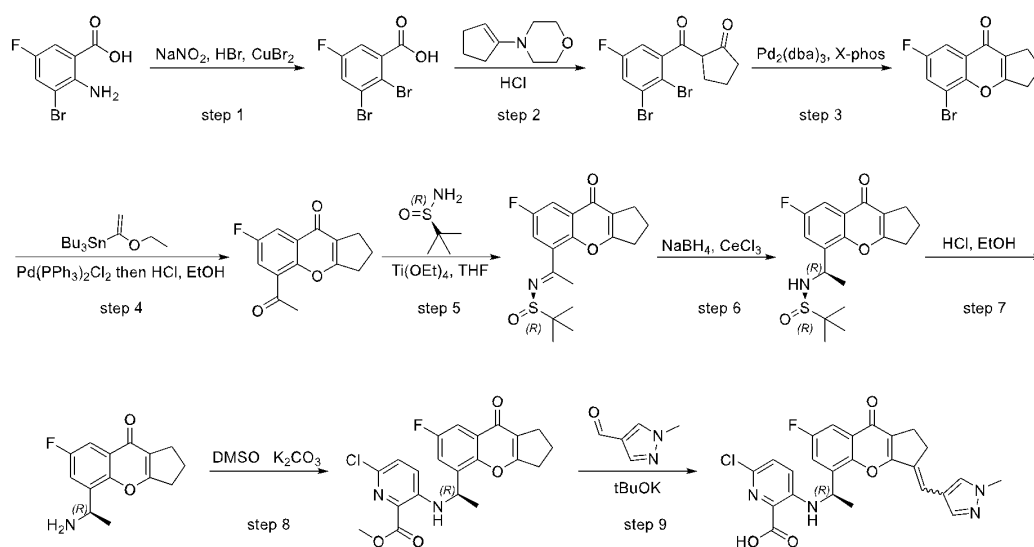
To the mixture of (R)-1-(8-fluoro-4-((1-methyl-1H-pyrazol-4-yl)methylene)-3,4-dihydro-2H-
20 pyrano[2,3-b]quinoxalin-6-yl)ethan-1-amine and (R)-1-(7-fluoro-4-((1-methyl-1H-pyrazol-4-yl)methylene)-3,4-dihydro-2H-pyrano[2,3-b]quinoxalin-9-yl)ethan-1-amine (50 mg in total, 147 μmol) in DMSO was added methyl 6-chloro-3-fluoro-pyridine-2-carboxylate (55.9 mg, 295 μmol). The resulting mixture was stirred at 120 °C with microwave irradiation for 2 hours. Upon completion, the mixture was diluted with EtOAc (30 mL) and washed with water (15 mL × 3). The organic layer
25 was dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to give crude product methyl (R)-6-chloro-3-((1-(8-fluoro-4-((1-methyl-1H-pyrazol-4-yl)methylene)-3,4-dihydro-2H-pyrano[2,3-b]quinoxalin-6-yl)ethyl)amino)picolinate and methyl (R)-6-chloro-3-((1-(7-fluoro-4-((1-methyl-1H-pyrazol-4-yl)methylene)-3,4-dihydro-2H-pyrano[2,3-b]quinoxalin-9-yl)ethyl)amino)picolinate as a mixture, which was used in the next step without further purification. LC-MS: m/z 509.2 $[M+H]^+$.

Step 12:

To the above generated mixture of methyl (R)-6-chloro-3-((1-(8-fluoro-4-((1-methyl-1H-pyrazol-4-yl)methylene)-3,4-dihydro-2H-pyrano[2,3-b]quinoxalin-6-yl)ethyl)amino)picolinate and methyl (R)-
35 6-chloro-3-((1-(7-fluoro-4-((1-methyl-1H-pyrazol-4-yl)methylene)-3,4-dihydro-2H-pyrano[2,3-b]quinoxalin-9-yl)ethyl)amino)picolinate in mixed solvent of water (0.5 mL) and DMSO (2 mL) was added LiOH·H₂O (20 mg, 835 μmol). The mixture was stirred at 60 °C with microwave irradiation for 20 minutes. Upon completion, the mixture was acidified with 1 M HCl and then concentrated *in vacuo*. The residue was purified by prep-HPLC to give (R)-6-chloro-3-((1-(8-fluoro-4-((1-methyl-1H-

pyrazol-4-yl)methylene)-3,4-dihydro-2H-pyrano[2,3-b]quinoxalin-6-yl)ethyl)amino)picolinic acid (0.1 mg, 0.1% yield over 2 steps) as a white solid and (R)-6-chloro-3-((1-(7-fluoro-4-((1-methyl-1H-pyrazol-4-yl)methylene)-3,4-dihydro-2H-pyrano[2,3-b]quinoxalin-9-yl)ethyl)amino)picolinic acid (1.3 mg, 1.8% yield over 2 steps) as a white solid. Both LCMS: m/z 495.1 $[M+H]^+$.

5

Example 188**Step 1:**

To a stirred solution of 2-amino-3-bromo-5-fluoro-benzoic acid (12 g, 51.3 mmol) in HBr (48% in water, 60 mL) was added NaNO_2 (5.3 g, 76.9 mmol) under N_2 . The mixture was stirred at 25 °C for 1 hour. Then CuBr_2 (22.9 g, 102.6 mmol) was added. The mixture was then stirred at 80 °C for 15 hours. The mixture was cooled to rt, concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel to afford 2,3-dibromo-5-fluoro-benzoic acid (6 g, 39.3% yield) as a yellow solid. LC-MS: m/z 296.8 $[M+H]^+$.

Step 2:

To a stirred mixture of 2,3-dibromo-5-fluoro-benzoic acid (6 g, 20.1 mmol) and 4-(cyclopenten-1-yl)morpholine (4.6 g, 30.2 mmol) in DCM (150 mL) was added conc. HCl (20 mL) under N_2 . The mixture was stirred at 25 °C for 1 hour and 50 °C for 8 hours. The mixture was cooled to rt, concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel to afford 2-(2,3-dibromo-5-fluoro-benzoyl)cyclopentanone (4.4 g, 60% yield) as a yellow solid. LC-MS: m/z 362.8 $[M+H]^+$.

Step 3:

To a stirred solution of 2-(2,3-dibromo-5-fluoro-benzoyl)cyclopentanone (2 g, 5.5 mmol) in dioxane (20 mL) was added $\text{Pd}_2(\text{dba})_3$ (853 mg, 824.2 μmol), X-phos (785 mg, 1.7 mmol) and Cs_2CO_3 (4.5 g, 13.7 mmol) under N_2 . The mixture was stirred at 105 °C for 8 hours. The mixture was cooled to rt,

concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel to afford 5-bromo-7-fluoro-2,3-dihydro-1H-cyclopenta[b]chromen-9-one (400 mg, 25.7% yield) as a yellow solid. LC-MS: m/z 282.8 $[M+H]^+$.

Steps 4-8:

- 5 Methyl (R)-6-chloro-3-((1-(7-fluoro-9-oxo-1,2,3,9-tetrahydrocyclopenta[b]chromen-5-yl)ethyl)amino)picolinate was prepared in analogy to the representative procedures (steps 3-7) described for Example 166.

Step 9:

- To a stirred solution of methyl (R)-6-chloro-3-((1-(7-fluoro-9-oxo-1,2,3,9-tetrahydrocyclopenta[b]chromen-5-yl)ethyl)amino)picolinate (8 mg, 19.2 μ mol) and 1-methylpyrazole-4-carbaldehyde (4 mg, 38.4 μ mol) in THF (1.5 mL) was added t-BuOK (4 mg, 38.4 μ mol). The mixture was stirred at 90 °C for 15 hours and cooled to rt. The mixture was added H₂O (10 mL) and adjusted pH to 2 with HCl (aq, 1 N). The mixture was extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by prep-HPLC to give (R)-6-chloro-3-((1-(7-fluoro-3-((1-methyl-1H-pyrazol-4-yl)methylene)-9-oxo-1,2,3,9-tetrahydrocyclopenta[b]chromen-5-yl)ethyl)amino)picolinic acid (1.5 mg, 15.8% yield) as a white solid. LC-MS: m/z 494.8 $[M+H]^+$.

Section 3. Biological Assays

- 20 Method A: An assay for monitoring PI3K α -catalyzed phosphorylation of lipid substrates was performed using ADP-Glo lipid kinase assay kit (Promega, V9102) in a 384-well format. The enzymatic reaction was carried out in a 10 μ L volume containing PI3K α enzyme (*e.g.*, 1 nM H1047R mutant protein (Promega, V1741) or 4 nM wild-type protein (Promega, V1721)), 100 μ M ATP, 25 μ M diC8-PIP2 (Echelon, P-4508) and 1% DMSO (or the test articles at appropriate dilutions in
- 25 DMSO) in the assay buffer (50 mM HEPES PH=7.4, 50 mM NaCl, 3 mM MgCl₂, 5 mM DTT and 0.01% TritonX-100). All the components were added to the 384-well plate and then incubated at room temperature for 150 minutes. The reaction was terminated by adding 5 μ L ADP-Glo reagent and incubating for 40 minutes at room temperature. Then, 10 μ L ADP-Glo Detection reagent was added and incubated for 30 minutes at room temperature. The plate was loaded on Envision Reader
- 30 (PerkinElmer, 1041099) to measure luminescence intensity, and IC₅₀ values of the test articles were calculated using the GraphPad Prism 9 software.

Table A: the IC₅₀ results of PI3K α (PIK3CA) wild-type and H1047R mutant biochemical assay.

35

Table A

Example #	Method A: PI3K α wild-type IC ₅₀ A: $\leq 0.5 \mu\text{M}$ B: $> 0.5 \mu\text{M}$ and $\leq 1 \mu\text{M}$ C: $> 1 \mu\text{M}$ and $\leq 5 \mu\text{M}$ D: $> 5 \mu\text{M}$ and $\leq 10 \mu\text{M}$ E: $> 10 \mu\text{M}$	Method A: PI3K α H1047R IC ₅₀ A: $\leq 0.5 \mu\text{M}$ B: $> 0.5 \mu\text{M}$ and $\leq 1 \mu\text{M}$ C: $> 1 \mu\text{M}$ and $\leq 5 \mu\text{M}$ D: $> 5 \mu\text{M}$ and $\leq 10 \mu\text{M}$ E: $> 10 \mu\text{M}$
Example 29	--	A
Example 30	--	A
Example 31	--	A
Example 32	--	A
Example 33	--	A
Example 14	E	A
Example 1	--	A
Example 3	C*	A
Example 10	C*	A
Example 34	--	A
Example 35	--	A
Example 25	C*	A
Example 26	--	A
Example 4	--	A
Example 2	--	A

* Method B was used

Method B: An assay for monitoring PI3K α -catalyzed phosphorylation of lipid substrates was performed using ADP-Glo lipid kinase assay kit (Promega, V9102) in a 384-well format. The enzymatic reaction was carried out in a 10 μL volume containing PI3K α enzyme (*e.g.*, 0.5 nM H1047R mutant protein (Promega, V1741) or 1 nM wild-type protein (Promega, V1721)), 100 μM ATP, 10 μM Soy PI (Avanti Polar Lipids, 840044P) and 1% DMSO (or the test articles at appropriate dilutions in DMSO) in the assay buffer (50 mM HEPES PH=7.4, 50 mM NaCl, 3 mM MgCl₂, 5 mM DTT and 0.01% TritonX-100). All the components were added to the 384-well plate and then incubated at room temperature for 150 minutes. The reaction was terminated by adding 5 μL ADP-Glo reagent and incubating for 40 minutes at room temperature. Then, 10 μL ADP-Glo Detection reagent was added and incubated for 30 minutes at room temperature. The plate was loaded on Envision Reader (PerkinElmer, 1041099) to measure luminescence intensity, and IC₅₀ values of the test articles were calculated using the GraphPad Prism 9 software.

15

Table B: the IC₅₀ results of PI3K α (PIK3CA) wild-type and H1047R mutant biochemical assay.

