KIF MODULATOR COMPOUNDS AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 63/590,326, filed Oct. 13, 2023; U.S. 63/553,744, filed Feb. 15, 2024; and U.S. 63/563,021, filed March 8, 2024, each of which is incorporated herein by reference in its entirety.

BACKGROUND OF INVENTION

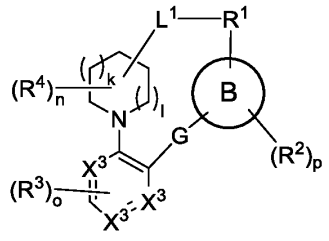
[0002] Kinase-like protein 18A (KIF18A) is a mitotic kinesin motor protein that regulates chromosome positioning during cell division. KIF18A is overexpressed in a subset of human cancers.

BRIEF SUMMARY OF THE INVENTION

[0003] Chromosomal instability (CIN) is a hallmark of cancer that results from errors in chromosome segregation during mitosis. In some instances, targeting of CIN-associated vulnerabilities is a therapeutic strategy for treating cancer. In some instances, KIF18A plays a role in maintaining bipolar spindle integrity, such as promoting viability of CIN cancer cells. In some instances, cancer cells with chromosomal instability depend on KIF18A for cell division and survival, making KIF18A a potential therapeutic target.

[0004] Provided in some embodiments herein are KIF18A modulators (e.g., inhibitors). In some embodiments, the compounds provided herein are useful for treating cancer, such as cancers that depend on KIF18A for cell division and survival.

[0005] Provided in some embodiments herein is a compound having the structure of Formula (I-0), or a pharmaceutically acceptable salt or solvate thereof:



(I-0)

wherein:

each X^3 is independently CH or N;

ring B is a 5- or 6- membered heteroaryl or phenyl;

L^1 is a linker comprising the structure $-L^{1a}-L^{1b}-$;

L^{1a} is a bond, -O-, $-NL^{1a1}-$, -S-, or $-SO_2-$;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene;

G is -(C=O)-NH- or -NH-(C=O)-;

R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-Q-, -NR^{1a}-CO-, -CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a};

R^{1a} is hydrogen, -C(=O)R^{1a1}, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

R^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

Q is optionally substituted C_1-C_6alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene;

each R^2 is independently halogen, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl, or two R^2 are taken together to form an oxo, an optionally substituted C_3-C_8 cycloalkyl, an optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl;

each R^{2a} is independently hydrogen or optionally substituted C_1-C_6 alkyl;

each R^3 is independently halogen, -CN, -$(CH_2)_m$-$N(R^{3a})_2$-, -OR^{3a}, -$N(R^{3a})_2$, -$N(SO_2R^{3b})R^{3a}$, -SR^{3a}, -SO_2R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-R^{3a}, -NH-S(O)(NH)-R^{3a}, -NH-S(O)(NH)-$(CH_2)_m$-R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-OR^{3b}, -NH-S(O)R^{3a}-$(CH_2)_m$-OR^{3b}, -NH-$S(O)_2$-R^{3c}, -$B(R^{3a})_3$, -$P(R^{3a})_3$, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl;

each R^{3a} is independently hydrogen, -C(O)OR^{3b}, optionally substituted C_1-C_6 alkyl, or -$N(R^{3b})_2$;

R^{3b} is hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_2-C_6 alkenyl;

R^{3c} is C_3-C_8 cycloalkyl or 3- to 8- membered heterocycle;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, two or more R^4 combine to form a C_3-C_8 cycloalkyl, or two R^4 combine to form a C_1-C_3 alkylene bridge;

k is 0 to 2;

l is 0 to 2 ;

m is 0 to 6;

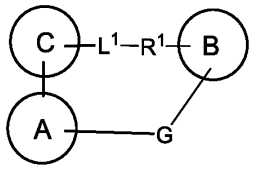
n is 0 to 9;

o is 0 to 4;

p is 0 to 4; and

wherein when any one of variable G, L^1, R^1, R^2, R^3, or R^4 are present, the bond to variable G, L^1, R^1, R^2, R^3 or R^4 replaces a hydrogen on a carbon or nitrogen atom.

[0006] Provided in some embodiments herein is an adduct comprising a KIF18A and a compound of Formula (B), wherein the structure of Formula (B) is:



(B)

wherein:

ring A is optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12-membered heteroaryl;

ring B is optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12-membered heteroaryl;

ring C is optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 5- to 12 membered heterocyclyl, optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12- membered heteroaryl;

G is -(C=O)-NH- or -NH-(C=O)-;

L^1 is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond, -O-, -NL^{1a1}-, -S-, or -SO_2-;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene;

R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-Q-, -NR^{1a}-CO-, -CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a};

R^{1a} is hydrogen, -C(=O)H, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl; and

Q is optionally substituted C_1-C_6alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene.

[0007] Provided in some embodiments herein is a composition comprising a protein and a compound, wherein the protein is KIF18A, the compound is a compound of Formula (B), and the protein and the compound form the adduct described herein.

DETAILED DESCRIPTION OF THE INVENTION

[0008] The KIF18A gene is part of the Kinesin-8 subfamily. KIF18A is a plus-end-directed motor. In some instances, KIF18A influences dynamics at the plus end of kinetochore microtubules, such as controlling chromosomal positioning and spindle tension. In some instances, depletion of KIF18A leads to longer spindles, increased chromosome oscillation at metaphase, and activation of the mitotic spindle assembly checkpoint.

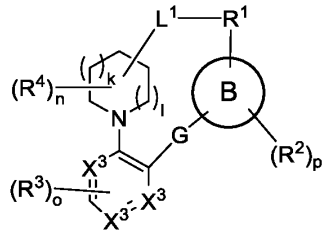
[0009] KIF18A is a potential target for treating cancer, such as cancers where KIF18A is overexpressed and/or that depend on KIF18A for cell division and survival. For example, such cancers include colon, breast, lung, pancreas, prostate, bladder, head, neck, cervix, and ovarian cancers. In some instances, genetic deletion, knockdown, or inhibition of KIF18A affects mitotic spindle apparatus. In some instances, inhibition of KIF18A induces mitotic cell arrest. In some instances, mitotic cell arrest is a vulnerability that can promote cell death in mitosis via apoptosis, mitotic catastrophe, or multipolarity driven lethality or death after mitotic slippage in interphase.

[00010] Provided in some embodiments herein are KIF18A modulators.

Compounds

[00011] The compounds described herein can be useful as KIF18A modulators. In some embodiments, the compounds described herein are KIF18A inhibitors.

[00012] Provided in some embodiments herein is a compound having the structure of Formula (I-1), or a pharmaceutically acceptable salt or solvate thereof:



(I-0)

wherein:

each X^3 is independently CH or N;

ring B is a 5- or 6- membered heteroaryl or phenyl;

L^1 is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond, -O-, -NL^{1a1}-, -S-, or -SO_2-;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene;

G is -(C=O)-NH- or -NH-(C=O)-;

R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-Q-, -NR^{1a}-CO-, -CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a};

R^{1a} is hydrogen, -C(=O)R^{1a1}, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

R^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

Q is optionally substituted C_1-C_6alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene;

each R^2 is independently halogen, -CN, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl, or two R^2 are taken together to form an oxo, an optionally substituted C_3-C_8 cycloalkyl, an optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl;

each R^{2a} is independently hydrogen or optionally substituted C_1-C_6 alkyl;

each R^3 is independently halogen, -CN, -$(CH_2)_m$-$N(R^{3a})_2$-, -OR^{3a}, -$N(R^{3a})_2$, -$N(SO_2R^{3b})R^{3a}$, -SR^{3a}, -SO_2R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-R^{3a}, -NH-S(O)(NH)-R^{3a}, -NH-S(O)(NH)-$(CH_2)_m$-R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-OR^{3b}, -NH-S(O)R^{3a}-$(CH_2)_m$-OR^{3b}, -NH-$S(O)_2$-R^{3c}, -$B(R^{3a})_3$, -$P(R^{3a})_3$, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl;

each R^{3a} is independently hydrogen, -C(O)OR^{3b}, optionally substituted C_1-C_6 alkyl, or -$N(R^{3b})_2$;

R^{3b} is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, or optionally substituted C_3-C_6 cycloalkyl;

R^{3c} is C_3-C_8 cycloalkyl or 3- to 8- membered heterocycle;

each R^4 is independently halogen, -OH, -CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, two

or more R^4 combine to form a C_3-C_8 cycloalkyl, or two R^4 combine to form a C_1-C_3 alkylene bridge; or two R^4 combine to form an oxo;

k is 0 to 2;

l is 0 to 2 ;

m is 1 to 6;

n is 0 to 9;

o is 0 to 4;

p is 0 to 4; and

wherein when any one of variable G, L^1, R^1, R^2, R^3, or R^4 are present, the bond to variable G, L^1, R^1, R^2, R^3 or R^4 replaces a hydrogen on a carbon or nitrogen atom

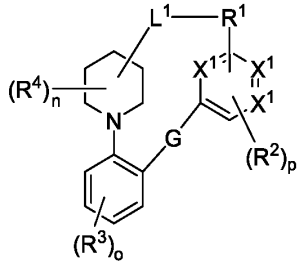
[00013] In some embodiments, ring B is phenyl or a 6-membered heteroaryl. In some embodiments, ring B is a 6-membered heteroaryl. In some embodiments, ring B is triazine, pyridine, pyrimidine, pyridazine, pyrazinone, pyrazine, or imidazopyrizine.

[00014] In some embodiments, k is 0 or 1.

[00015] In some embodiments, l is 0 or 1.

[00016] In some embodiments, each X^3 is CH.

[00017] Provided in some embodiments herein, the compound of Formula (I-1) is a compound having the structure of Formula (I-1a):



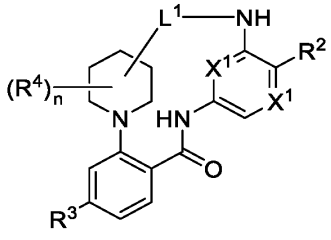
(I-1a)

or a pharmaceutical salt or solvate thereof, wherein: each X^1 is independently CH or N.