Table B

Example #	Method B: PI3K α wild-type IC ₅₀ A: $\leq 0.5 \mu\text{M}$ B: $>0.5 \mu\text{M}$ and $\leq 1 \mu\text{M}$ C: $>1 \mu\text{M}$ and $\leq 5 \mu\text{M}$ D: $>5 \mu\text{M}$ and $\leq 10 \mu\text{M}$ E: $>10 \mu\text{M}$	Method B: PI3K α H1047R IC ₅₀ A: $\leq 0.5 \mu\text{M}$ B: $>0.5 \mu\text{M}$ and $\leq 1 \mu\text{M}$ C: $>1 \mu\text{M}$ and $\leq 5 \mu\text{M}$ D: $>5 \mu\text{M}$ and $\leq 10 \mu\text{M}$ E: $>10 \mu\text{M}$
Example 20	--	C
Example 5	C	A
Example 6	C	A
Example 7	--	A
Example 13	--	A
Example 11	--	A
Example 36	B	A
Example 15	B	A
Example 27	A	A
Example 28	--	A
Example 9	--	A
Example 12	--	A
Example 22	--	A
Example 21	--	A
Example 16	--	A
Example 23	--	A
Example 38	--	A
Example 37	--	A
Example 17	--	A
Example 40	--	A
Example 41	--	A
Example 39	--	A
Example 18	--	A
Example 19	--	A
Example 42	B	A
Example 43	--	D
Example 44	B	A

Example 45	--	A
Example 46	A	A
Example 47	--	A
Example 49	C	A
Example 50	B	A
Example 54	--	A
Example 55	C	A
Example 56	C	A
Example 57	--	A
Example 58	--	A
Example 59	--	A
Example 60	--	C
Example 61	B	A
Example 62	C	A
Example 63	--	A
Example 64	A	A
Example 67	--	A
Example 68	A	A
Example 69	--	A
Example 70	--	A
Example 71	--	A
Example 74	--	A
Example 76	B	A
Example 77	--	A
Example 78	B	A
Example 79	--	A
Example 80	--	A
Example 81	--	A
Example 82	--	A
Example 83	--	C
Example 84	B	A
Example 85	--	A
Example 86	--	A
Example 88	--	A
Example 89	--	A

Example 90	--	B
Example 91	--	A
Example 92	--	A
Example 93	--	A
Example 101	--	A
Example 102	--	A
Example 103	--	A
Example 104	--	A
Example 105	--	A
Example 106	--	C
Example 107	--	A
Example 108	--	A
Example 109	--	C
Example 110	--	A
Example 111	--	C
Example 112	--	A
Example 113	--	A
Example 114	--	A
Example 115	--	A
Example 116	A	A
Example 117	--	A
Example 118	--	A
Example 119	--	A
Example 120	--	A
Example 121	--	A
Example 122	--	A
Example 123	--	A
Example 124	--	A
Example 125	--	A
Example 126	--	A
Example 127	--	A
Example 128	--	A
Example 129	--	A
Example 130	--	C
Example 131	--	A

Example 132	--	A
Example 133	A	A
Example 134	--	A
Example 135	--	D
Example 136	--	A
Example 137	--	A
Example 138	--	D
Example 139	--	B
Example 140	--	A
Example 141	--	A
Example 147	--	D
Example 148	--	A
Example 149	--	A
Example 150	--	B
Example 151	--	C
Example 152	--	A
Example 153	--	D
Example 154	--	E
Example 155	--	C
Example 156	--	D
Example 157	--	E
Example 158	--	C
Example 159	--	A
Example 160	--	D
Example 161	--	A
Example 162	--	A
Example 163	--	B
Example 164	--	A
Example 165	--	A
Example 166	--	A
Example 167	--	A
Example 168	--	A
Example 169	C	A
Example 170	--	A
Example 171	--	A

Example 172	C	A
Example 173	--	A
Example 174	--	A
Example 175	--	A
Example 176	--	A
Example 177	C	A
Example 178	--	A
Example 179	--	A
Example 180	--	A
Example 181	--	A
Example 182	--	A
Example 183	B	A
Example 184	--	E
Example 185	--	A
Example 186	--	A
Example 187	C	A
Example 188	--	A
Example 189	--	A

Method C: An assay for monitoring PI3K α -catalyzed phosphorylation of lipid substrates was performed using ADP-Glo lipid kinase assay kit (Promega, V9102) in a 384-well format. The enzymatic reaction was carried out in a 10 μ L volume containing PI3K α enzyme (e.g., 0.5 nM H1047R mutant protein (Promega, V1741) or 1 nM wild-type protein (Promega, V1721)), 100 μ M ATP, 10 μ M Soy PI (Avanti Polar Lipids, 840044P) or 25 μ M diC8-PIP2 (Echelon, P-4508) and 1% DMSO (or the test articles at appropriate dilutions in DMSO) in the assay buffer (50 mM HEPES PH=7.4, 50 mM NaCl, 3 mM MgCl₂, 5 mM DTT and 0.01% TritonX-100). First, H1047R mutant or wild-type PI3K α enzyme were incubated with or without compound at room temperature for 120 minutes. After preincubation, enzymatic reaction was initiated by the addition of ATP and substrate. Reaction mixture was incubated at room temperature for 150 minutes. The reaction was terminated by adding 5 μ L ADP-Glo reagent and incubating for 40 minutes at room temperature. Then, 10 μ L ADP-Glo Detection reagent was added and incubated for 30 minutes at room temperature. The plate was loaded on Envision Reader (PerkinElmer, 1041099) to measure luminescence intensity, and IC₅₀ values of the test articles were calculated using the GraphPad Prism 9 software.

Table C: the IC₅₀ results of PI3K α (PIK3CA) wild-type and H1047R mutant biochemical assay.

Table C

Example #	Method C: PI3K α wild-type IC ₅₀ A: $\leq 0.5 \mu\text{M}$ B: $> 0.5 \mu\text{M}$ and $\leq 1 \mu\text{M}$ C: $> 1 \mu\text{M}$ and $\leq 5 \mu\text{M}$ D: $> 5 \mu\text{M}$ and $\leq 10 \mu\text{M}$ E: $> 10 \mu\text{M}$	Method C: PI3K α H1047R IC ₅₀ A: $\leq 0.5 \mu\text{M}$ B: $> 0.5 \mu\text{M}$ and $\leq 1 \mu\text{M}$ C: $> 1 \mu\text{M}$ and $\leq 5 \mu\text{M}$ D: $> 5 \mu\text{M}$ and $\leq 10 \mu\text{M}$ E: $> 10 \mu\text{M}$
Example 48	B	A
Example 51	A	A
Example 52	A	A
Example 53	--	A
Example 65	--	A
Example 66	C	A
Example 72	--	A
Example 87	--	A
Example 94	--	A
Example 95	--	C
Example 96	--	A
Example 97	--	A
Example 98	--	A
Example 99	--	A
Example 100	--	A
Example 142	--	B
Example 143	--	B
Example 144	--	A
Example 145	--	A
Example 146	--	A
Example 190	--	E
Example 191	--	A
Example 192	--	A
Example 193	--	A
Example 194	--	A

Method D: An assay for quantitating the level of phospho-AKT (Ser473) protein in cancer cells was performed using AlphaLISA SureFire® Ultra™ phospho-AKT (Ser473) assay kit (PerkinElmer, ALSU-PAKT-B10K) in a 384-well format. SK-BR-3 (ATCC, HTB-30) and T47D (ATCC, HTB-133) breast cancer cells were plated at 25,000 cells/well in 96-well plates and incubated in complete culture medium (followed ATCC medium with 10% FBS and 1% P/S) (day 1). Cells were then allowed to adhere overnight at 37°C, 5% CO₂. In the following day, SK-BR-3 cells were grown in FBS-free medium for 16 hours, while T47D cells were still incubated in complete culture medium containing 10% FBS. On day 3, culture medium of both SK-BR-3 and T47D cells was refreshed with FBS-free medium. Compounds were titrated into FBS-free culture medium with a 3-fold dilution scheme in duplicates, and the final concentration of DMSO in the culture medium was 0.2%. After 4 hours of incubation with compounds, cells were lysed in 50 µL lysis buffer. For assay, 6 µL cell lysate was transferred to 384-well plate containing 3 µL acceptor beads mix and incubated for 1 hour at room temperature. Then, 3 µL donor beads mix was added to each well and incubated for 1 hour at room temperature. All additions and incubations of acceptor and donor beads mix were carried out under low light conditions. Plates were read on the Envision Reader (PerkinElmer, 1041099) and IC₅₀ values of test articles were calculated using GraphPad Prism 9 software.

Table D: the IC₅₀ results of phospho-AKT assay in PI3Kα wild-type and H1047R mutant cell lines.

20

Table D

Example #	Method D: SK-BR-3 (PI3Kα wild-type) IC ₅₀ A: ≤0.05 µM B: >0.05 µM and ≤1 µM C: >1 µM and ≤5 µM D: >5 µM and ≤10 µM E: >10 µM	Method D: T47D (PI3Kα H1047R) IC ₅₀ A: ≤0.05 µM B: >0.05 µM and ≤1 µM C: >1 µM and ≤5 µM D: >5 µM and ≤10 µM E: >10 µM
Example 30	--	A
Example 32	--	A
Example 14	B	A
Example 3	C	A
Example 10	E	A
Example 25	C	A
Example 5	D	A
Example 6	D	A
Example 36	C	A

Example 15	C	A
Example 27	D	A
Example 44	--	A
Example 46	--	A
Example 49	--	A
Example 55	--	A
Example 56	--	A
Example 61	--	A
Example 66	C	A
Example 68	--	A
Example 76	--	A
Example 169	B	A
Example 174	--	A

Method E: CellTiter Glo assay was used to quantitate the cell number and measure cell proliferation in a 96-well format. SK-BR-3 (ATCC, HTB-30) and T47D (ATCC, HTB-133) breast cancer cells were seeded at 3000-4000 cells/well in 96-well plates and incubated in complete culture medium containing 10% FBS and 1% P/S. Cells were then allowed to adhere overnight. In the following day (day 0), cell numbers of plate 1 were quantitated using CellTiter Glo assay kit (Promega, G7571) and measured with Envision Reader (PerkinElmer, 1041099) following manufacturer's instructions. The average luminescence intensity of plate 1 measured at day 0 was defined as baseline value (HPE). Other plates were titrated with serially diluted compounds at a nine-point dose concentration in a 3-fold dilution scheme as duplicates. After 5 days of compound treatment, cell numbers were quantitated using CellTiter Glo assay kit and measured with Envision Reader. Cell proliferation inhibition was calculated using the formula: Proliferation inhibition% = 100 - 100 x (Day 5 readout - Day 0 baseline readout) / (Day 5 readout of vehicle group - Day 0 baseline readout). The proliferation inhibition% was used to determine IC₅₀ values of the test articles using GraphPad Prism 9 software.

Table E: the IC₅₀ values of cell proliferation assay in PI3K α wild-type and H1047R mutant cell lines.

Table E

Example #	Method E: SK-BR-3 (PI3K α wild-type) IC ₅₀ A: ≤ 1 μ M B: >1 μ M and ≤ 5 μ M C: >5 μ M and ≤ 10 μ M D: >10 μ M and ≤ 20 μ M E: >20 μ M	Method E: T47D (PI3K α H1047R) IC ₅₀ A: ≤ 1 μ M B: >1 μ M and ≤ 5 μ M C: >5 μ M and ≤ 10 μ M D: >10 μ M and ≤ 20 μ M E: >20 μ M
Example 29	E	A
Example 30	E	A
Example 31	E	A
Example 32	D	A
Example 33	E	A
Example 14	C	A
Example 1	D	A
Example 3	C	A
Example 10	C	A
Example 34	C	A
Example 35	E	A
Example 25	C	A
Example 26	E	B
Example 4	C	A
Example 2	C	A
Example 20	B	C
Example 5	D	A
Example 6	C	A
Example 7	E	B
Example 13	C	A
Example 11	D	B
Example 36	C	A
Example 15	C	A
Example 27	B	A
Example 28	D	B
Example 9	E	A
Example 12	C	B

Example 22	D	A
Example 21	E	A
Example 16	C	A
Example 23	D	A
Example 42	C	A
Example 43	D	B
Example 44	D	A
Example 45	C	A
Example 46	B	A
Example 47	D	B
Example 48	B	A
Example 49	D	A
Example 50	B	A
Example 51	C	A
Example 52	B	A
Example 53	B	A
Example 54	D	A
Example 55	D	A
Example 56	D	A
Example 57	E	A
Example 58	E	B
Example 61	C	A
Example 62	D	A
Example 63	B	A
Example 64	B	A
Example 65	C	A
Example 66	C	A
Example 67	E	B
Example 68	B	A
Example 69	E	B
Example 70	C	A
Example 71	C	A
Example 72	E	A
Example 74	D	A
Example 76	B	A

Example 77	C	B
Example 78	D	A
Example 79	E	A
Example 80	B	A
Example 81	C	A
Example 82	B	A
Example 83	D	B
Example 84	D	A
Example 85	E	C
Example 86	D	A
Example 87	E	A
Example 88	B	A
Example 89	B	A
Example 90	C	A
Example 91	C	B
Example 92	E	B
Example 93	E	B
Example 94	D	A
Example 95	C	B
Example 96	C	A
Example 97	D	C
Example 98	D	A
Example 99	C	B
Example 100	C	A
Example 101	D	A
Example 102	B	A
Example 103	B	A
Example 104	B	A
Example 105	E	A
Example 106	E	E
Example 107	C	A
Example 108	C	B
Example 109	B	B
Example 110	C	A
Example 111	C	B

Example 112	B	A
Example 113	B	B
Example 114	B	A
Example 115	B	A
Example 116	B	A
Example 117	B	A
Example 118	B	A
Example 119	C	A
Example 120	B	A
Example 121	B	A
Example 122	B	A
Example 123	B	A
Example 124	C	A
Example 125	B	A
Example 126	B	A
Example 127	C	A
Example 128	B	A
Example 129	E	A
Example 131	C	A
Example 132	A	A
Example 133	B	A
Example 134	B	A
Example 135	D	D
Example 136	D	A
Example 137	B	A
Example 138	D	D
Example 139	E	A
Example 140	B	A
Example 141	C	A
Example 142	D	B
Example 143	C	B
Example 144	D	A
Example 145	C	A
Example 146	C	A
Example 148	B	A

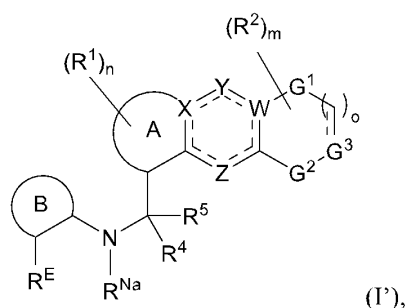
Example 149	B	A
Example 150	C	B
Example 151	D	B
Example 152	D	A
Example 153	C	B
Example 154	E	E
Example 155	B	B
Example 156	D	C
Example 157	C	C
Example 158	D	B
Example 159	B	A
Example 160	C	B
Example 161	D	A
Example 162	C	A
Example 163	B	A
Example 164	B	A
Example 165	B	A
Example 166	D	A
Example 167	E	A
Example 168	D	A
Example 169	D	A
Example 170	D	A
Example 171	E	A
Example 172	C	A
Example 173	E	A
Example 174	C	A
Example 175	C	A
Example 176	B	A
Example 177	D	A
Example 178	B	A
Example 179	C	A
Example 180	C	A
Example 181	D	A
Example 182	D	B
Example 183	B	A

Example 185	B	A
Example 186	D	B
Example 187	C	A
Example 188	C	A
Example 189	B	A
Example 190	E	E
Example 191	E	A
Example 192	D	A
Example 193	D	B
Example 194	B	A

CLAIMS

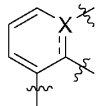
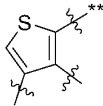
What is claimed is:

1. A compound of Formula (I'):



- 5 or a pharmaceutically acceptable salt thereof, wherein:

==== is a single bond or a double bond as valency permits;

Ring A is  or , wherein ** is the attachment point to Y;

(i) when W is C and Y is N or CR^{Z1}, then X is C, and Z is N or CR^{Z1};

(ii) when W is C and Y is C(O), then X is C or N, and Z is CR^{Z1}, N, NR^{N1}, or O;

- 10 (iii) when W is N, then Y is C(O), X is C, and Z is N or CR^{Z1};

G¹, G², and G³ are each, independently, C(R^{G2})₂, NR^{N2}, or O;

n is 0, 1, 2, or 3;

m is 0, 1, 2, 3, or 4;

o is 0, 1, 2, 3, or 4;

- 15 R^{Na} is H;

R^{N1} is H, C₁₋₆alkyl, C₁₋₆haloalkyl, -C(O)R^{1a}, C₃₋₆cycloalkyl, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl represented by R^{N1} are each optionally substituted with one to three substituents selected from halo, C₁₋₃alkyl, and C₁₋₃haloalkyl;

- 20 R^{Z1} is H, halo, cyano, NO₂, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxylalkyl, C₁₋₆alkoxylalkyl, C₁₋₆hydroxyalkoxy, NR^{N1a}R^{N1b}, -C(O)R^{1a}, -C(O)OR^{O1a}, -C(O)NR^{N1a}R^{N1b}, -OR^{O1a}, 3-12 membered carbocyclyl, phenyl, 5- or 6-membered heteroaryl, or 4-12 membered heterocyclyl, wherein the carbocyclyl, phenyl, 5- or 6-membered heteroaryl, or 4-12 membered heterocyclyl represented by R^{Z1} are each optionally substituted by one to four R^{1b};

- 25 each R¹ is, independently, halo, cyano, NO₂, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxylalkyl, C₁₋₆alkoxylalkyl, C₁₋₆hydroxyalkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, NR^{N1a}R^{N1b}, -C(O)R^{1a}, -C(O)OR^{O1a}, -C(O)NR^{N1a}R^{N1b}, -OR^{O1a}, -(CH₂)_{0 or 1-3-12} membered carbocyclyl,

- $-(CH_2)_{0 \text{ or } 1}$ -4-12 membered heterocyclyl, $-(CH_2)_{0 \text{ or } 1}$ -6-10 membered aryl, or
 $-(CH_2)_{0 \text{ or } 1}$ -5-10 membered heteroaryl, wherein the C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl,
 heterocyclyl, aryl, or heteroaryl represented by R^1 are each optionally substituted by one to four R^{1b} ;
 R^{1a} , R^{O1a} , R^{N1a} , and R^{N1b} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl,
- 5 C_{3-6} cycloalkyl, or 4-6 membered heterocyclyl;
 each R^{1b} is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxylalkyl,
 C_{1-6} alkoxylalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkoxy, $-C(O)R^{1a}$, $-C(O)OR^{O1a}$,
 $-C(O)NR^{N1a}R^{N1b}$, $-SO_2R^{1a}$, $-NR^{N1a}R^{N1b}$, $-NR^{N1a}C(O)R^{1a}$, $-NR^{N1a}C(O)OR^{1a}$, $-NR^{N1a}SO_2R^{1a}$,
 $-NR^{N1a}SO_2NR^{N1a}R^{N1b}$, cyano, NO_2 , or OR^{O1a} ,
- 10 R^{N2} is H, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C(O)R^{2a}$, C_{3-6} cycloalkyl, phenyl, or 5-to 6-membered
 heteroaryl, wherein the phenyl and 5-to 6-membered heteroaryl represented by R^{N2} are each
 optionally substituted with one to three substituents selected from halo,
 C_{1-3} alkyl, and C_{1-3} haloalkyl;
 each R^{G2} is, independently, H, halo, cyano, oxo (as appropriate), NO_2 , C_{1-6} alkyl,
- 15 C_{1-6} haloalkyl, $*=CH-R^7$ (as appropriate), C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} hydroxylalkyl,
 C_{1-6} alkoxylalkyl, C_{1-6} hydroxyalkoxy, $-C(O)R^{2a}$, $-C(O)OR^{O2a}$, $-C(O)NR^{N2a}R^{N2b}$, OR^{O2a} , $NR^{N2a}R^{N2b}$,
 SO_2R^{2a} , $-NR^{N2a}C(O)R^{2a}$, $-NR^{N2a}C(O)OR^{2a}$, $-NR^{N2a}SO_3R^{2a}$, $-NR^{N2a}SO_3NR^{N2a}R^{N2a}$,
 $-(CH_2)_{0 \text{ or } 1}$ -3-12 membered carbocyclyl, $-(CH_2)_{0 \text{ or } 1}$ -4-12 membered heterocyclyl,
 $-(CH_2)_{0 \text{ or } 1}$ -6-10 membered aryl, or $-(CH_2)_{0 \text{ or } 1}$ -5-10 membered heteroaryl, wherein the carbocyclyl,
 heterocyclyl, aryl, or heteroaryl represented by R^{G2} are each optionally substituted by one to four halo,
- 20 C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxylalkyl, C_{1-6} alkoxylalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkoxy,
 $-C(O)R^{2a}$, $-C(O)OR^{O2a}$, $-C(O)NR^{N2a}R^{N2b}$, cyano, NO_2 , OR^{O2a} , $NR^{N2a}R^{N2b}$,
 SO_3R^{2a} , $-NR^{N2a}C(O)R^{2a}$, $-NR^{N2a}C(O)OR^{2a}$, $-NR^{N2a}SO_3R^{2a}$, or
 $-NR^{N2a}SO_3NR^{N2a}R^{N2a}$, and wherein the C_2 alkenyl is optionally substituted with phenyl or
- 25 5- to 6-membered heteroaryl;
 each R^2 is independently halo, cyano, oxo (as appropriate), NO_2 , C_{1-6} alkyl,
 C_{1-6} haloalkyl, $*=CH-R^7$ (as appropriate), C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} hydroxylalkyl,
 C_{1-6} alkoxylalkyl, C_{1-6} hydroxyalkoxy, $-C(O)R^{2a}$, $-C(O)OR^{O2a}$, $-C(O)NR^{N2a}R^{N2b}$, OR^{O2a} , $NR^{N2a}R^{N2b}$,
 SO_2R^{2a} , $-NR^{N2a}C(O)R^{2a}$, $-NR^{N2a}C(O)OR^{2a}$, $-NR^{N2a}SO_3R^{2a}$, $-NR^{N2a}SO_3NR^{N2a}R^{N2a}$,
- 30 $-(CH_2)_{0 \text{ or } 1}$ -3-12 membered carbocyclyl, $-(CH_2)_{0 \text{ or } 1}$ -4-12 membered heterocyclyl,
 $-(CH_2)_{0 \text{ or } 1}$ -6-10 membered aryl, or $-(CH_2)_{0 \text{ or } 1}$ -5-10 membered heteroaryl, wherein the carbocyclyl,
 heterocyclyl, aryl, or heteroaryl represented by R^2 are each optionally substituted by one to four halo,
 C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxylalkyl, C_{1-6} alkoxylalkyl, C_{1-6} alkoxy,
 C_{1-6} haloalkoxy, C_{1-6} hydroxyalkoxy, $-C(O)R^{2a}$, $-C(O)OR^{O2a}$, $-C(O)NR^{N2a}R^{N2b}$, cyano, NO_2 , OR^{O2a} ,
- 35 $NR^{N2a}R^{N2b}$, SO_3R^{2a} , $-NR^{N2a}C(O)R^{2a}$, $-NR^{N2a}C(O)OR^{2a}$, $-NR^{N2a}SO_3R^{2a}$, or
 $-NR^{N2a}SO_3NR^{N2a}R^{N2a}$, and wherein the C_2 alkenyl is optionally substituted with phenyl or
 5- to 6-membered heteroaryl; or

two R^2 , two R^{G2} , one R^2 and one R^{N2} , one R^2 and one R^{G2} , or one R^{G2} and one R^{N2} , together with the atoms to which they are connected, form 3- to 12 membered carbocyclyl, 4- to 12 membered heterocyclyl, phenyl, naphthyl or 5- to 10-membered heteroaryl, each of which is optionally substituted by one to four R^6 ;

5 R^{2a} and R^{O2a} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, or 4-6 membered heterocyclyl;

R^{N2a} and R^{N2b} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{O2a} , or C_{3-6} cycloalkyl;

* is the connection point to the tricyclic core ring;

10 R^7 is C_{1-4} alkyl, 3- to 12 membered carbocyclyl, 4- to 12 membered heterocyclyl, phenyl, naphthyl, or 5- to 10-membered heteroaryl, each of which is optionally substituted by one to four halo, -OH, -NH₂, cyano, NO₂, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, or heteroaryl; each R^6 is independently halo, cyano, oxo (as appropriate), NO₂, C_{1-6} alkyl,

C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} hydroxylalkyl, C_{1-6} alkoxylalkyl, 15 C_{1-6} hydroxyalkoxy, $-C(O)R^{6a}$, $-C(O)OR^{O6a}$, $-C(O)NR^{N6a}R^{N6b}$, OR^{O6a} , $NR^{N6a}R^{N6b}$, SO_2R^{6a} , $-NR^{N6a}C(O)R^{6a}$, $-NR^{N6a}C(O)OR^{6a}$, $-NR^{N6a}SO_3R^{6a}$, $-NR^{N6a}SO_3NR^{N6a}R^{N6a}$, $-(CH_2)_{0 \text{ or } 1-3-12}$ membered carbocyclyl, $-(CH_2)_{0 \text{ or } 1-4-12}$ membered heterocyclyl, $-(CH_2)_{0 \text{ or } 1-6-10}$ membered aryl, or $-(CH_2)_{0 \text{ or } 1-5-10}$ membered heteroaryl, wherein the carbocyclyl, heterocyclyl, aryl, or heteroaryl represented by R^6 are each optionally substituted by one to four halo,