[00018] In some embodiments, o is 1; and p is 0 to 1.

[00019] In some embodiments, G is -(C=O)-NH-.

[00020] Provided in some embodiments herein, the compound of Formula (I-1) is a compound having the structure of Formula (II-1):

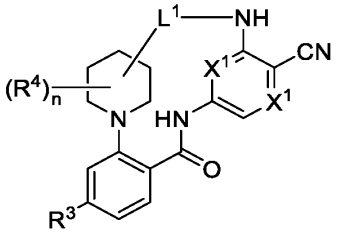


(II-1)

or a pharmaceutical salt or solvate thereof, wherein: each X^1 is independently CH or N; $L^1$is a linker comprising the structure -L^{1a}-L^{1b}-; L^{1a} is a bond or -O-; L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene; and n is 1 or 2.

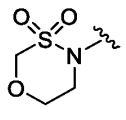
[00021] In some embodiments, R^2 is halogen, -CN, -OR^{2a}, -$N(R^{2a})_2$, optionally substituted C_1-C_6 alkyl, or -$S(O)_2N(R^{2a})_2$.

[00022] Provided in some embodiments herein, the compound of Formula (I-1) is a compound having the structure of Formula (III-1):



(III-1)

or a pharmaceutical salt or solvate thereof, wherein: each X^1 is independently CH or N; $L^1$is a linker comprising the structure -L^{1a}-L^{1b}-; L^{1a} is a bond or -O-; L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene; and n is 1 or 2.

[00023] In some embodiments, R^3 is -$N(R^{3a})_2$, -$N(SO_2R^{3b})R^{3a}$, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-OR^{3b}, -NH-$S(O)_2$-R^{3c}, or optionally substituted 5- to 8- membered heterocycle; each R^{3a} is independently hydrogen, methyl, or ethyl, wherein the ethyl is optionally substituted with one or more substituents selected from methyl and -OH; and R^{3b} is hydrogen, methyl, ethyl, or propyl. In some embodiments, R^3 is independently -$NHSO_2(CH_2)_2OH$, -$NMeSO_2(CH_2)_2OH$, -$NHSO_2CH_2CH_3$, -$NHSO_2$-oxetanyl, -$NMeSO_2CH_3$, -$N(SO_2Me)(CH_2)_2OH$, or 

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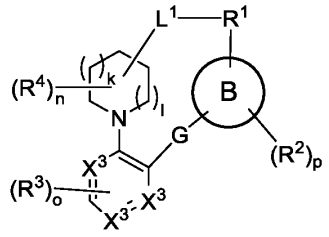
[00024] In some embodiments, each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, two or more R^4 combine to form a C_3-C_8 cycloalkyl, or two R^4 combine to form a C_1-C_3 alkylene bridge.

[00025] In some embodiments, R^{3b} is hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_2-C_6 alkenyl.

[00026] In some embodiments, each R^2 is independently halogen, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-

C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl, or two R^2 are taken together to form an oxo, an optionally substituted C_3-C_8 cycloalkyl, an optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl.

[00027] Provided in some embodiments herein, the compound of Formula (I-1) is a compound having the structure of Formula (I-0), or a pharmaceutically acceptable salt or solvate thereof:



(I-0)

wherein:

each X^3 is independently CH or N;

ring B is a 5- or 6- membered heteroaryl or phenyl;

L^1 is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond, -O-, -NL^{1a1}-, -S-, or -SO_2-;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene;

G is -(C=O)-NH- or -NH-(C=O)-;

R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-Q-, -NR^{1a}-CO-, -CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a};

R^{1a} is hydrogen, -C(=O)R^{1a1}, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

R^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

Q is optionally substituted C_1-C_6alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene;

each R^2 is independently halogen, oxo, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl; or two R^2 are taken together to form an oxo, an optionally substituted C_3-C_8 cycloalkyl, an optionally substituted 5-

to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl;

each R^{2a} is independently hydrogen or optionally substituted C_1-C_6 alkyl;

each R^3 is independently halogen, -CN, $-(CH_2)_m-N(R^{3a})_2-$, $-OR^{3a}$, $-N(R^{3a})_2$, $-N(SO_2R^{3b})R^{3a}$, $-SR^{3a}$, $-SO_2R^{3a}$, $-NR^{3a}-S(O)_2-(CH_2)_m-R^{3a}$, $-NH-S(O)(NH)-R^{3a}$, $-NH-S(O)(NH)-(CH_2)_m-R^{3a}$, $-NR^{3a}-S(O)_2-(CH_2)_m-OR^{3b}$, $-NH-S(O)R^{3a}-(CH_2)_m-OR^{3b}$, $-NH-S(O)_2-R^{3c}$, $-B(R^{3a})_3$, $-P(R^{3a})_3$, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl;

each R^{3a} is independently hydrogen, $-C(O)OR^{3b}$, optionally substituted C_1-C_6 alkyl, or $-N(R^{3b})_2$;

R^{3b} is hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_2-C_6 alkenyl;

R^{3c} is C_3-C_8 cycloalkyl or 3- to 8- membered heterocycle;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, two or more R^4 combine to form a C_3-C_8 cycloalkyl, or two R^4 combine to form a C_1-C_3 alkylene bridge;

k is 0 to 2;

l is 0 to 2;

m is 1 to 6;

n is 0 to 9;

o is 1 to 4;

p is 0 to 4; and

wherein when any one of variable G, L^1, R^1, R^2, R^3, or R^4 are present, the bond to variable G, L^1, R^1, R^2, R^3 or R^4 replaces a hydrogen on a carbon or nitrogen atom.

[00028] In some embodiments, ring B can be any suitable functional group described herein. In some embodiments, ring B is a 5- to 12- membered heteroaryl or C_6-C_{12} aryl. In some embodiments, ring B is a 5- to 12- membered heteroaryl or phenyl. In some embodiments, ring B is a 5- to 8- membered heteroaryl or phenyl. In some embodiments, ring B is a 5- or 6- membered heteroaryl or phenyl. In some embodiments, ring B is a phenyl. In some embodiments, ring B is a 5-membered heteroaryl. In some embodiments, ring B is a 6-membered heteroaryl. In some embodiments, ring B is triazine, pyridine, pyrimidine, pyridazine, pyrazinone, or pyrazine. In some embodiments, ring B is pyridine, pyrimidine,

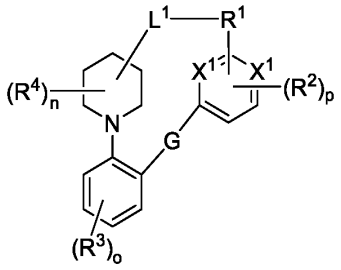
pyridazine, or pyrazine. In some embodiments, ring B is pyridine or pyrimidine. In some embodiments, ring B is pyridine. In some embodiments, ring B is pyrimidine.

[00029] In some embodiments, k can be any suitable integer described herein. In some embodiments, k is 0 to 2. In some embodiments, k is 0 or 1. In some embodiments, k is 0. In some embodiments, k is 1.

[00030] In some embodiments, l can be any suitable integer described herein. In some embodiments, l is 0 to 2. In some embodiments, l is 0 to 1. In some embodiments, l is 0. In some embodiments, l is 1.

[00031] In some embodiments, each X^3 can be any suitable functional group described herein. In some embodiments, each X^3 is independently CH or N. In some embodiments, each X^3 is CH. In some embodiments, each X^3 is N. In some embodiments, one X^3 is N and two X^3 are CH. In some embodiments, one X^3 is CH and two X^3 are N. In some embodiments, at least one X^3 is CH and at least one R^3 substituent replaces the hydrogen atom on the CH.

[00032] Provided in some embodiments herein is a compound having the structure of Formula (I-0a), or a pharmaceutically acceptable salt or solvate thereof:



(I-0a)

wherein:

each X^1 is independently CH or N.

[00033] In some embodiments, X^1 can be any suitable functional group described herein. In some embodiments, each X^1 is CH. In some embodiments, each X^1 is N. In some embodiments, one X^1 is CH, and one X^1 is N.

[00034] In some embodiments, o is any suitable integer described herein. In some embodiments, o is 1 to 4. In some embodiments, o is 1 to 2. In some embodiments, o is 1. In some embodiments, o is 2. In some embodiments, o is 3. In some embodiments, o is 4.

[00035] In some embodiments, p is any suitable integer described herein. In some embodiments, p is 0 to 4. In some embodiments, p is 0 to 2. In some embodiments, p is 0 or 1. In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, p is 2. In some embodiments, p is 3. In some embodiments, p is 4.

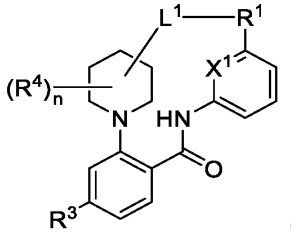
[00036] In some embodiments, G is any suitable functional group described herein. In some embodiments, G is -(C=X)-NH- or -NH-(C=X)- and X is O or NR, wherein R is hydrogen, C_1-C_6 alkyl, or optionally combined with an R^3 to form a heterocyclic ring, or optionally combined with an R^4 to form a heterocyclic ring. In some embodiments, G is -(C=NR)-NH- or -NH-(C=NR)-, R is being combined with an R^3 to form a heterocyclic ring. In some embodiments, G is -(C=O)-NH- or -NH(C=O)-. In some embodiments, G is -(C=O)NH-. In some embodiments, G is -NH(C=O)-.

[00037] In some embodiments, R is optionally combined with an R^3 to form a ring. In some embodiments, R is combined with an R^3 to form a ring (e.g., a heterocycle, such as forming a quinazoline). In some embodiments, R is combined with an R^3 to form a heterocycle. In some embodiments, R is taken together with an R^3 and the atoms to which R and R^3 are attached to form a quinazoline. In some embodiments, R is taken together with an R^3 and the atoms to which R and R^3 are attached to form a pyrimidine.

[00038] In some embodiments, G is -(C=NR)-NH- and R is combined with an R^3 to form a heterocycle. In some embodiments, G is -(C=NR)-NH- and R is taken together with an R^3 and the atoms to which R and R^3 are attached to form a quinazoline.