20 C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxylalkyl, C_{1-6} alkoxylalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkoxy, $-C(O)R^{6a}$, $-C(O)OR^{O6a}$, $-C(O)NR^{N6a}R^{N6b}$, cyano, NO₂, OR^{O6a} , $NR^{N6a}R^{N6b}$, SO_3R^{6a} , $-NR^{N6a}C(O)R^{6a}$, $-NR^{N6a}C(O)OR^{6a}$, $-NR^{N6a}SO_3R^{6a}$, or $-NR^{N6a}SO_3NR^{N6a}R^{N6a}$,

or two R^6 , together with the atoms to which they are attached, form C_{3-6} cycloalkyl;

25 R^{6a} and R^{O6a} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, or 4-6 membered heterocyclyl;

R^{N6a} and R^{N6b} are each independently H, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{O6a} , or C_{3-6} cycloalkyl;

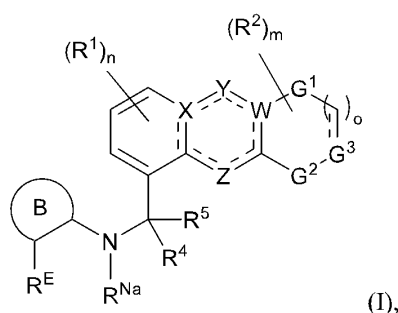
30 Ring B is phenyl or 5- to 10-membered monocyclic or bicyclic heteroaryl, each of which is substituted with R^E ortho to the $N(R^{Na})$ substituent, and optionally substituted with one to four R^3 ;

each R^3 is independently halo, cyano, NO₂, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} hydroxylalkyl, C_{1-6} alkoxylalkyl, C_{1-6} hydroxyalkoxy, $-C(O)R^{3a}$, $-C(O)OR^{O3a}$, $-C(O)NR^{N3a}R^{N3b}$, OR^{O3a} , $NR^{N3a}R^{N3b}$, SO_2R^{3a} , $-NR^{N3a}C(O)R^{3a}$, $-NR^{N3a}C(O)OR^{3a}$, $-NR^{N3a}SO_3R^{3a}$, $-NR^{N3a}SO_3NR^{N3a}R^{N3a}$, $-(CH_2)_{0 \text{ or } 1-3-12}$ membered carbocyclyl, $-(CH_2)_{0 \text{ or } 1-4-12}$ membered heterocyclyl, $-(CH_2)_{0 \text{ or } 1-6-10}$ membered aryl, or $-(CH_2)_{0 \text{ or } 1-5-10}$ membered heteroaryl, wherein the carbocyclyl, heterocyclyl, aryl, or heteroaryl represented by R^3 are each optionally substituted by one to four halo, C_{1-6} alkyl,

C₁₋₆haloalkyl, C₁₋₆hydroxylalkyl, C₁₋₆alkoxylalkyl, C₁₋₆hydroxyalkoxy, -C(O)R^{3a},
 -C(O)OR^{O3a}, -C(O)NR^{N3a}R^{N3b}, cyano, NO₂, OR^{O3a}, NR^{N3a}R^{N3b}, SO₃R^{3a}, -NR^{N3a}C(O)R^{3a},
 -NR^{N3a}C(O)OR^{3a}, -NR^{N3a}SO₃R^{3a}, or -NR^{N3a}SO₃NR^{N3a}R^{N3a},

- R^E is H, cyano, C₁₋₄alkyl, -C(O)R⁸, -C(NH)NR^{N3E}R^{N3E}, -S(O₂)NR^{N3E}R^{N3E}, -C(O)OR^{O3a}, -
 5 C(O)NR^{N3a}R^{N3b}, phenyl, 5- to 10-membered heteroaryl, or 4- to 12-membered heterocyclyl, wherein
 the C₁₋₄alkyl is optionally substituted by one to four R^{Ea}, and the phenyl, 5- to 10-membered
 heteroaryl, and 4- to 12-membered heterocyclyl are each optionally substituted with one or two R^{Eb};
 or R^E and R³, together with the atoms to which they are attached, form a 5- to 6-membered
 monocyclic heterocyclyl;
- 10 R⁸ is H, C₁₋₃alkyl, C₁₋₃haloalkyl, C₁₋₄thioalkyl, C₁₋₄thiohaloalkyl, or SH;
 each R^{Ea} is, independently, halo, cyano, OH, or NR^{N3E}R^{N3E};
 each R^{Eb} is, independently, oxo, =S, halo, C₁₋₃alkyl, C₁₋₃haloalkyl, cyano, C₁₋₃alkoxy, -OH, or
 -C(O)NR^{N3E}R^{N3E}, wherein the C₁₋₃alkyl represented by R^{Eb} is optionally substituted by 4- to 6-
 membered heterocyclyl optionally substituted with C₁₋₃alkyl;
- 15 each R^{N3E} is, independently, H, OH or C₁₋₃alkyl;
 R^{3a} and R^{O3a} are each independently H, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, or 4-6
 membered heterocyclyl, wherein the C₁₋₆alkyl represented by R^{3a} or R^{O3a} is optionally substituted by a
 4-6 membered heterocyclyl;
- R^{N3a} and R^{N3b} are each independently H, cyano, C₁₋₆alkyl, C₁₋₆haloalkyl, OR^{O3a},
 20 -SO₂C₁₋₄alkyl, or C₃₋₆cycloalkyl, wherein the C₁₋₆alkyl represented by R^{N3a} or R^{N3b} is optionally
 substituted by C₁₋₃alkoxy or a 5- to 6-membered heteroaryl;
- R⁴ is C₁₋₃alkyl and
 R⁵ is H.

2. The compound of claim 1, wherein the compound is of Formula (I):

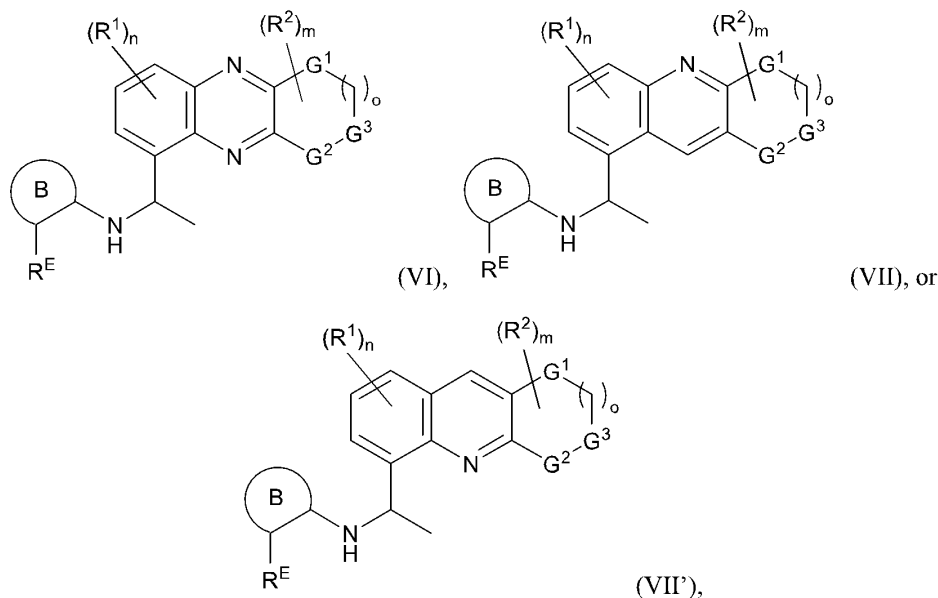


a pharmaceutically acceptable salt, wherein:

each R⁶ is independently halo, cyano, oxo (as appropriate), NO₂, C₁₋₆alkyl,
 C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆haloalkyl, C₁₋₆hydroxylalkyl, C₁₋₆alkoxylalkyl,
 C₁₋₆hydroxyalkoxy, -C(O)R^{6a}, -C(O)OR^{O6a}, -C(O)NR^{N6a}R^{N6b}, OR^{O6a}, NR^{N6a}R^{N6b}, SO₂R^{6a},

- $-\text{NR}^{\text{N6a}}\text{C}(\text{O})\text{R}^{\text{6a}}$, $-\text{NR}^{\text{N6a}}\text{C}(\text{O})\text{OR}^{\text{6a}}$, $-\text{NR}^{\text{N6a}}\text{SO}_3\text{R}^{\text{6a}}$, $-\text{NR}^{\text{N6a}}\text{SO}_3\text{NR}^{\text{N6a}}\text{R}^{\text{N6a}}$,
 $-(\text{CH}_2)_{0 \text{ or } 1-3-12}$ membered carbocyclyl, $-(\text{CH}_2)_{0 \text{ or } 1-4-12}$ membered heterocyclyl,
 $-(\text{CH}_2)_{0 \text{ or } 1-6-10}$ membered aryl, or $-(\text{CH}_2)_{0 \text{ or } 1-5-10}$ membered heteroaryl, wherein the carbocyclyl,
 heterocyclyl, aryl, or heteroaryl represented by R^6 are each optionally substituted by one to four halo,
 5 C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxylalkyl, C_{1-6} alkoxylalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkoxy, $-\text{C}(\text{O})\text{R}^{\text{6a}}$, $-\text{C}(\text{O})\text{OR}^{\text{6a}}$, $-\text{C}(\text{O})\text{NR}^{\text{N6a}}\text{R}^{\text{N6b}}$, cyano, NO_2 , OR^{O6a} , $\text{NR}^{\text{N6a}}\text{R}^{\text{N6b}}$,
 $\text{SO}_3\text{R}^{\text{6a}}$, $-\text{NR}^{\text{N6a}}\text{C}(\text{O})\text{R}^{\text{6a}}$, $-\text{NR}^{\text{N6a}}\text{C}(\text{O})\text{OR}^{\text{6a}}$, $-\text{NR}^{\text{N6a}}\text{SO}_3\text{R}^{\text{6a}}$, or $-\text{NR}^{\text{N6a}}\text{SO}_3\text{NR}^{\text{N6a}}\text{R}^{\text{N6a}}$,
 R^7 is 3- to 12 membered carbocyclyl, 4- to 12 membered heterocyclyl, phenyl, naphthyl, or
 5- to 10-membered heteroaryl, each of which is optionally substituted by one to four halo, $-\text{OH}$, $-\text{NH}_2$,
 10 cyano, NO_2 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, or heteroaryl;
 R^{E} is $-\text{C}(\text{O})\text{OR}^{\text{O3a}}$ or $-\text{C}(\text{O})\text{NR}^{\text{N3a}}\text{R}^{\text{N3b}}$,
 R^{3a} and R^{O3a} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, or 4-6
 membered heterocyclyl; and
 R^{N3a} and R^{N3b} are each independently H, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{O3a} , or
 15 C_{3-6} cycloalkyl.

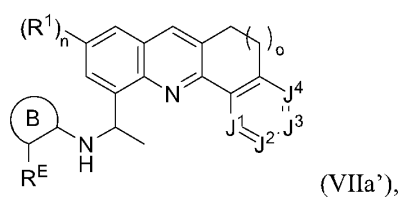
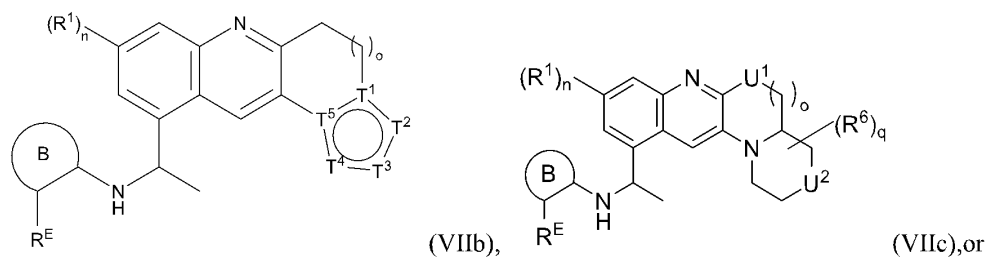
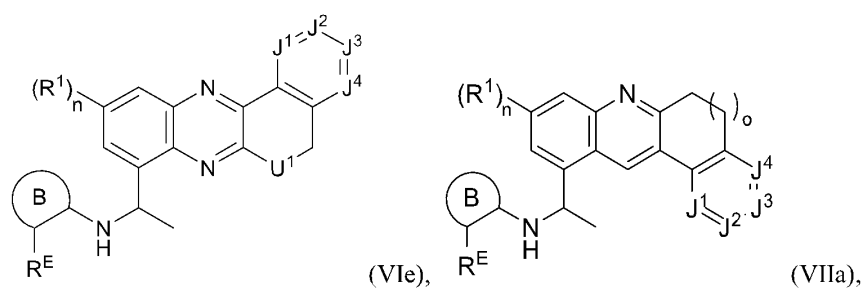
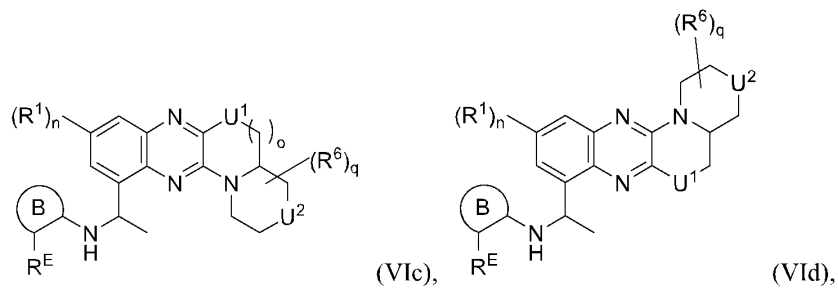
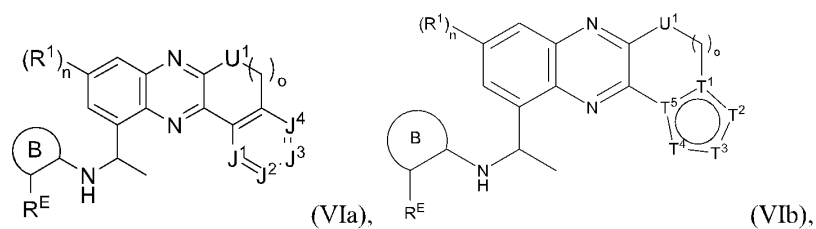
3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by Formula (VI), (VII), or (VII'):



20

wherein m and n are each, independently, 0, 1 or 2; and o is 0 or 1.

4. The compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein the
 compound is represented by Formula (VIa), (VIb), (VIc), (VId), (VIe), (VIIa), (VIIb), (VIIc), or
 25 (VIIa'):



5

wherein:

n and o, are each, independently 0 or 1;

q is 0, 1, or 2;

J¹, J², J³, and J⁴, are each, independently, N, CH, or CR⁶;

10

T¹ and T⁵, are each, independently, N or C;

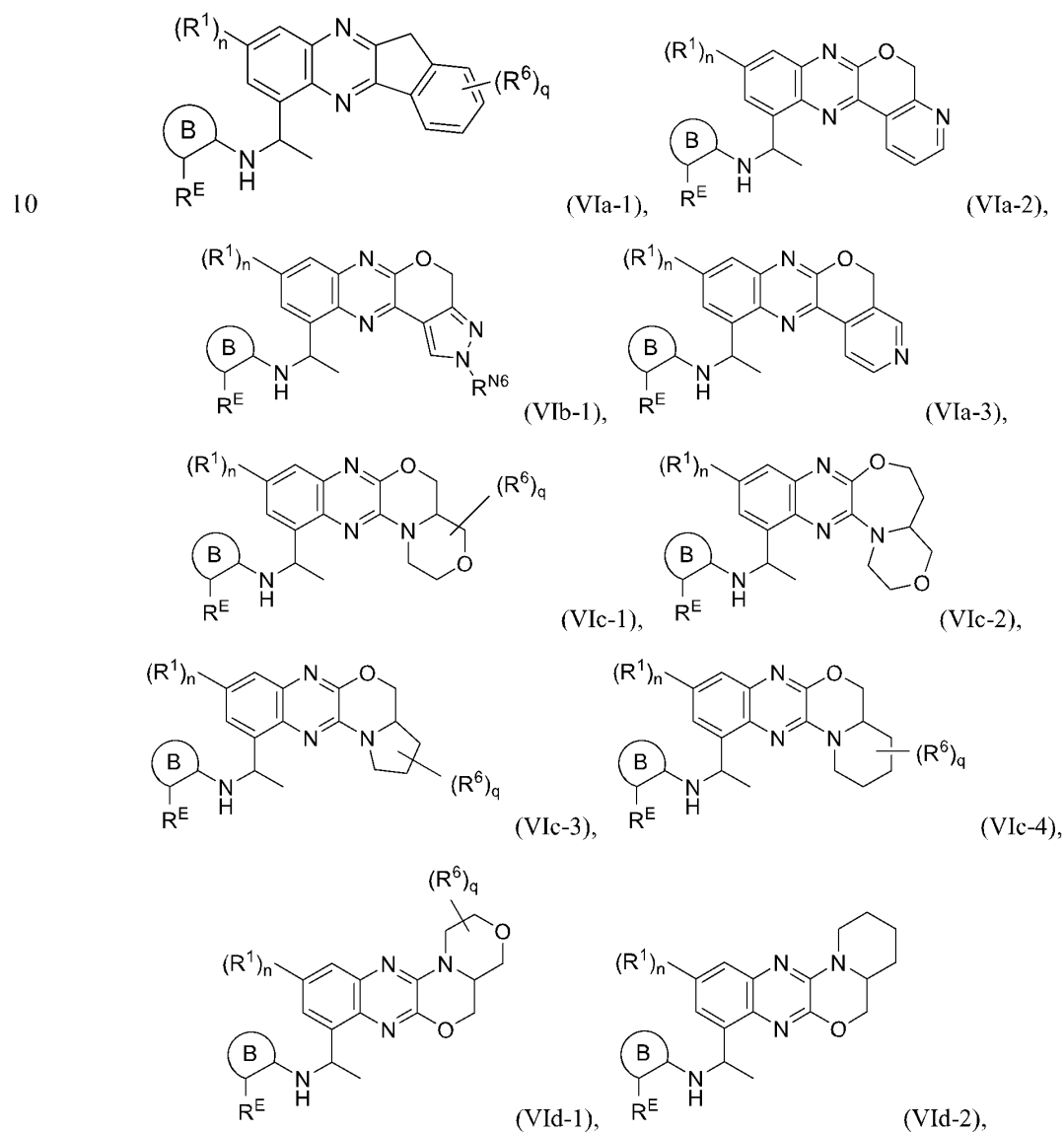
T², T³, and T⁴, are each, independently, N, NR⁶, O, S, CH, or CR⁶;

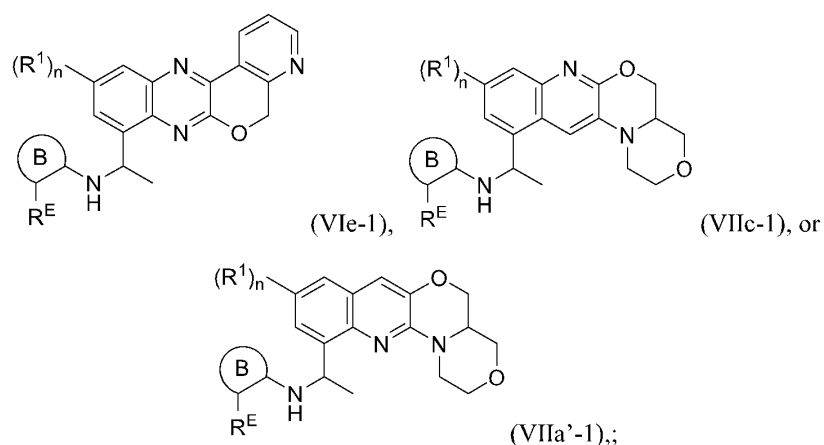
R^{N6} is H, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{3-6} cycloalkyl, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl represented by R^{N6} are each optionally substituted by one to three halo, C_{1-3} alkyl, C_{1-3} haloalkyl, cyano, OH, C_{1-3} alkoxy, or C_{1-3} haloalkoxy;

U^1 is NR^{N2} , CH_2 , or O;

5 U^2 is absent, NR^{N6} , CH_2 , or O.

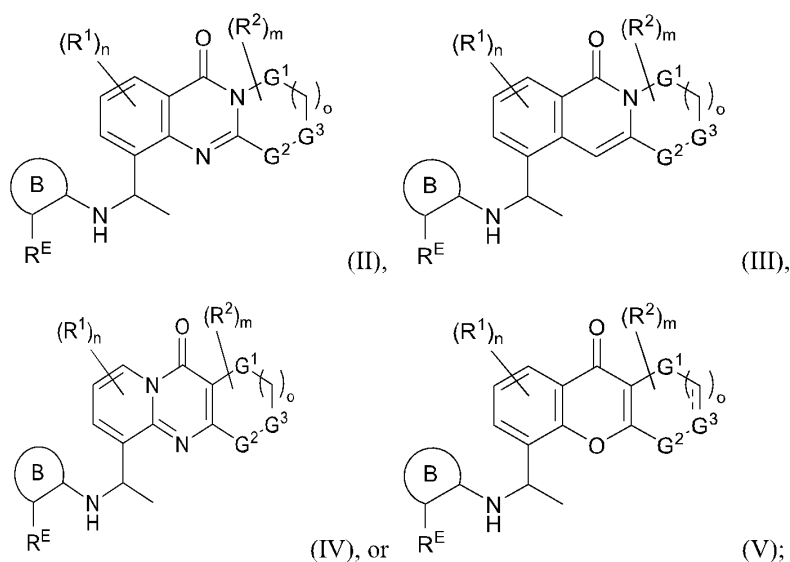
5. The compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by Formula (VIa-1), (VIa-2), (VIb-1), (VIc-1), (VIc-2), (VIc-3), (VIc-4), (VIId-1), (VIId-2), (VIe-1), or (VIId-1):





wherein n is 0 or 1 and q is 0, 1, or 2.

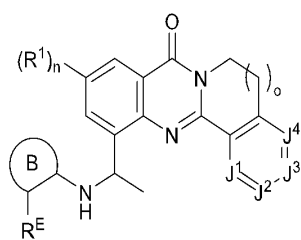
- 5 6. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by Formula (II), (III), (IV), or (V):



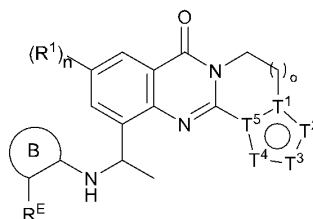
wherein m and n are each, independently, 0, 1, or 2; o is 0 or 1.

10

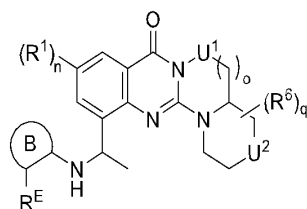
7. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by Formula (IIa), (IIb), (IIc), (IIId), (IIIa), (IIIb), (IIIc), (IVa), (IVb), (IVc), (Va), (Vb), (Vc), or (Vd):



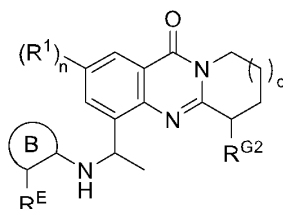
(IIa),



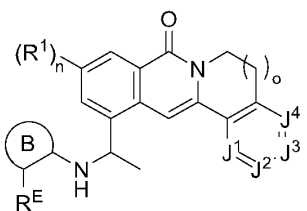
(IIb),



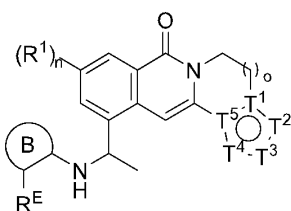
(IIc),



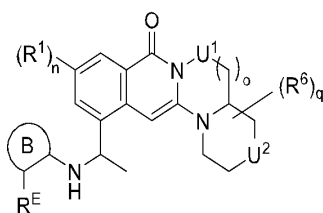
(IId),



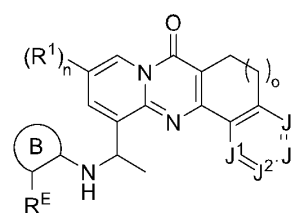
(IIIa),



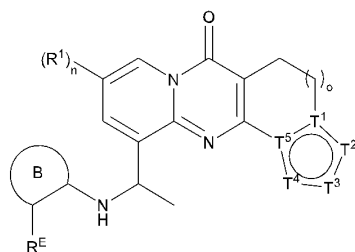
(IIIb),



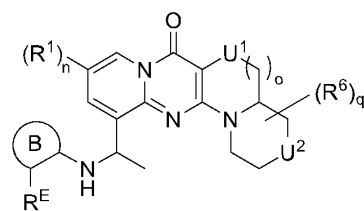
(IIIc),



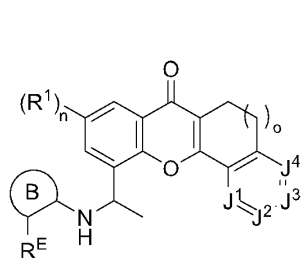
(IVa),



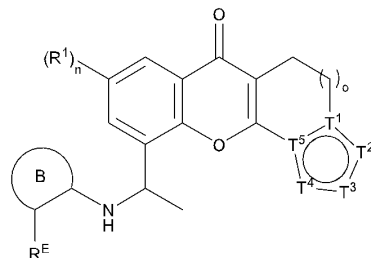
(IVb),



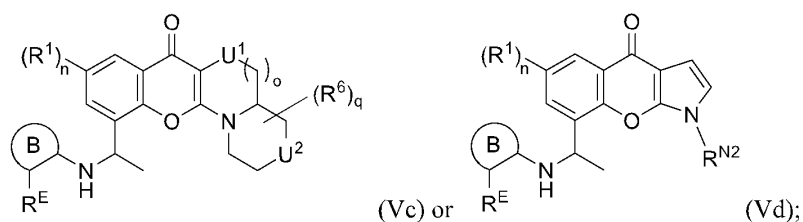
(IVc),



(Va),



(Vb),



wherein:

n and o, are each, independently, 0 or 1;

q is 0, 1, or 2;