[00039] In some embodiments, o is 2, G is -(C=NR)-NH- and R is combined with an R^3 to form a heterocycle. In some embodiments, o is 2, G is -(C=NR)-NH- and R is taken together with an R^3 and the atoms to which R and R^3 are attached to form a quinazoline.

[00040] In some embodiments, a compound provided herein has the structure of Formula (II), or a pharmaceutical salt or solvate thereof:



(II)

wherein:

X^1 is CH or N;

$L^1$is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond, -O-, or -NL^{1a1}-;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

L^{1b} is optionally substituted C_1-C_8 alkylene;

R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-C_1-C_6alkylene-, -NR^{1a}-CO-,-CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a};

R^{1a} is hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

R^3 is halogen, -CN, -OR^{3a}, -$N(R^{3a})_2$, -SO_2R^{3a}, or -NH-$S(O)_2$-$(CH_2)_m$-OR^{3b},

each R^{3a} is independently hydrogen or C_1-C_6 alkyl;

R^{3b} is hydrogen or C_1-C_6 alkyl;

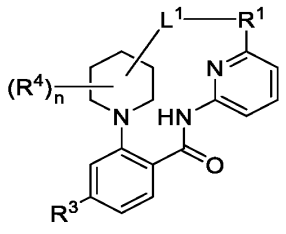
each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, two or more R^4 combine to form a C_3-C_8 cycloalkyl, or two R^4 combine to form a C_1-C_3 alkylene bridge;

m is 1 to 3; and

n is 1 or 2.

[00041] In some embodiments, X^1 can be any suitable functional group described herein. In some embodiments, X^1 is CH or N. In some embodiments, X^1 is CH. In some embodiments, X^1 is N.

[00042] In some embodiments, a compound provided herein has the structure of Formula (III-A), or a pharmaceutical salt or solvate thereof:



(III-A)

wherein:

$L^1$is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond or -O-;

L^{1b} is optionally substituted C_1-C_8 alkylene;

R^1 is a bond, -O-, or -NR^{1a}-, or -NR^{1a}-C_1-C_3 alkylene-;

R^{1a} is hydrogen, -C(=O)H, optionally substituted C_1-C_6 alkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl;

R^3 is halogen, -NH-$S(O)_2$-$(CH_2)_m$-R^{3a}, or -NH-$S(O)_2$-$(CH_2)_m$-OR^{3b},

R^{3a} is C_1-C_6 alkyl;

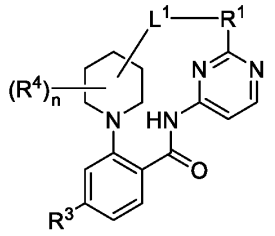
R^{3b} is hydrogen or C_1-C_6 alkyl;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, or two or more R^4 combine to form a C_3-C_8 cycloalkyl;

m is 1 to 3; and

n is 0 to 2.

[00043] In some embodiments, a compound provided herein has the structure of Formula (III-B), or a pharmaceutical salt or solvate thereof:



(III-B)

wherein:

$L^1$is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond or -O-;

L^{1b} is optionally substituted C_1-C_8 alkylene;

R^1 is a bond, -O-, -NR^{1a}-, or -NR^{1a}-C_1-C_3 alkylene-

R^{1a} is hydrogen, -C(=O)H, optionally substituted C_1-C_6 alkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl;

R^3 is halogen, -NH-$S(O)_2$-$(CH_2)_m$-R^{3a}, or -NH-$S(O)_2$-$(CH_2)_m$-OR^{3b},

R^{3a} is C_1-C_6 alkyl;

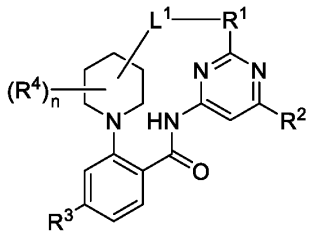
R^{3b} is hydrogen or C_1-C_6 alkyl;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, or two or more R^4 combine to form a C_3-C_8 cycloalkyl;

m is 1 to 3; and

n is 0 to 2.

[00044] In some embodiments, p is 1. In some embodiments, a compound provided herein has the structure of Formula (III-C), or a pharmaceutical salt or solvate thereof:



(III-C)

wherein:

L^1 is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond, -O-, or -NL^{1a1}-;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

L^{1b} is optionally substituted C_1-C_8 alkylene;

R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-C_1-C_6alkylene-, -NR^{1a}-CO-,-CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a};

R^{1a} is hydrogen, -C(=O)H, C_1-C_6 alkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl;

R^2 is halogen, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl;

each R^{2a} is independently hydrogen or C_1-C_6 alkyl;

R^3 is halogen, -CN, -OR^{3a}, -$N(R^{3a})_2$, -SO_2R^{3a}, or -NH-$S(O)_2$-$(CH_2)_m$-OR^{3b},

R^{3a} is hydrogen or C_1-C_6 alkyl;

R^{3b} is hydrogen or C_1-C_6 alkyl;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, or two or more R^4 combine to form a C_3-C_8 cycloalkyl;

m is 1 to 3; and

n is 0, 1, or 2.

[00045] In some embodiments, R^2 is any suitable functional group described herein.

[00046] In some embodiments, each R^2 is independently halogen, -CN, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl, or two R^2 are taken together to form an oxo, an optionally substituted C_3-C_8 cycloalkyl, an optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl. In some embodiments, R^2 is halogen, -CN, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl. In some embodiments, R^2 is halogen, -CN, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl. In some embodiments, R^2 is halogen, -CN, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl. In some embodiments, R^2 is halogen, -CN, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl. In some embodiments, R^2 is halogen, -CN, -OR^{2a}, -$N(R^{2a})_2$, or -$S(O)_2N(R^{2a})_2$. In some embodiments, R^2 is -$S(O)_2N(R^{2a})_2$ or -SO_2-C_1-C_6 alkyl. In some embodiments, R^2 is -$S(O)_2N(R^{2a})_2$.

[00047] In some embodiments, R^2 is halogen, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally

substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl. In some embodiments, R^2 is halogen, $-OR^{2a}$, $-N(R^{2a})_2$, $-S(O)_2N(R^{2a})_2$, $-SO_2$-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl. In some embodiments, R^2 is halogen, $-S(O)_2N(R^{2a})_2$, $-SO_2$-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl. In some embodiments, R^2 is halogen, $-OR^{2a}$, $-N(R^{2a})_2$, $-S(O)_2N(R^{2a})_2$, $-SO_2$-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl. In some embodiments, R^2 is halogen, $-OR^{2a}$, $-N(R^{2a})_2$, or $-S(O)_2N(R^{2a})_2$. In some embodiments, R^2 is $-S(O)_2N(R^{2a})_2$ or $-SO_2$-C_1-C_6 alkyl. In some embodiments, R^2 is $-S(O)_2N(R^{2a})_2$.

[00048] In some embodiments, R^2 is halogen. In some embodiments, R^2 is -CN. In some embodiments, R^2 is $-OR^{2a}$. In some embodiments, R^2 is $-N(R^{2a})_2$. In some embodiments, R^2 is $-S(O)_2N(R^{2a})_2$. In some embodiments, R^2 is $-SO_2$-C_1-C_6 alkyl. In some embodiments, R^2 is optionally substituted C_1-C_6 alkyl. In some embodiments, R^2 is optionally substituted C_3-C_8 cycloalkyl. In some embodiments, R^2 is optionally substituted 5- to 8- membered heterocycle. In some embodiments, R^2 is optionally substituted 5- to 8- membered heteroaryl.

[00049] In some embodiments, each R^{2a} is any suitable functional group described herein. In some embodiments, each R^{2a} is independently hydrogen or optionally substituted C_1-C_6 alkyl. In some embodiments, each R^{2a} is independently optionally substituted C_1-C_4 alkyl. In some embodiments, each R^{2a} is independently methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, or tert-butyl. In some embodiments, each R^{2a} is methyl. In some embodiments, one R^{2a} is hydrogen and the other R^{2a} is optionally substituted C_1-C_6 alkyl. In some embodiments, R^2 is $-S(O)_2N(R^{2a})_2$ and each R^{2a} is hydrogen. In some embodiments, R^2 is $-S(O)_2N(R^{2a})_2$ and each R^{2a} is independently optionally substituted C_1-C_6 alkyl. In some embodiments, R^2 is $-S(O)_2N(R^{2a})_2$ and each R^{2a} is methyl. In some embodiments, R^2 is $S(O)_2NHC(CH_3)_3$.

[00050] In some embodiments, R^2 is a 5- to 8- membered heteroaryl. In some embodiments, R^2 is a 5- to 6- membered heteroaryl. In some embodiments, R^2 is a 5- membered heteroaryl. In some embodiments, R^2 is a 6- membered heteroaryl. In some embodiments, R^2 is a furanyl, furanonyl, isothiazolyl, imidazolyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl. In some embodiments, R^2 is a pyrazolyl.

[00051] In some embodiments, L^1 can be any suitable linker structure in any combination of variables L^{1a} and L^{1b} described herein. In some embodiments, L^1 is a linker comprising the structure $-L^{1a}$-L^{1b}-.

[00052] In some embodiments, L^{1a} can be any suitable functional group described herein. In some embodiments, L^{1a} is a bond, -O-, -NL^{1a1}-, -S-, or -SO_2-. In some embodiments, L^{1a} is a bond, -O-, or -NL^{1a1}-. In some embodiments, L^{1a} is a bond or -O-. In some embodiments, L^{1a} is a bond. In some embodiments, L^{1a} is -O-. In some embodiments, L^{1a} is -NL^{1a1}-. In some embodiments, L^{1a} is -S-. In some embodiments, L^{1a} is -SO_2-.

[00053] In some embodiments, L^{1a1} is any suitable functional group described herein. In some embodiments, L^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, L^{1a1} is hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, L^{1a1} is hydrogen, C_1-C_6 alkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl. In some embodiments, L^{1a1} is hydrogen or C_1-C_6 alkyl. In some embodiments, L^{1a1} is hydrogen. In some embodiments, L^{1a1} is C_1-C_6 alkyl. In some embodiments, L^{1a1} is methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, or tert-butyl. In some embodiments, L^{1a1} is methyl.

[00054] In some embodiments, L^{1a} is -NL^{1a1}- and L^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, L^{1a} is -NL^{1a1}- and L^{1a1} is hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, L^{1a} is -NL^{1a1}- and L^{1a1} is hydrogen or C_1-C_6 alkyl. In some embodiments, L^{1a} is -NL^{1a1}- and L^{1a1} is hydrogen. In some embodiments, L^{1a} is -NL^{1a1}- and L^{1a1} is C_1-C_6 alkyl. In some embodiments, L^{1a} is -NL^{1a1}- and L^{1a1} is methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, or tert-butyl. In some embodiments, L^{1a} is -NL^{1a1}- and L^{1a1} is methyl.

[00055] In some embodiments, L^{1b} is any suitable functional group described herein. In some embodiments, L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene. In some embodiments, L^{1b} is optionally substituted C_1-C_6 alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene. In some embodiments, L^{1b} is optionally substituted C_1-C_6 alkylene. In some embodiments, L^{1b} is optionally substituted C_1-C_4 alkylene. L^{1b} can be substituted with any suitable substituent described herein. In some embodiments, L^{1b} is C_1-C_4 alkylene substituted with oxo, C_3-C_6 cycloalkyl, or 3- to 6- membered heterocyclyl. In some embodiments, L^{1b} is C_1-C_4 alkylene substituted with oxo or C_3-C_6 cycloalkyl. In some embodiments, L^{1b} is C_1-C_4 alkylene substituted with oxo, cyclopropyl, or cyclobutyl. In some embodiments, L^{1b} is C_1-C_4 alkylene substituted with oxo. In some embodiments, L^{1b} is C_1-C_4 alkylene substituted with cyclopropyl. In some embodiments, L^{1b} is methylene, ethylene, propylene, butylene, or pentylene. In some embodiments, L^{1b} is methylene. In some embodiments, L^{1b} is ethylene. In

some embodiments, L^{1b} is propylene. In some embodiments, L^{1b} is butylene. In some embodiments, L^{1b} is pentylene.

[00056] In some embodiments, L^{1a} is a bond, -O-, or -NL^{1a1}- and L^{1b} is optionally substituted C_1-C_6 alkylene. In some embodiments, L^{1a} is a bond and L^{1b} is optionally substituted C_1-C_6 alkylene. In some embodiments, L^{1a} is -O- and L^{1b} is optionally substituted C_1-C_6 alkylene. In some embodiments, L^{1a} is -NL^{1a1}-, L^{1a1} is hydrogen or C_1-C_6 alkyl, and L^{1b} is optionally substituted C_1-C_6 alkylene.

[00057] In some embodiments, L^1 is -O(optionally substituted alkylene)-, -(optionally substituted alkylene)O-, or optionally substituted alkylene. In some embodiments, L^1 is -O(unsubstituted alkylene)-, -(unsubstituted alkylene)O-, unsubstituted alkylene, or substituted alkylene. In some embodiments, L^1 is -O(unsubstituted alkylene)-. In some embodiments, L^1 is -(unsubstituted alkylene)O-. In some embodiments, L^1 is unsubstituted alkylene. In some embodiments, L^1 is substituted alkylene.

[00058] In some embodiments, L^1 is $–(CH_2)_4–$, $–(CH_2)_3–$, $–(CH_2)_2–$, $–CH_2–$ –cyclopropyl-$(CH_2)_3–$, –cyclopropyl-$(CH_2)_2–$, $–O(CH_2)_3–$, $–O(CH_2)_2–$, or $–O(CH_2)–$. In some embodiments, L^1 is $–(CH_2)_4–$, –cyclopropyl-$(CH_2)_3–$, $–(CH_2)_3–$, $–(CH_2)_2CO–$, $–(CH_2)_2–$, $–O(CH_2)_2–$, or $–CH_2–$.

[00059] In some embodiments, R^1 is any suitable functional group described herein. In some embodiments, R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-Q-, -NR^{1a}-CO-, -CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a}. In some embodiments, R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-C_1-C_6alkylene-, -NR^{1a}-CO-,-CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a}. In some embodiments, R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-Q-, -NR^{1a}-CO-, -CO-NR^{1a}-, -NR^{1a}-SO_2-, or -SO_2-NR^{1a}. In some embodiments, R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-C_1-C_6alkylene-, -NR^{1a}-CO-, -CO-NR^{1a}-, -NR^{1a}-SO_2-, or -SO_2-NR^{1a}. In some embodiments, R^1 is a bond. In some embodiments, R^1 is -O-. In some embodiments, R^1 is -NR^{1a}-Q-. In some embodiments, R^1 is -O-. In some embodiments, R^1 is -NR^{1a}-. In some embodiments, R^1 is -NR^{1a}-CO-. In some embodiments, R^1 is -CO-NR^{1a}-. In some embodiments, R^1 is -NR^{1a}-SO_2-. In some embodiments, R^1 is -SO_2-NR^{1a}.

[00060] In some embodiments, R^{1a} is hydrogen, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, R^{1a} is hydrogen, C_1-C_6 alkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl. In some embodiments, R^{1a} is hydrogen, C_1-C_3 alkyl, C_1-C_3 alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, R^{1a} is hydrogen. In some embodiments, R^{1a} is optionally substituted C_1-C_6 alkyl. In some embodiments, R^{1a} is methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, or tert-butyl. In

some embodiments, R^{1a} is methyl. In some embodiments, R^{1a} is substituted C_1-C_6 alkyl. In some embodiments, R^{1a} is C_1-C_6alkylene-C_3-C_6 cycloalkyl. In some embodiments, R^{1a} is methylene-C_3-C_6 cycloalkyl. In some embodiments, R^{1a} is methylene-cyclopropyl. In some embodiments, R^{1a} is -SO_2-C_1-C_6 alkyl. In some embodiments, R^{1a} is -SO_2-Me.

[00061] In some embodiments, R^1 is -NR^{1a}-Q- and R^{1a} is hydrogen, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, R^1 is a -NR^{1a}-Q- and R^{1a} is hydrogen. In some embodiments, R^1 is -NR^{1a}-Q- and R^{1a} is optionally substituted C_1-C_6 alkyl. In some embodiments, R^1 is -NR^{1a}-Q- and R^{1a} is C_1-C_6alkylene-C_3-C_6 cycloalkyl. In some embodiments, R^1 is -NR^{1a}-Q- and R^{1a} is -SO_2-C_1-C_6 alkyl.

[00062] In some embodiments, Q is optionally substituted C_1-C_6alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene. In some embodiments, Q is optionally substituted C_1-C_6alkylene. In some embodiments, Q is methylene, ethylene, propylene, or butylene. In some embodiments, Q is methylene.

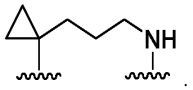
[00063] In some embodiments, R^1 is -NR^{1a}-Q-, Q is optionally substituted C_1-C_6alkylene, and R^{1a} is hydrogen, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, R^1 is -NR^{1a}-Q-, Q is optionally substituted C_1-C_6alkylene, and R^{1a} is hydrogen. In some embodiments, R^1 is -NR^{1a}-Q-, Q is optionally substituted C_1-C_6alkylene, and R^{1a} is optionally substituted C_1-C_6 alkyl. In some embodiments, R^1 is -NR^{1a}-Q-, Q is optionally substituted C_1-C_6alkylene, and R^{1a} is C_1-C_6alkylene-C_3-C_6 cycloalkyl. In some embodiments, R^1 is -NR^{1a}-Q-, Q is optionally substituted C_1-C_6alkylene, and R^{1a} is -SO_2-C_1-C_6 alkyl.

[00064] In some embodiments, R^1 is -NR^{1a}- and R^{1a} is hydrogen, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, R^1 is -NR^{1a}- and R^{1a} is hydrogen. In some embodiments, R^1 is -NR^{1a}- and R^{1a} is optionally substituted C_1-C_6 alkyl (e.g., methyl). In some embodiments, R^1 is -NR^{1a}- and R^{1a} is C_1-C_6alkylene-C_3-C_6 cycloalkyl (e.g., methylene-cyclopropyl). In some embodiments, R^1 is -NR^{1a}- and R^{1a} is -SO_2-C_1-C_6 alkyl (e.g., methyl).

[00065] In some embodiments, R^1 is -NR^{1a}-CO- or -CO-NR^{1a}- and R^{1a} is hydrogen, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, R^1 is -NR^{1a}-CO- or -CO-NR^{1a}- and R^{1a} is hydrogen. In some embodiments, R^1 is -NR^{1a}-CO- or -CO-NR^{1a}- and R^{1a} is optionally substituted C_1-C_6 alkyl (e.g., methyl). In some embodiments, R^1 is -NR^{1a}-CO- or -CO-NR^{1a}- and R^{1a} is C_1-C_6alkylene-C_3-C_6 cycloalkyl (e.g., methylene-cyclopropyl). In some embodiments, R^1 is -NR^{1a}-CO- or -CO-NR^{1a}- and R^{1a} is -SO_2-C_1-C_6 alkyl (e.g., methyl).

[00066] In some embodiments, R^1 is -NR^{1a}-SO_2- or -SO_2-NR^{1a} and R^{1a} is hydrogen, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, R^1 is -NR^{1a}-SO_2- or -SO_2-NR^{1a} and R^{1a} is hydrogen. In some embodiments, R^1 is -NR^{1a}-SO_2- or -SO_2-NR^{1a} and R^{1a} is optionally substituted C_1-C_6 alkyl (e.g., methyl). In some embodiments, R^1 is -NR^{1a}-SO_2- or -SO_2-NR^{1a} and R^{1a} is C_1-C_6alkylene-C_3-C_6 cycloalkyl (e.g., methylene-cyclopropyl). In some embodiments, R^1 is -NR^{1a}-SO_2- or -SO_2-NR^{1a} and R^{1a} is -SO_2-C_1-C_6 alkyl (e.g., methyl).