5 J¹, J², J³, and J⁴, are each, independently, N, CH, or CR⁶;

T¹ and T⁵, are each, independently, N or C;

T², T³, and T⁴, are each, independently, N, NR^{N6}, O, S, CH, or CR⁶;

R^{N6} is H, C₁₋₃alkyl, C₁₋₃haloalkyl, C₃₋₆cycloalkyl, phenyl, naphthyl, or

5- to 6-membered heteroaryl, wherein the phenyl, naphthyl, and 5- to 6-membered heteroaryl

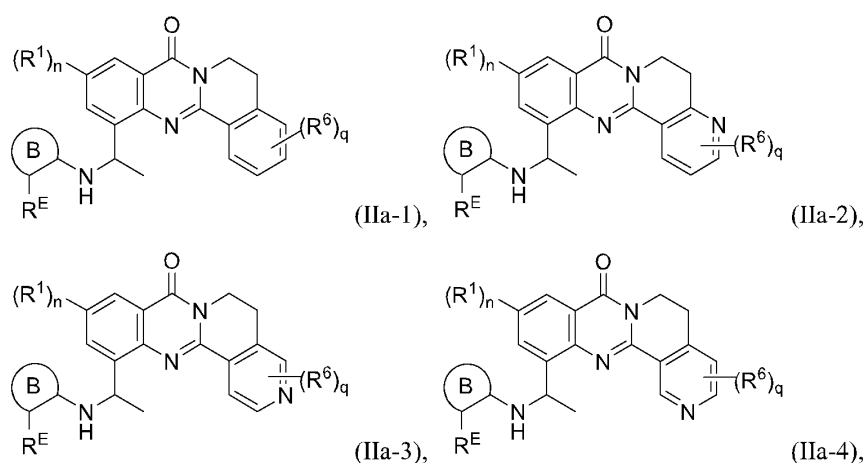
10 represented by R^{N6} are each optionally substituted by one to three halo, C₁₋₃alkyl,

C₁₋₃haloalkyl, cyano, OH, C₁₋₃alkoxy, or C₁₋₃haloalkoxy;

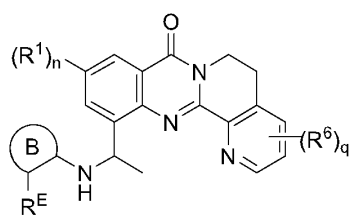
U¹ is NR^{N2}, CH₂, or O;

U² is NR^{N6}, CH₂, or O.

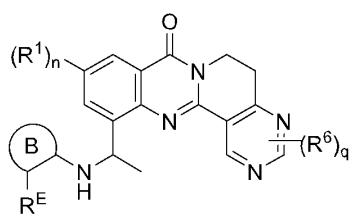
15 8. The compound of claim 7, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by Formula (IIa-1), (IIa-2), (IIa-3), (IIa-4), (IIa-5), (IIa-6), (IIa-7), (IIb-1), (IIb-2), (IIb-3), (IIb-4), (IIb-5), (IIb-6), (IIb-7), (IIb-8), (IIb-9), (IIb-10), (IIb-11), (IIc-1), (IIa-1), (IIb-1), (IIc-1), (IVc-1), (Va-1), (Va-2), (Va-3), or (Vc-1):



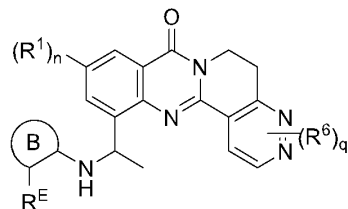
20



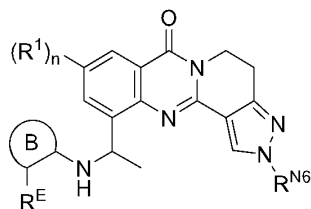
(IIa-5),



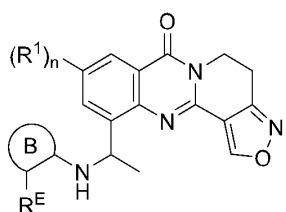
(IIa-6),



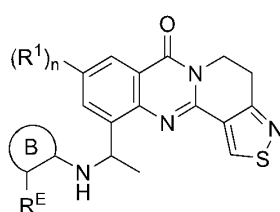
(IIa-7),



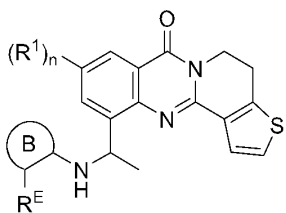
(IIb-1),



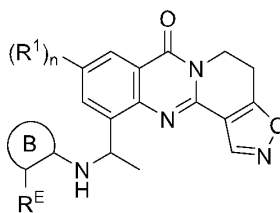
(IIb-2),



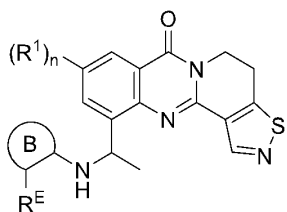
(IIb-3),



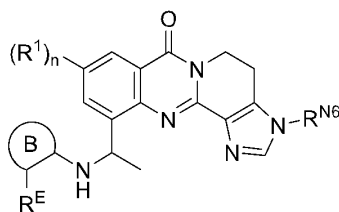
(IIb-4),



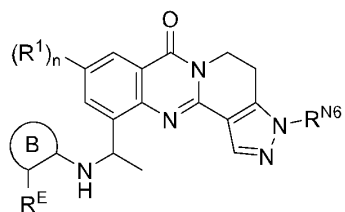
(IIb-5),



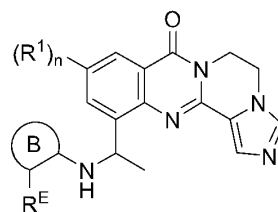
(IIb-6),



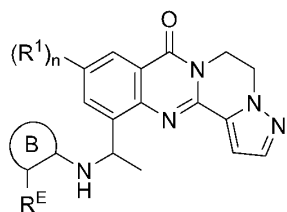
(IIb-7),



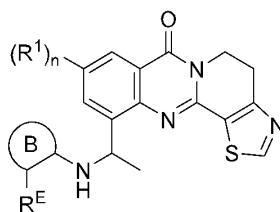
(IIb-8),



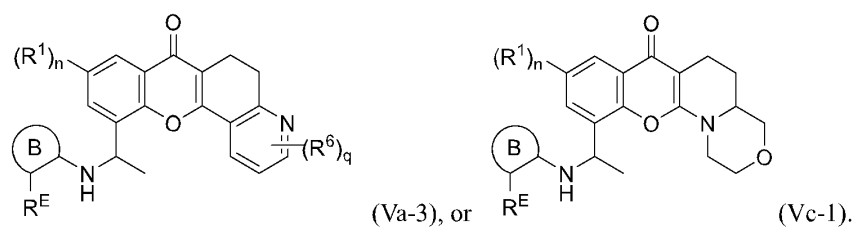
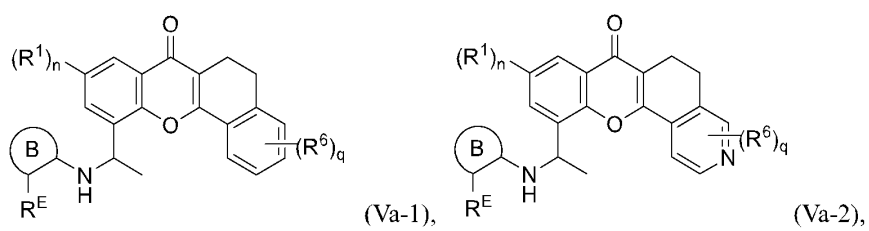
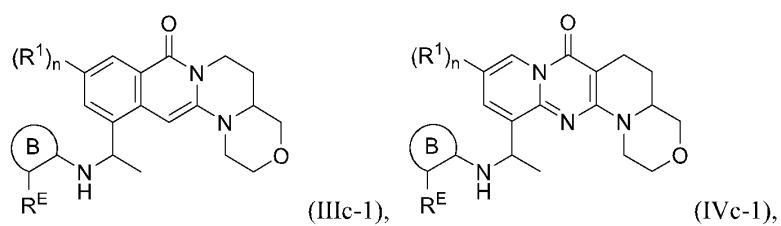
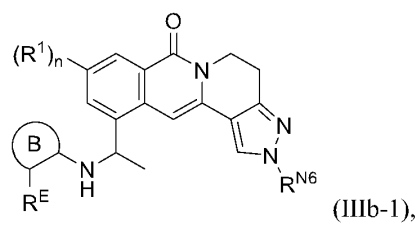
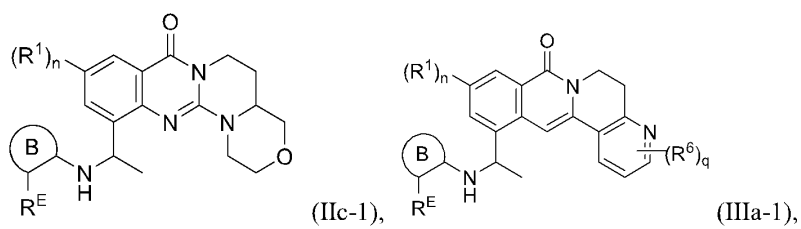
(IIb-9),



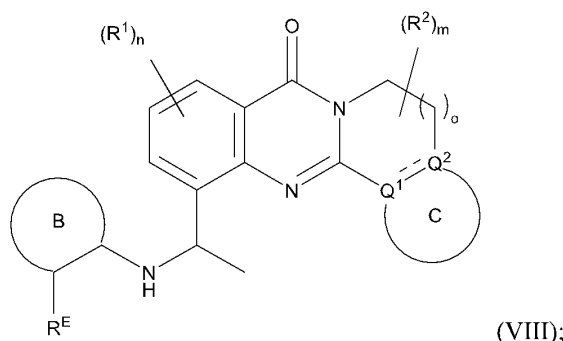
(IIb-10),



(IIb-11),



9. The compound of claim 1 or 2, wherein the compound is represented by Formula (VIII):



or a pharmaceutically acceptable salt thereof, wherein:

n is 0, 1, or 2;

5 m is 0, 1, or 2;

o is 0 or 1;

each R¹ is, independently, halo, cyano, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -NR^{N1a}R^{N1b}, -C(O)R^{1a}, -C(O)OR^{O1a}, -C(O)NR^{N1a}R^{N1b}, OR^{O1a}, C₃₋₆cycloalkyl, phenyl, or 5-to 6-membered monocyclic heteroaryl, wherein the C₃₋₆cycloalkyl, phenyl, and 5-to 6-membered monocyclic heteroaryl represented by R¹ are each optionally substituted by one to three halo,

10 C₁₋₃alkyl, C₁₋₃haloalkyl, OH, C₁₋₃alkoxy, C₁₋₃haloalkoxy, -C(O)R^{1a}, -C(O)OR^{O1a}, or -C(O)NR^{N1a}R^{N1b};

each R² is independently halo, oxo, cyano, C₁₋₆alkyl, C₁₋₆haloalkyl, -NR^{N2a}R^{N2b}, -C(O)R^{2a}, -C(O)OR^{O2a}, -C(O)NR^{N2a}R^{N2b}, OR^{O2a}, C₃₋₆cycloalkyl, phenyl, or 5-to 6-membered monocyclic heteroaryl, wherein the C₃₋₆cycloalkyl, phenyl, and 5-to 6-membered monocyclic heteroaryl represented by R² are each optionally substituted by one to three halo, C₁₋₃alkyl, C₁₋₃haloalkyl, OH,

15 C₁₋₃alkoxy, C₁₋₃haloalkoxy, -C(O)R^{2a}, -C(O)OR^{O2a}, or -C(O)NR^{N2a}R^{N2b};

R^{2a}, R^{O2a}, R^{N2a}, and R^{N2b} are each independently H, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, or 4-6 membered heterocyclyl;

Ring B is phenyl or 5- to 6-membered monocyclic heteroaryl, each of which is substituted with R^E ortho to the NH substituent, and one to three R³;

20

each R³ is independently halo, cyano, C₁₋₆alkyl, C₁₋₆haloalkyl, -NR^{N3a}R^{N3b}, -C(O)R^{3a}, -C(O)OR^{O3a}, -C(O)NR^{N3a}R^{N3b}, OR^{O3a}, C₃₋₆cycloalkyl, phenyl, or 5-to 6-membered monocyclic heteroaryl, wherein the C₃₋₆cycloalkyl, phenyl, and 5-to 6-membered monocyclic heteroaryl represented by R³ are each optionally substituted by one to three halo, C₃₋₃alkyl, C₃₋₃haloalkyl, OH,

25 C₁₋₃alkoxy, C₁₋₃haloalkoxy, -C(O)R^{3a}, -C(O)OR^{O3a}, or -C(O)NR^{N3a}R^{N3b};

R^{3a}, R^{O3a}, R^{N3a}, and R^{N3b} are each independently H, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, or 4-6 membered heterocyclyl;

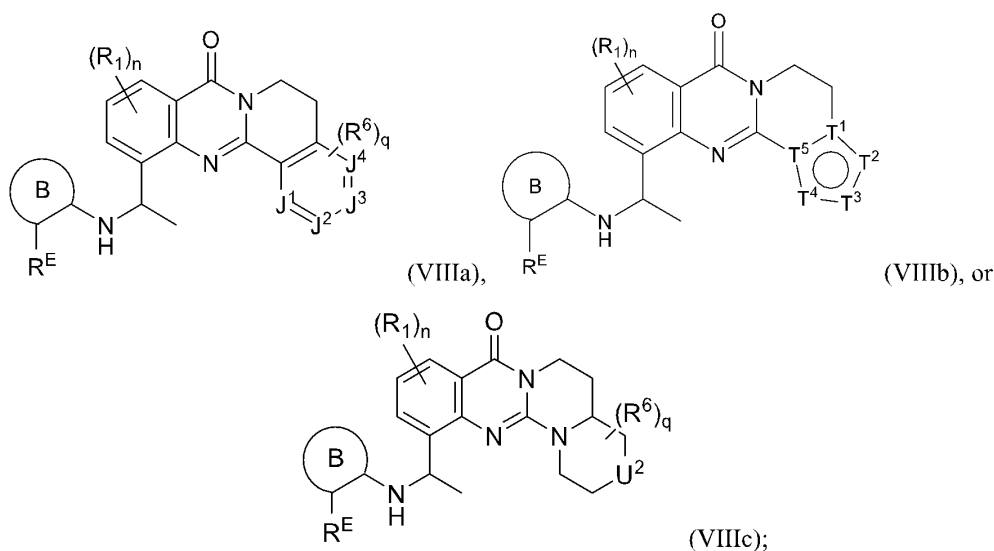
Ring C is 6-membered monocyclic heterocyclyl, phenyl, or 5- to 6-membered monocyclic heteroaryl, each of which is optionally substituted with one to three R⁶;

Q^1 and Q^2 are each, independently, C, CH, or N, provided that at least one of Q^1 or Q^2 is C or CH;

- each R^6 is, independently, halo, oxo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, $-NR^{N6a}R^{N6b}$, $-C(O)R^{6a}$, $-C(O)OR^{O6a}$, $-C(O)NR^{N6a}R^{N6b}$, OR^{O6a} , C_{1-6} cycloalkyl, phenyl, or 5-to 6-membered monocyclic heteroaryl, wherein the C_{1-6} cycloalkyl, phenyl, and 5-to 6-membered monocyclic heteroaryl represented by R^6 are each independently substituted by one to three halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-C(O)R^{6a}$, $-C(O)OR^{O6a}$, or $-C(O)NR^{N6a}R^{N6b}$;
- R^{6a} , R^{O6a} , R^{N6a} , and R^{N6b} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} cycloalkyl, or 4-6 membered heterocycl.

10

10. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by Formula (VIIIa), (VIIIb), or (VIIIc):



15 wherein:

n is 0 or 1;

q is 0, 1, or 2;

U^2 is NR^{N6} , CH_2 , or O;

J^1 , J^2 , J^3 , and J^4 , are each, independently, N or CH, wherein at least one of J^1 , J^2 , J^3 , and J^4 is

20 CH;

T^1 and T^5 , are each, independently, N or C;

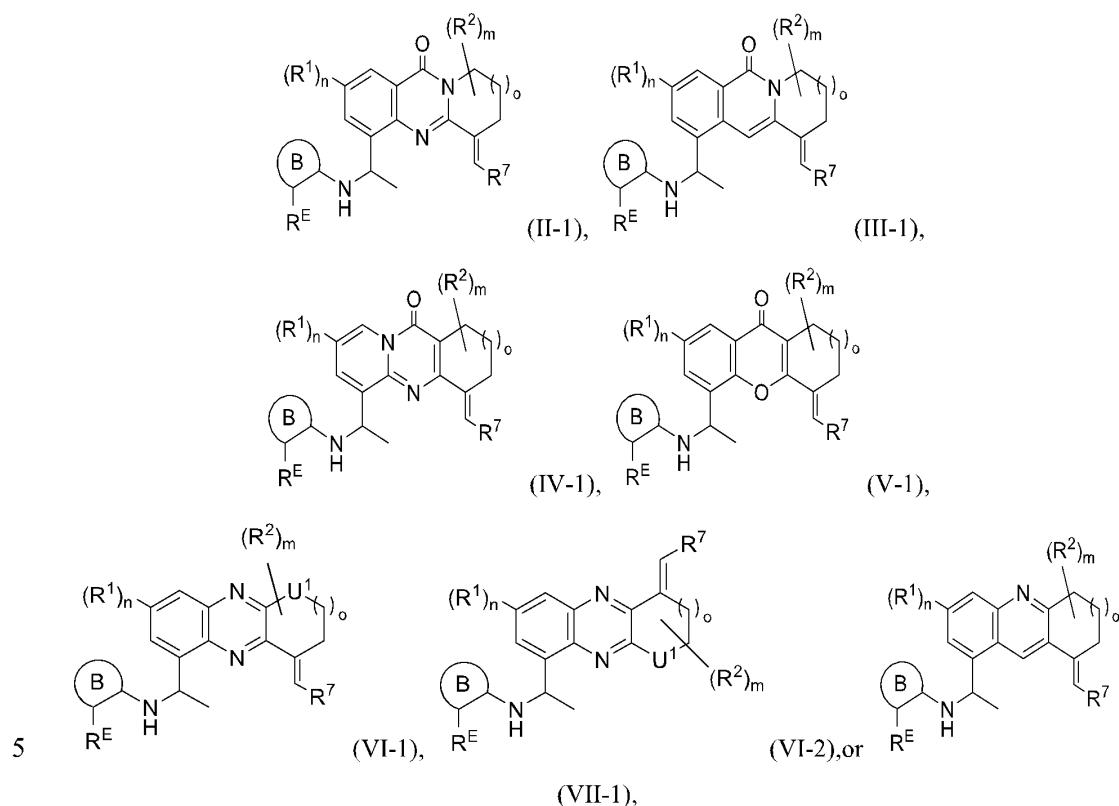
T^2 , T^3 , and T^4 , are each, independently, N, NR^{N6} , O, S, or CH;

R^{N6} is H, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{3-6} cycloalkyl, phenyl, or 5- to 6-membered heteroaryl,

wherein the phenyl and 5- to 6-membered heteroaryl represented by R^{N6} are each optionally

25 substituted by one to three halo, C_{1-3} alkyl, C_{1-3} haloalkyl, cyano, OH, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.

11. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by Formula (II-1), (III-1), (IV-1), (V-1), (VI-1), (VI-2), or (VII-1):



wherein

m, n, and o, are each, independently 0 or 1;

U¹ is NR^{N2}, CH₂, or O;

10 R⁷ is C₁₋₄alkyl, 5- or 6-membered heterocyclyl, phenyl, or 5- or 6-membered heteroaryl, wherein the 5- or 6-membered heterocyclyl, phenyl, or 5- or 6-membered heteroaryl are each optionally substituted by one to two halo, -OH, -NH₂, cyano, C₁₋₃alkyl, C₁₋₃alkyl-OR^{O7a}, C₃₋₆cycloalkyl, C₁₋₃haloalkyl, or 4-to 6 membered heterocyclyl;

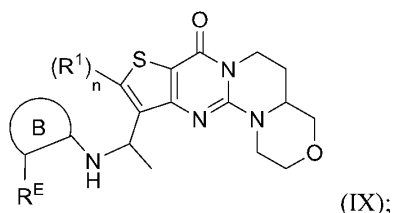
R^{O7a} is H or C₁₋₃alkyl.

15

12. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein R⁷ is C₁₋₃alkyl, phenyl, pyridyl, isoxazolyl, pyrazolyl, imidazolyl, tetrahydrofuranyl, or tetrahydro-2H-pyranyl, wherein the phenyl, pyridyl, isoxazolyl, pyrazolyl, imidazolyl, tetrahydrofuranyl, and tetrahydro-2H-pyranyl are each optionally substituted by one to two halo, -OH, C₁₋₃alkoxy, -NH₂, cyano, C₁₋₃alkyl, C₁₋₃haloalkyl, C₁₋₃alkyl-OR^{O7a}, or cyclopropyl, or morpholinyl;

R^{O7a} is H or C₁₋₃alkyl.

13. The compound of claim 1, wherein the compound is represented by Formula (IX):

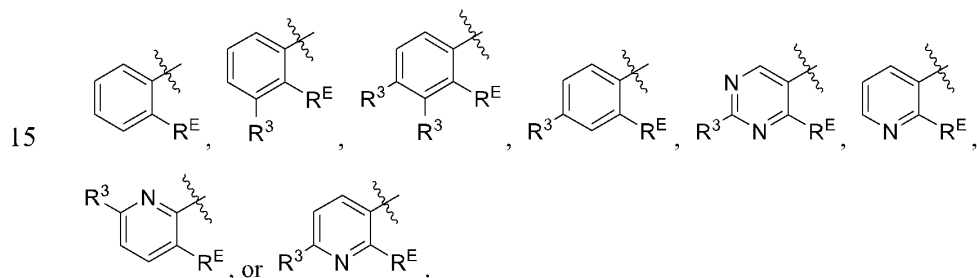


or a pharmaceutically acceptable salt thereof.

14. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein Ring B is phenyl or 6-membered monocyclic heteroaryl, each of which is substituted with R^E ortho to the NR^{Na} substituent, and further optionally substituted with one or two R³.

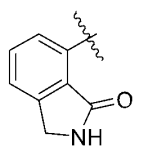
15. The compound of claim 14, or a pharmaceutically acceptable salt thereof, wherein Ring B is phenyl, pyrimidinyl, or pyridinyl, each of which is substituted with R^E ortho to the NR^{Na} substituent, and further optionally substituted with one or two R³.

16. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein Ring B and R^E, together with optionally substituted R³, are represented by:



17. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof,

wherein Ring B and R^E, together with optionally substituted R³, are represented by:



20

18. The compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein:

R^E is cyano, C_{1-4} alkyl, $-C(O)R^8$, $-C(NH)NR^{N3E}R^{N3E}$, $-S(O_2)NR^{N3E}R^{N3E}$, $-C(O)OR^{O3a}$, $-C(O)NR^{N3a}R^{N3b}$, phenyl, 5- to 6-membered heteroaryl, or 4- to 10-membered heterocyclyl, wherein the C_{1-4} alkyl is optionally substituted by one to four R^{Ea} , and the phenyl, 5- to 6-membered heteroaryl, and 4- to 10-membered heterocyclyl are each optionally substituted with one or two R^{Eb} ;

- 5 R^8 is H, C_{1-3} alkyl, C_{1-3} haloalkyl, or SH;
 each R^{Ea} is, independently halo, cyano, OH, or $NR^{N3E}R^{N3E}$;
 each R^{Eb} is, independently, oxo, =S, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, cyano, C_{1-3} alkoxy, -OH, or $-C(O)NR^{N3E}R^{N3E}$, wherein the C_{1-3} alkyl is optionally substituted by 4- to 6-membered heterocyclyl optionally substituted with C_{1-3} alkyl;
- 10 each R^{N3E} is, independently, H, OH or C_{1-3} alkyl; R^{O3a} is H, C_{1-3} alkyl, or 4- to 6-membered monocyclic heterocyclyl, wherein the C_{1-3} alkyl is optionally substituted by a 4- to 6-membered monocyclic heterocyclyl;
- R^{N3a} and R^{N3b} are each independently H, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, -OH, $-S(O)_2C_{1-3}$ alkyl, or cyclopropyl, wherein the C_{1-3} alkyl is optionally substituted by C_{1-3} alkoxy or
- 15 6-membered heteroaryl.