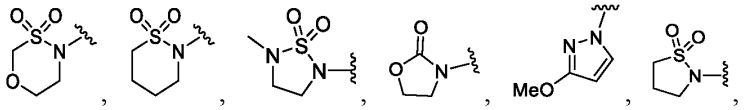
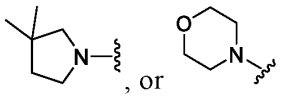
[00067] In some embodiments, an L^1 described herein is attached to R^1 to form -L^1-R^1-, such as tethering two parts of a compound described herein. In some embodiments, L^1R^1 can be any suitable combination of the L^1 and R^1 functional groups described herein. In some embodiments, L^1-R^1 is –$(CH_2)_4NH$–, –cyclopropyl-$(CH_2)_3NH$–, –$(CH_2)_3NH$–, –$(CH_2)_3NCH_3$–, –$(CH_2)_3$N-(CH_2-cyclopropyl)–, –$(CH_2)_2NH$–, –$(CH_2)_3$–, –$(CH_2)_3$–, –$(CH_2)_2$–, –CH_2–, –$O(CH_2)_3$–, –$O(CH_2)_2$–, –$O(CH_2)_2O$–, –$O(CH_2)_2NH$–, –$(CH_2)_3NSO_2$–, –$(CH_2)_2N(SO_2Me)CH_2$–, -–$(CH_2)_2N(Me)CH_2$–, –$(CH_2)_2N(CH_2$-cyclopropyl)CH_2–, –$(CH_2)_2NHCH_2$–, –$(CH_2)_2CONH$–, –$(CH_2)_2CONMe$–, –$(CH_2)_2CON(CH_2$-cyclopropyl)–, –$(CH_2)_2SO_2NH$–, –$(CH_2)_2NHCO$–, –$(CH_2)_2N(Me)CO$–, –$(CH_2)_2N(CH_2$-cyclopropyl)CO–, or –$(CH_2)_2NHSO_2$–. In some embodiments, L^1-R^1 is –$(CH_2)_4NH$–, –cyclopropyl-$(CH_2)_3NH$–, –$(CH_2)_3NH$–, –$(CH_2)_3NCH_3$–, –$(CH_2)_3$N-(CH_2-cyclopropyl)–, –$(CH_2)_2NH$–, –$O(CH_2)_2NH$–, –$(CH_2)_3NSO_2$–, –$(CH_2)_2N(SO_2Me)CH_2$–, -–$(CH_2)_2N(Me)CH_2$–, –$(CH_2)_2N(CH_2$-cyclopropyl)CH_2–, –$(CH_2)_2NHCH_2$–, –$(CH_2)_2CONH$–, –$(CH_2)_2CONMe$–, –$(CH_2)_2CON(CH_2$-cyclopropyl)–, –$(CH_2)_2NHCO$–, –$(CH_2)_2N(Me)CO$–, or –$(CH_2)_2N(CH_2$-cyclopropyl)CO–. In some embodiments, L^1-R^1 is –$(CH_2)_4NH$–, –cyclopropyl-$(CH_2)_3NH$–, –$(CH_2)_3NH$–, –$(CH_2)_3NCH_3$–, –$(CH_2)_3$N-(CH_2-cyclopropyl)–, –$(CH_2)_2NH$–, –$O(CH_2)_2NH$–, –$(CH_2)_2N(Me)CH_2$–, –$(CH_2)_2N(CH_2$-cyclopropyl)CH_2–, or –$(CH_2)_2NHCH_2$–. In some embodiments, L^1-R^1 is –$(CH_2)_4NH$– or –$(CH_2)_3NH$–. In some embodiments, L^1-R^1 is:



[00068] In some embodiments, each R^3 is any suitable functional group described herein. In some embodiments each R^3 is independently halogen, -CN, -$(CH_2)_m$-$N(R^{3a})_2$-, -OR^{3a}, -$N(R^{3a})_2$, -$N(SO_2R^{3b})R^{3a}$, -SR^{3a}, -SO_2R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-R^{3a}, -NH-S(O)(NH)-R^{3a}, -NH-S(O)(NH)-$(CH_2)_m$-R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-OR^{3b}, -NH-S(O)R^{3a}-$(CH_2)_m$-OR^{3b}, -NH-$S(O)_2$-R^{3c}, -$B(R^{3a})_3$, -$P(R^{3a})_3$, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8-membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl. In some embodiments, each R^3 is independently -$(CH_2)_m$-$N(R^{3a})_2$-, -OR^{3a}, -$N(R^{3a})_2$, -$N(SO_2R^{3b})R^{3a}$, -

SR^{3a}, $-SO_2R^{3a}$, $-NR^{3a}-S(O)_2-(CH_2)_m-R^{3a}$, $-NH-S(O)(NH)-R^{3a}$, $-NH-S(O)(NH)-(CH_2)_m-R^{3a}$, $-NR^{3a}-S(O)_2-(CH_2)_m-OR^{3b}$, $-NH-S(O)R^{3a}-(CH_2)_m-OR^{3b}$, $-NH-S(O)_2-R^{3c}$, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8-membered heterocycle. In some embodiments, In some embodiments, each R^3 is independently $-NR^{3a}S(O)_2-(CH_2)_m-OR^{3b}$ or $-NR^{3a}-S(O)_2-(CH_2)_m-R^{3a}$.

[00069] In some embodiments, each R^3 is independently halogen, -CN, $-OR^{3a}$, $-N(R^{3a})_2$, $-SR^{3a}$, $-SO_2R^{3a}$, $-NH-S(O)(NH)-R^{3a}$, $-NH-S(O)_2-(CH_2)_m-R^{3a}$, $-NH-S(O)_2-(CH_2)_m-OR^{3b}$, $-B(R^{3a})_3$, or $-P(R^{3a})_3$. In some embodiments, each R^3 is independently halogen, -CN, $-OR^{3a}$, $-N(R^{3a})_2$, $-SO_2R^{3a}$, or $-NH-S(O)_2-(CH_2)_m-OR^{3b}$. In some embodiments, each R^3 is $-SO_2R^{3a}$ or $-NH-S(O)_2-(CH_2)_m-OR^{3b}$. In some embodiments, each R^3 is $-SO_2R^{3a}$. In some embodiments, each R^3 is independently $-NH-S(O)_2-(CH_2)_m-OR^{3b}$. In some embodiments, an R^3 is a point of attachment to G.

[00070] In some embodiments, wherein R^3 is optionally substituted 5- to 8- membered heterocycle, which is optionally substituted with one or more substituents selected from oxo, methyl, ethyl, propyl, methoxy, or ethoxy. In some embodiments, wherein R^3 is optionally substituted 5- to 8- membered heterocycle, which is optionally substituted with one or more substituents selected from oxo, methyl, and methoxy. In some embodiments, the 5- to 8-membered heterocycle is  ,  , or .

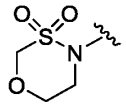
[00071] In some embodiments, each R^{3a} is independently hydrogen, $-C(O)OR^{3b}$, optionally substituted C_1-C_6 alkyl, or $-N(R^{3b})_2$. In some embodiments, each R^{3a} is independently hydrogen or C_1-C_6 alkyl. In some embodiments, each R^{3a} is independently hydrogen methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, or tert-butyl. In some embodiments, each R^{3a} is independently hydrogen, methyl, or ethyl, wherein the ethyl is optionally substituted with one or more substituents selected from methyl and -OH. In some embodiments, each R^{3a} is hydrogen. In some embodiments, each R^{3a} is independently C_1-C_6 alkyl. In some embodiments, R^{3a} is methyl.

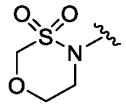
[00072] In some embodiments, R^{3b} is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, or optionally substituted C_3-C_6 cycloalkyl. In some embodiments, R^{3b} is hydrogen or C_1-C_6 alkyl. In some embodiments, R^{3b} is hydrogen. In some embodiments, R^{3b} is C_1-C_6 alkyl. In some embodiments, R^{3b} is hydrogen, methyl, ethyl, or

propyl. In some embodiments, R^{3b} is methyl. In some embodiments, R^{3b} is ethyl. In some embodiments, R^{3b} is n-propyl or isopropyl. In some embodiments, R^{3b} is optionally substituted C_3-C_6 cycloalkyl. In some embodiments, R^{3b} is optionally substituted cyclopropyl. In some embodiments, R^{3b} is cyclopropyl optionally substituted with C_1-C_6 alkyl or C_1-C_6 hydroxyalkyl.

[00073] In some embodiments, R^{3b} is hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_2-C_6 alkenyl. In some embodiments, R^{3b} is hydrogen or C_1-C_6 alkyl. In some embodiments, R^{3b} is hydrogen. In some embodiments, R^{3b} is C_1-C_6 alkyl. In some embodiments, R^{3b} is hydrogen, methyl, ethyl, or propyl. In some embodiments, R^{3b} is methyl. In some embodiments, R^{3b} is ethyl. In some embodiments, R^{3b} is n-propyl or isopropyl.

[00074] In some embodiments, R^{3c} is C_3-C_8 cycloalkyl or 3- to 8- membered heterocycle. In some embodiments, R^{3c} is C_3-C_8 cycloalkyl. In some embodiments, R^{3c} is 3- to 8- membered heterocycle. In some embodiments, 4- to 6- membered heterocycle. In some embodiments, R^{3c} is oxetanyl, azetidinyl, or thietanyl. In some embodiments, R^{3c} is oxetanyl or azetidinyl. In some embodiments, R^{3c} is oxetanyl.

[00075] In some embodiments, each R^3 is independently -$NHSO_2(CH_2)_2OH$, -$NHSO_2C(CH_3)_2CH_2OH$, -$NHSO_2C$(cyclopropyl)CH_2OH, -$NHSO_2CH(CH_3)CH_2OH$, -$NMeSO_2(CH_2)_2OH$, -$NHSO_2CH_2CH_3$, -$NHSO_2CHCH_2$, -$NHSO_2$-oxetanyl, -$NMeSO_2CH_3$, -$N(SO_2Me)(CH_2)_2OH$, or  .