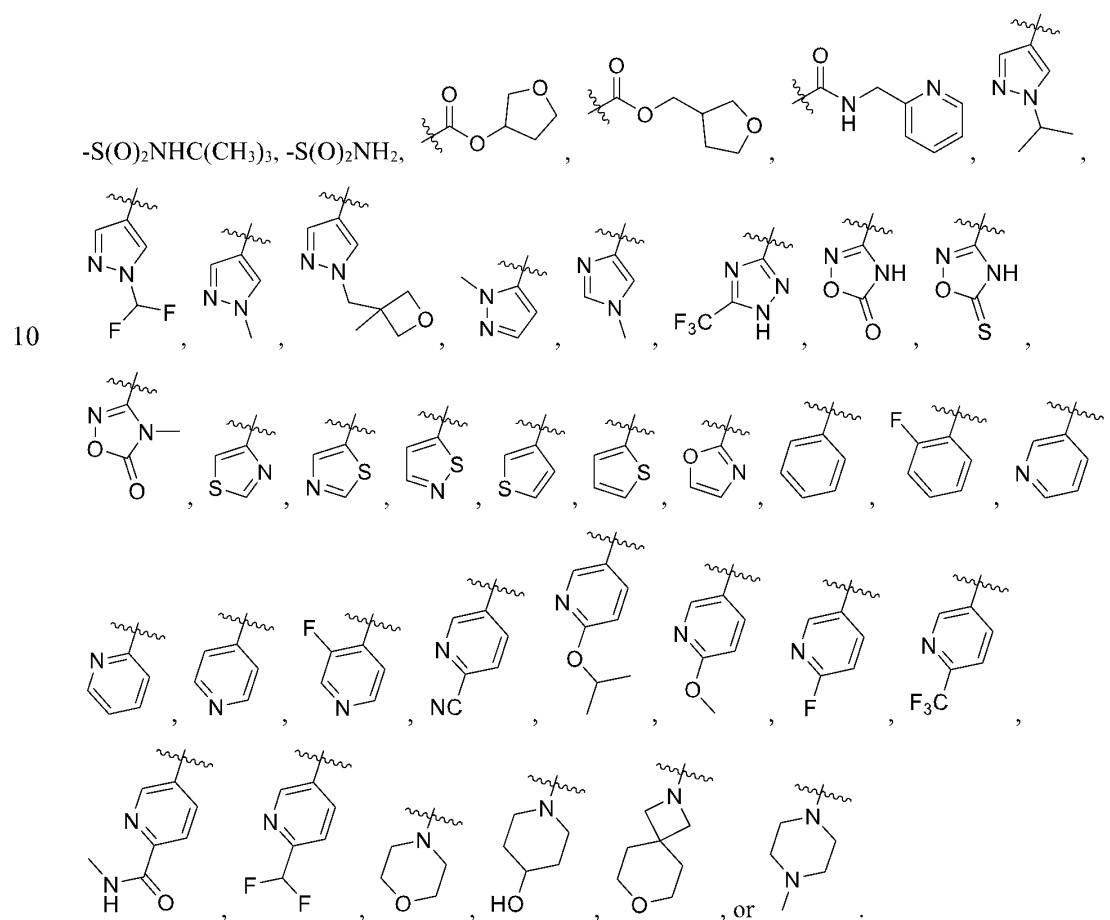
19. The compound of claim 18, or a pharmaceutically acceptable salt thereof, wherein:

- R^E is cyano, C_{1-4} alkyl, $-C(O)R^8$, $-C(NH)NR^{N3E}R^{N3E}$, $-S(O_2)NR^{N3E}R^{N3E}$, $-C(O)OR^{O3a}$, $-C(O)NR^{N3a}R^{N3b}$, phenyl, pyridinyl, pyrazolyl, oxadiazolyl, imidazolyl, thiazolyl, isothiazolyl, triazolyl, oxazolyl, thiophenyl, morpholinyl, piperdinyl, piperizinyl, or 7-oxa-2-azaspiro[3.5]nonanyl, wherein the C_{1-4} alkyl is optionally substituted by one to four R^{Ea} , and the phenyl, pyridinyl, pyrazolyl, oxadiazolyl, imidazolyl, thiazolyl, isothiazolyl, triazolyl, oxazolyl, thiophenyl, morpholinyl, piperdinyl, piperizinyl, and 7-oxa-2-azaspiro[3.5]nonanyl are each optionally substituted with one or two R^{Eb} ;
- 20 R^8 is H, C_{1-3} alkyl, C_{1-3} haloalkyl, or SH;
 each R^{Ea} is, independently halo, cyano, OH, or $NR^{N3E}R^{N3E}$;
 each R^{Eb} is, independently, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, cyano, C_{1-3} alkoxy, -OH, or $-C(O)NR^{N3E}R^{N3E}$, wherein the C_{1-3} alkyl is optionally substituted oxetanyl substituted with C_{1-3} alkyl;
 each R^{N3E} is, independently, H, OH or C_{1-3} alkyl;
- 30 R^{O3a} is H, C_{1-3} alkyl, or tetrahydrofuranlyl, wherein the C_{1-3} alkyl is optionally substituted by tetrahydrofuranlyl;
- R^{N3a} and R^{N3b} are each independently H, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, -OH, $-S(O)_2C_{1-3}$ alkyl, or cyclopropyl, wherein the C_{1-3} alkyl is optionally substituted by C_{1-3} alkoxy or pyridinyl.

35

20. The compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein R^E is $-C(O)OR^{O3a}$ or $-C(O)NR^{N3a}R^{N3b}$; R^{O3a} is H or C_{1-3} alkyl; and R^{N3a} and R^{N3b} are each independently H, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, $-OH$, or cyclopropyl.

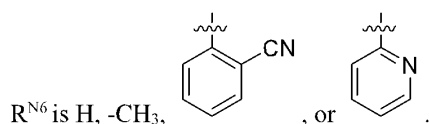
- 5 21. The compound of claim 18 or 19, or a pharmaceutically acceptable salt thereof, wherein R^E is $-C(O)OH$, $-C(O)OCH_3$, $-C(O)OCH_2CH_3$, $-C(O)OC(CH_3)_3$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)NHS(O)_2CH_3$, $-C(O)NHCH_2CH_2OCH_3$, $-C(O)N(CH_3)OCH_3$, cyano, $-C(O)H$, $-C(O)CH_3$, $-C(O)CF_3$, $-C(O)SH$, $-CH_3$, $-C(CH_2CN)_2OH$, $-C(NH)NHOH$, $-CH_2OH$, $-CH(OH)CF_3$,



- 15 22. The compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein R^E is $-C(O)OH$.

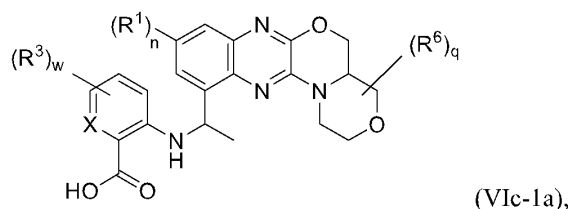
23. The compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, wherein each R^3 is, independently, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, or 6-membered monocyclic heterocyclyl, wherein the 6-membered monocyclic heterocyclyl is optionally substituted with halo.
- 20

24. The compound of claim 23, or a pharmaceutically acceptable salt thereof, wherein each R^3 is, independently, -Br, -Cl, -F, -CH₃, -CF₃, or pyridinyl, wherein the pyridinyl is optionally substituted with -F.
- 5 25. The compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, wherein each R^1 is, independently, CN, C₂₋₄alkenyl, C₂₋₄alkynyl, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxyalkyl, or halo.
26. The compound of claim 25, or a pharmaceutically acceptable salt thereof, wherein each R^1 is, independently, C₁₋₃alkyl, C₁₋₃haloalkyl, or halo, preferably wherein R^1 is -CH₃ or -F.
- 10 27. The compound of any one of claims 1 to 26, or a pharmaceutically acceptable salt thereof, wherein:
- each R^6 is, independently, oxo, halo, cyano, -OH, C₁₋₃alkyl, C₁₋₃alkoxy, -C(O)NH₂, or -NH₂;
- 15 or two R^6 , together with the atoms to which they are attached, form cyclopropyl;
- R^{N6} is H, C₁₋₃alkyl, phenyl, or pyridinyl, wherein the phenyl is optionally substituted with -CN.
28. The compound of claim 27, or a pharmaceutically acceptable salt thereof, wherein:
- 20 each R^6 is, independently, oxo, -Cl, -F, -OH, -CH₃, -OCH₃, -OCH(CH₃)₃, CN, -C(O)NH₂, or -NH₂;



29. The compound of any one of claims 1 to 28, or a pharmaceutically acceptable salt thereof,
- 25 wherein each R^2 is independently halo, C₁₋₃alkyl, or C₁₋₃haloalkyl.

30. A compound of claim 1 or 2, wherein the compound is represented by Formula (VIc-1a):



- 30 or a pharmaceutically acceptable salt thereof, wherein:

X is N or CH;

n is 0 or 1;

R¹ is halo or C₁₋₃alkyl;

w is 0, 1, or 2;

5 each R³ is, independently, halo or C₁₋₃alkyl;

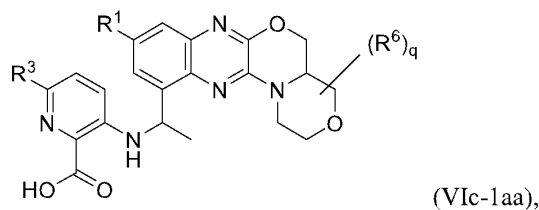
q is 0, 1, or 2; and

each R⁶ is, independently, halo or C₁₋₃alkyl.

31. The compound of claim 30, or a pharmaceutically acceptable salt thereof, wherein R¹ is -F or
10 -CH₃.

32. The compound of claim 30 or 31, or a pharmaceutically acceptable salt thereof, wherein each
R³ is, independently, -F, -Cl, -Br, or -CH₃.

15 33. The compound of any one of claims 30 to 32, wherein the compound is represented by
Formula (VIc-1aa):



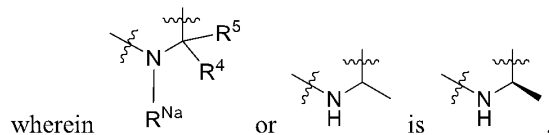
or a pharmaceutically acceptable salt thereof.

20 34. The compound of any one of claims 30 to 33, or a pharmaceutically acceptable salt thereof,
wherein each R⁶ is, independently, C₁₋₃alkyl, preferably wherein each R⁶ is -CH₃.

35. The compound of any one of claims 30 to 33, or a pharmaceutically acceptable salt thereof,
wherein q is 0.

25

36. The compound of any one of claims 1 to 35, or a pharmaceutically acceptable salt thereof,



37. A pharmaceutical composition comprising the compound of any one of claims 1 to 36, a
pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

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38. A method of treating a disease or disorder associated with modulation of the alpha (α) isoform of phosphoinositide 3-kinase (PI3K α), comprising administering to a patient in need thereof a therapeutically effective amount of a compound of any one of claims 1 to 36, a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 37.

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39. The method of claim 38, wherein the PI3K α associated with the disease or disorder has or is characterized by a mutation.

40. The method of claim 38 or 39, wherein the PI3K α associated with the disease or disorder has or is characterized by a H1047R or H1047L mutation.

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41. The method of any one of claims 38 to 40, wherein the disease or disorder is a cancer.

42. The method of claim 41, wherein the cancer is breast cancer (such as hormone receptor positive, HER2 negative breast cancer, HER2 positive breast cancer and triple negative breast cancer), endometrial cancer, uterine cancer, gastric cancer, leukemia, lymphoma, sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, head and neck cancer, brain cancer, or prostate cancer.

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43. The method of claim 41 or 42, wherein the disease or disorder is CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome), or PIK3CA-related overgrowth syndrome (PROS).

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44. A method of inhibiting the alpha (α) isoform of phosphoinositide 3-kinase (PI3K α), comprising administering to a patient in need thereof a therapeutically effective amount of a compound of any one of claims 1 to 36, a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 37.

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45. A method of treating cancer or a disorder, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of any one of claims 1 to 36, a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 37.

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46. The method of claim 45, wherein the cancer is breast cancer (such as hormone receptor positive, HER2 negative breast cancer, HER2 positive breast cancer and triple negative breast cancer), endometrial cancer, uterine cancer, gastric cancer, leukemia, lymphoma, sarcoma, colorectal cancer, lung cancer, ovarian cancer, skin cancer, head and neck cancer, brain cancer, or prostate cancer.

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47. The method of claim 45, wherein the disorder is CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome) or PIK3CA-related overgrowth syndrome (PROS).