[00076] In some embodiments, each R^3 is independently -$NHSO_2(CH_2)_2OH$, -$NMeSO_2(CH_2)_2OH$, -$NHSO_2CH_2CH_3$, -$NHSO_2$-oxetanyl, -$NMeSO_2CH_3$, -$N(SO_2Me)(CH_2)_2OH$, or  .

[00077] In some embodiments, R^3 is -SO_2R^{3a} and R^{3b} is methyl. In some embodiments, R^3 is -NH-$S(O)_2$-$(CH_2)_m$-OR^{3b} and R^{3b} is hydrogen. In some embodiments, each R^3 is independently -$NHS(O)_2$-$(CH_2)_2$-OH.

[00078] In some embodiments, m is 1 to 6. In some embodiments, m is 1 to 4. In some embodiments, m is 1 to 3. In some embodiments, m is 1 to 2. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3. In some embodiments, m is 4.

[00079] In some embodiments, o is any suitable integer described herein. In some embodiments, o is 1 to 4. In some embodiments, o is 1 to 3. In some embodiments, o is 1 to 2.

In some embodiments, o is 1. In some embodiments, o is 2. In some embodiments, o is 3. In some embodiments, o is 4.

[00080] In some embodiments, o is 1 and R^3 is $-SO_2R^{3a}$ or $-NH-S(O)_2-(CH_2)_m-OR^{3b}$.

[00081] In some embodiments, n is any suitable integer described herein. In some embodiments, n is 0 to 9. In some embodiments, n is 1 to 5. In some embodiments, n is 1 to 3. In some embodiments, n is 1 to 2. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4. In some embodiments, n is 5.

[00082] In some embodiments, R^4 is any suitable functional group described herein.

[00083] In some embodiments, each R^4 is independently halogen, -OH, -CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, two or more R^4 combine to form a C_3-C_8 cycloalkyl, or two R^4 combine to form a C_1-C_3 alkylene bridge, or two R^4 combine to form an oxo. In some embodiments, two R^4 combine to form a C_3-C_8 cycloalkyl. In some embodiments, two R^4 are on the same carbon atom. In some embodiments, the two R^4 groups combine to form a cyclopropyl. In some embodiments, the two R^4 groups combine to form a butyl. In some embodiments, two R^4 are on different carbon atoms. In some embodiments, two R^4 groups combine to form a (1R,5S)-8-azabicyclo[3.2.1]octane. In some embodiments, two R^4 combine to form a C_1-C_3 alkylene bridge. In some embodiments, n is 2 and two R^4 combine to form a C_3-C_8 cycloalkyl. In some embodiments, two R^4 combine to form an oxo.

[00084] In some embodiments, each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, two or more R^4 combine to form a C_3-C_8 cycloalkyl, or two R^4 combine to form a C_1-C_3 alkylene bridge. In some embodiments, two R^4 combine to form a C_3-C_8 cycloalkyl. In some embodiments, two R^4 are on the same carbon atom. In some embodiments, the two R^4 groups combine to form a cyclopropyl. In some embodiments, the two R^4 groups combine to form a butyl. In some embodiments, two R^4 are on different carbon atoms. In some embodiments, two R^4 groups combine to form a (1R,5S)-8-azabicyclo[3.2.1]octane. In some embodiments, two R^4 combine to form a C_1-C_3 alkylene bridge. In some embodiments, n is 2 and two R^4 combine to form a C_3-C_8 cycloalkyl.

[00085] In some embodiments of a compound of Formula (I-0) provided herein,

each X^3 is CH;

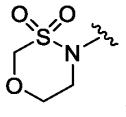
ring B is triazine, pyridine, pyrimidine, pyridazine, pyrazinone, pyrazine, or imidazopyrizine;

L^{1a} is a bond or -O-;

G is -(C=O)-NH-;

R^1 is $-NR^{1a}-$;

R^{1a} is hydrogen;

each R^3 is independently $-NHSO_2(CH_2)_2OH$, $-NHSO_2C(CH_3)_2CH_2OH$, $-NHSO_2C(cyclopropyl)CH_2OH$, $-NHSO_2CH(CH_3)CH_2OH$, $-NMeSO_2(CH_2)_2OH$, $-NHSO_2CH_2CH_3$, $-NHSO_2CHCH_2$, -$NHSO_2$-oxetanyl, $-NMeSO_2CH_3$, $-N(SO_2Me)(CH_2)_2OH$, or  ;

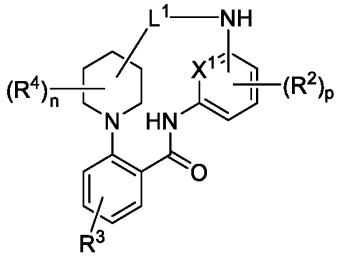
k is 0 or 1;

l is 0 or 1;

o is 1; and

p is 0 or 1.

[00086] That is, in some embodiments of a compound of Formula (I-0) provided herein, the compound has the structure of Formula (I-a):



(I-a),

or a pharmaceutical salt or solvate thereof, wherein:

X^1 is CH or N;

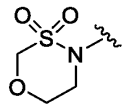
L^1 is a linker comprising the structure $-L^{1a}-L^{1b}-$;

L^{1a} is a bond or -O-;

L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene;

each R^2 is independently halogen, $-OR^{2a}$, $-N(R^{2a})_2$, $-S(O)_2N(R^{2a})_2$, $-SO_2$-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl, or two R^2 are taken together to form an oxo, an optionally substituted C_3-C_8 cycloalkyl, an optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl;

each R^{2a} is independently hydrogen or optionally substituted C_1-C_6 alkyl;

each R^3 is independently -$NHSO_2(CH_2)_2OH$, -$NHSO_2C(CH_3)_2CH_2OH$, -$NHSO_2C$(cyclopropyl)CH_2OH, -$NHSO_2CH(CH_3)CH_2OH$, -$NMeSO_2(CH_2)_2OH$, -$NHSO_2CH_2CH_3$, -$NHSO_2CHCH_2$, -$NHSO_2$-oxetanyl, -$NMeSO_2CH_3$, -$N(SO_2Me)(CH_2)_2OH$, or  ;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, two or more R^4 combine to form a C_3-C_8 cycloalkyl, or two R^4 combine to form a C_1-C_3 alkylene bridge;

k is 0 or 1;

l is 0 or 1;

n is 0 to 9;

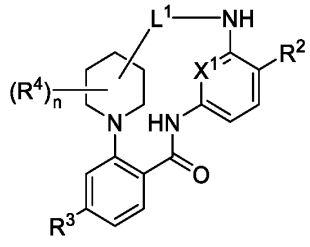
o is 1;

p is 0 or 1; and

wherein when any one of variable G, L^1, R^1, R^2, R^3, or R^4 are present, the bond to variable G, L^1, R^1, R^2, R^3 or R^4 replaces a hydrogen on a carbon or nitrogen atom.

[00087] In some embodiments, p is 0. In some embodiments, p is 1.

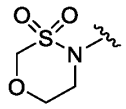
[00088] Accordingly, in some embodiments, the compound of Formula (I-0) has the structure of Formula (I-a):


(II-a),

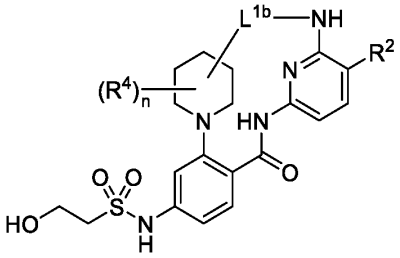
or a pharmaceutical salt or solvate thereof, wherein:

X^1 is CH or N.

[00089] In some embodiments, L^{1a} is a bond. In some embodiments, L^{1a} is -O-.

[00090] In some embodiments, R^3 is -$NHSO_2(CH_2)_2OH$, -$NMeSO_2(CH_2)_2OH$, -$NHSO_2CH_2CH_3$, -$NHSO_2$-oxetanyl, -$NMeSO_2CH_3$, -$N(SO_2Me)(CH_2)_2OH$, or  . In some embodiments, R^3 is -$NHS(O)_2$-$(CH_2)_2$-OH.

[00091] Accordingly, in some embodiments, the compound of Formula (I-0) has the structure of Formula (V), or a pharmaceutical salt or solvate thereof:



(V).

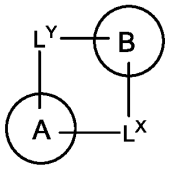
[00092] In some embodiments, R^2 is a 5- to 8- membered heteroaryl. In some embodiments, R^2 is a 5- to 6- membered heteroaryl. In some embodiments, R^2 is a 5- membered heteroaryl. In some embodiments, R^2 is a 6- membered heteroaryl. In some embodiments, R^2 is a furanyl, furanonyl, isothiazolyl, imidazolyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl. In some embodiments, R^2 is a pyrazolyl.

[00093] In some embodiments, L^{1b} is optionally substituted C_1-C_6 alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene. In some embodiments, L^{1b} is optionally substituted C_1-C_6 alkylene. In some embodiments, L^{1b} is optionally substituted C_2-C_6 alkenylene. In some embodiments, L^{1b} is optionally substituted C_2-C_6 alkynylene.

[00094] In some embodiments, each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, or optionally substituted C_1-C_6 alkoxy.

[00095] In some embodiments, n is 0 to 2. In some embodiments, n is 0.

[00096] Provided herein is a compound having the structure of Formula (A), or a pharmaceutically acceptable salt or solvate thereof:



(A).

[00097] In some embodiments, ring A is optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12- membered heteroaryl. In some embodiments, ring A is optionally substituted C_6-C_{12} aryl. In some embodiments, ring A is optionally substituted 5- to 12- membered heteroaryl.

[00098] In some embodiments, ring A is substituted C_6-C_{12} aryl. In some embodiments, ring A is optionally substituted phenyl. In some embodiments, ring A is substituted phenyl. In some

embodiments, ring A is phenyl substituted with one or more R^3, which is described elsewhere herein, such as hereinabove.

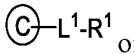
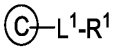
[00099] In some embodiments, ring A is substituted 5- to 12- membered heteroaryl. In some embodiments, ring A is optionally substituted quinazoline. In some embodiments, ring A is quinazoline substituted with one or more R^3, which is described elsewhere herein, such as hereinabove.

[000100] In some embodiments, ring B is optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12- membered heteroaryl. In some embodiments, ring B is optionally substituted C_6-C_{12} aryl. In some embodiments, ring B is optionally substituted 5- to 12- membered heteroaryl.

[000101] In some embodiments, ring B is substituted C_6-C_{12} aryl. In some embodiments, ring B is optionally substituted phenyl. In some embodiments, ring B is substituted phenyl. In some embodiments, ring B is phenyl substituted with one or more R^2, which is described elsewhere herein, such as hereinabove.

[000102] In some embodiments, ring B is substituted 5- to 12- membered heteroaryl. In some embodiments, ring B is optionally substituted pyridinyl. In some embodiments, ring B is substituted pyridinyl. In some embodiments, ring B is pyridinyl substituted with one or more R^2, which are each independently described elsewhere herein, such as hereinabove.

[000103] In some embodiments, L^X is absent, amino, optionally substituted C_1-C_6 alkylene or optionally substituted C_1-C_6 heteroalkylene. In some embodiments, L^X is amino, optionally substituted C_1-C_6 alkylene, or optionally substituted C_1-C_6 heteroalkylene. In some embodiments, L^X is amino. In some embodiments, L^X is optionally substituted C_1-C_6 alkylene. In some embodiments, L^X is optionally substituted C_1-C_6 heteroalkylene. In some embodiments, L^X is optionally substituted C_1-C_6 aminoalkylene. In some embodiments, L^X is described as G elsewhere herein, such as hereinabove.

[000104] In some embodiments, L^Y is  or L^1-R^1. In some embodiments, L^Y is  . In some embodiments, L^Y is L^1-R^1. In some embodiments, (L^1-R^1) is described elsewhere herein (e.g., hereinabove).

[000105] In some embodiments, ring C is optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 5- to 12 membered heterocyclyl (e.g., spirocyclyl), optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12- membered heteroaryl. In some embodiments, ring C is optionally substituted C_3-C_{10} cycloalkyl or optionally substituted 5- to 12 membered

heterocyclyl. In some embodiments, ring C is optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12- membered heteroaryl.

[000106] In some embodiments, ring C is optionally substituted C_3-C_{10} carbocyclyl. In some embodiments, ring C is optionally substituted C_3-C_{10} cycloalkyl. In some embodiments, ring C is spirocyclic.

[000107] In some embodiments, ring C is optionally substituted 5- to 12 membered heterocyclyl. In some embodiments, ring C is substituted 5- to 12 membered heterocyclyl. In some embodiments, ring C is spirocyclic.

[000108] In some embodiments, ring C is piperidinyl.

[000109] In some embodiments, ring C is 6-azaspiro[2.5]octanyl.

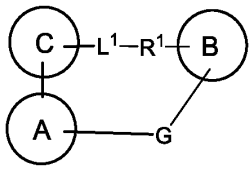
[000110] In some embodiments, ring C is 5-azaspiro[2.5]octanyl.

[000111] In some embodiments, ring C is 7-azaspiro[3.5]nonanyl.

[000112] In some embodiments, ring C is optionally substituted C_6-C_{12} aryl. In some embodiments, ring C is substituted C_6-C_{12} aryl.

[000113] In some embodiments, ring C is optionally substituted 5- to 12- membered heteroaryl. In some embodiments, ring C is substituted 5- to 12- membered heteroaryl.

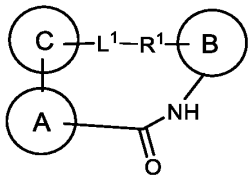
[000114] In some embodiments, a compound provided herein has the structure of Formula (B), or a pharmaceutical salt or solvate thereof:



(B).

[000115] In some embodiments, G is -(C=X)-NH- or -NH-(C=X)-. In some embodiments, X is O or NR. In some embodiments, R is optionally combined with an R^3 to form a ring (e.g., a heterocycle, such as forming a quinazoline), or optionally combined with an R^4 to form a heterocyclic ring. In some embodiments, G, X, R, R^3, and R^4 are each independently described elsewhere herein, such as hereinabove.

[000116] In some embodiments, a compound provided herein has the structure of Formula (C), or a pharmaceutical salt or solvate thereof:



(C).

[000117] In some embodiments, L^1 is a linker comprising the structure $-L^{1a}-L^{1b}-$. In some embodiments, L^1 is described elsewhere herein, such as hereinabove.

[000118] In some embodiments, L^{1a} is a bond, -O-, $-NL^{1a1}-$, -S-, or $-SO_2-$. In some embodiments, L^{1a} is described elsewhere herein, such as hereinabove.

[000119] In some embodiments, L^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, $-SO_2$-C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl. In some embodiments, L^{1a1} is described elsewhere herein, such as hereinabove.

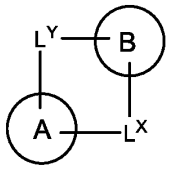
[000120] In some embodiments, L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene. In some embodiments, L^{1b} is optionally substituted C_1-C_6 alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene. In some embodiments, L^{1b} is described elsewhere herein, such as hereinabove.

[000121] In some embodiments, R^1 is a bond, -O-, -CO-, $-NR^{1a}-$, $-NR^{1a}$-Q-, $-NR^{1a}$-C_1-C_6alkylene-, $-NR^{1a}$-CO-, -CO-$NR^{1a}-$, $-NR^{1a}-SO_2-$, -S-, $-SO_2-$, or $-SO_2-NR^{1a}$. In some embodiments, R^1 is described elsewhere herein, such as hereinabove.

[000122] In some embodiments, R^{1a} is hydrogen, optionally substituted C_1-C_6 alkyl, $-SO_2$-C_1-C_6 alkyl, optionally substituted C_3-C_6 cycloalkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl. In some embodiments, R^{1a} is described elsewhere herein, such as hereinabove.

[000123] In some embodiments, Q is optionally substituted C_1-C_6alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene. In some embodiments, Q is described elsewhere herein, such as hereinabove.

[000124] In some embodiments, the structure of Formula (A) is:



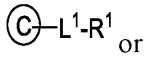
(A)

wherein:

ring A is optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12-membered heteroaryl;

ring B is optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12-membered heteroaryl;

L^X is absent, amino, optionally substituted C_1-C_6 alkylene or optionally substituted C_1-C_6 heteroalkylene (e.g., optionally substituted C_1-C_6 aminoalkylene);

L^Y is  or L^1-R^1;

ring C is optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 5- to 12 membered heterocyclyl (e.g., spirocyclyl), optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12- membered heteroaryl;

L^1 is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond, -O-, -NL^{1a1}-, -S-, or -SO_2-;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, -SO_2-C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl;

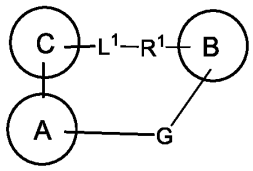
L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene;

R^1 is a bond, -O-, -CO-, -NR^{1a}-, -NR^{1a}-Q-, -NR^{1a}-C_1-C_6alkylene-, -NR^{1a}-CO-, -CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a};

R^{1a} is hydrogen, optionally substituted C_1-C_6 alkyl, -SO_2-C_1-C_6 alkyl, optionally substituted C_3-C_6 cycloalkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl; and

Q is optionally substituted C_1-C_6alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene.

[000125] In some embodiments, the structure of Formula (B) is:



(B)

wherein:

ring A is optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12- membered heteroaryl;

ring B is optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12- membered heteroaryl;

ring C is optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 5- to 12 membered heterocyclyl, optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12- membered heteroaryl;

G is -(C=O)-NH- or -NH-(C=O)-;

L^1 is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond, -O-, -NL^{1a1}-, -S-, or -SO_2-;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

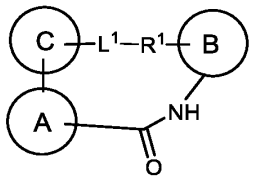
L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene;

R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-Q-, -NR^{1a}-CO-, -CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a};

R^{1a} is hydrogen, -C(=O)H, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl; and

Q is optionally substituted C_1-C_6alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene.

[000126] In some embodiments, the structure of Formula (C) is:



(C)

wherein:

ring A is optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12-membered heteroaryl;

ring B is optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12-membered heteroaryl;

ring C is optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 5- to 12 membered heterocyclyl (e.g., spirocyclyl), optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12- membered heteroaryl;

L^1 is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond, -O-, or -NL^{1a1}-;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

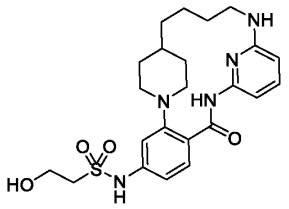
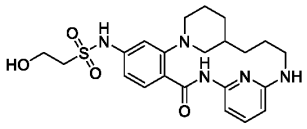
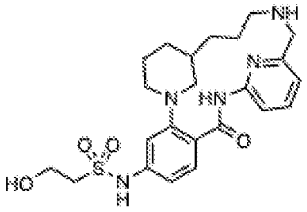
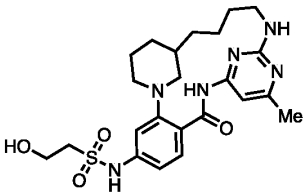
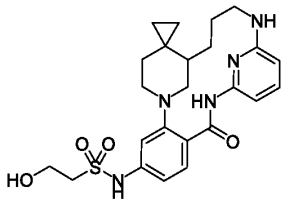
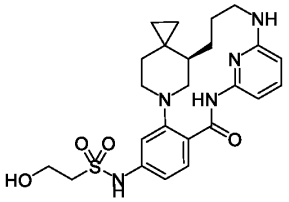
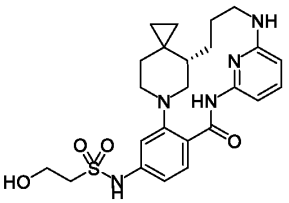
L^{1b} is optionally substituted C_1-C_6 alkylene;

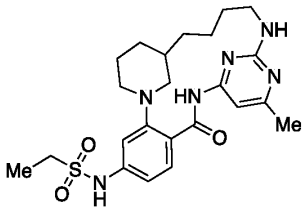
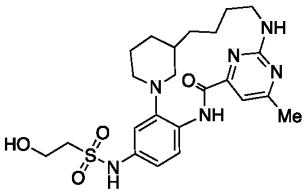
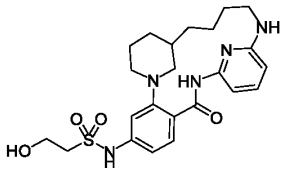
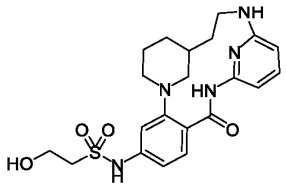
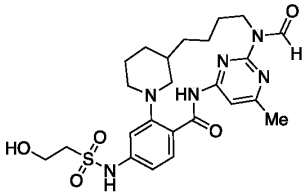
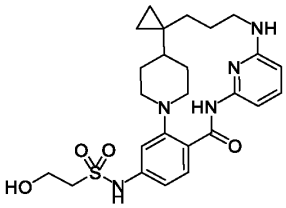
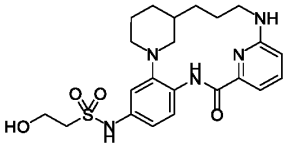
R^1 is a bond, -O-, -CO-, -NR^{1a}-, -NR^{1a}-C_1-C_6alkylene-, -NR^{1a}-CO-, -CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a}; and

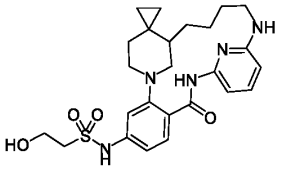
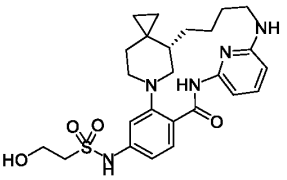
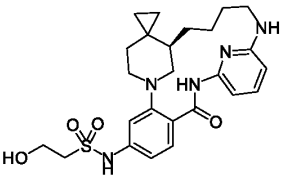
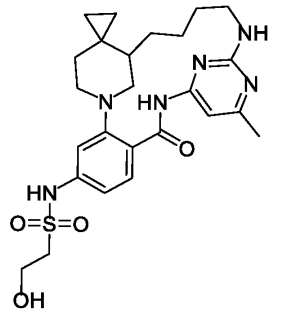
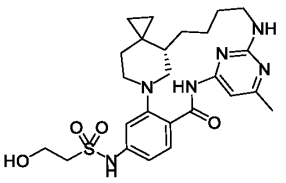
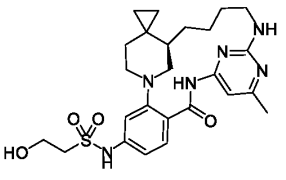
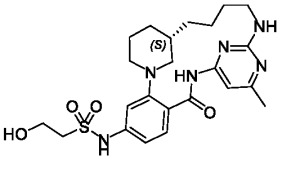
R^{1a} is hydrogen, C_1-C_6 alkyl, -SO_2-C_1-C_6 alkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl.

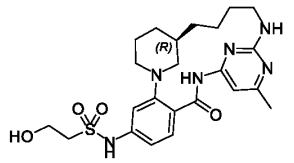
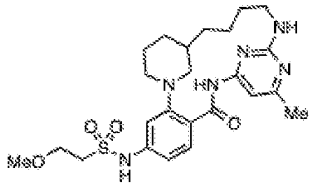
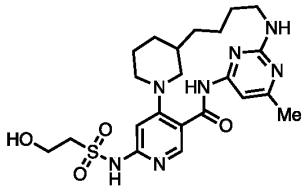
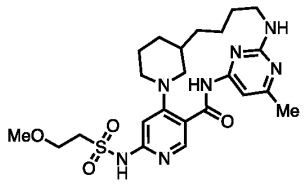
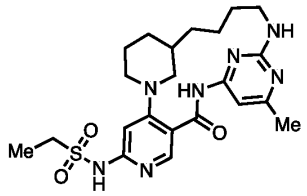
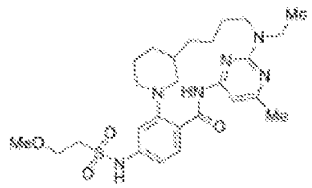
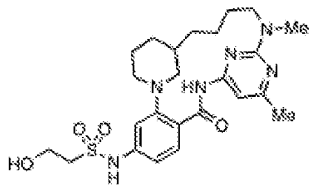
[000127] Provided in some embodiments herein is a compound having a structure provided in Table 1, a stereoisomer thereof, or a pharmaceutically acceptable salt or solvate of the compound or the stereoisomer.

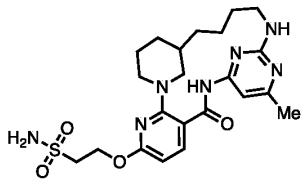
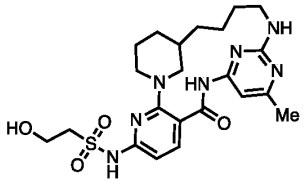
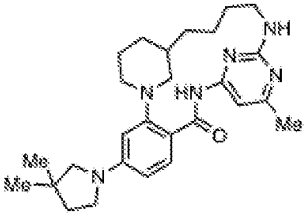
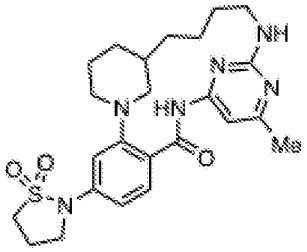
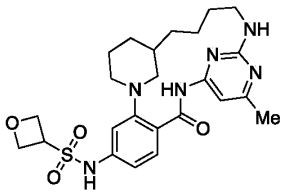
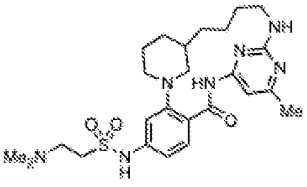
Table 1

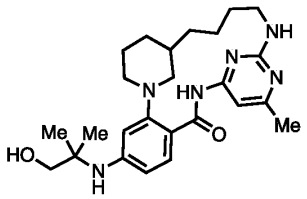
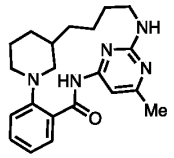
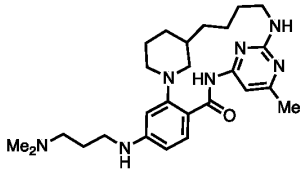
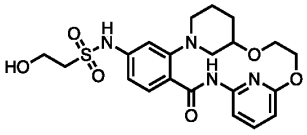
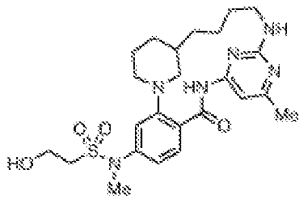
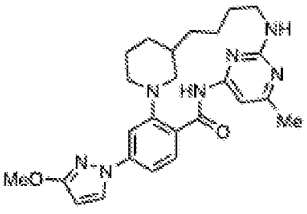
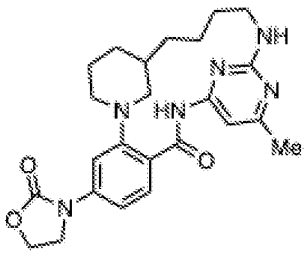
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
1		474.4	474.2172
2		460.2	460.2011
3		474.2	474.2168
4		489.2	489.2281
5		486.2	486.2173
6		486.2	486.2166
7		486.2	486.2171

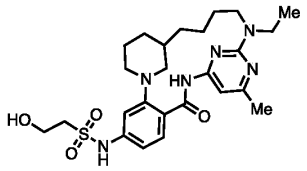
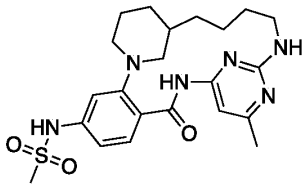
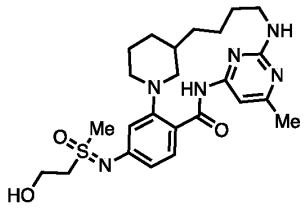
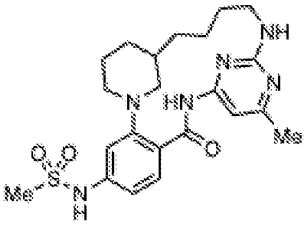
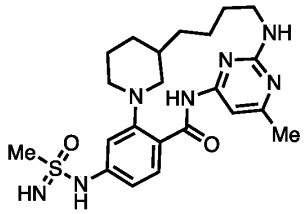
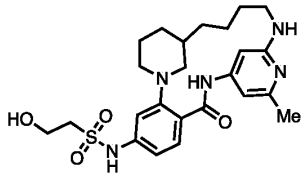
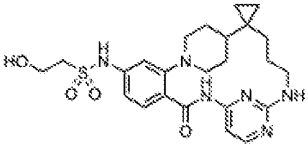
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
8		473.2	473.2334
9		489.3	489.2280
10		474.3	474.2164
11		446.4	446.1855
12		517.2	517.2225
13		500.3	500.2328
14		460.2	460.2013

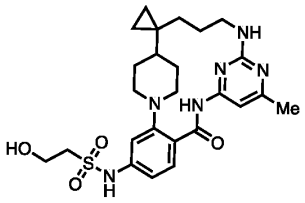
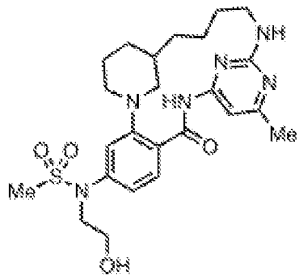
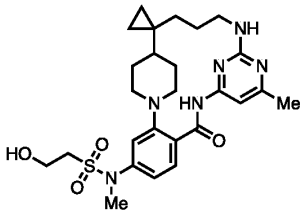
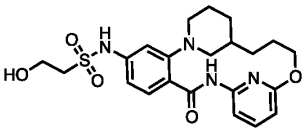
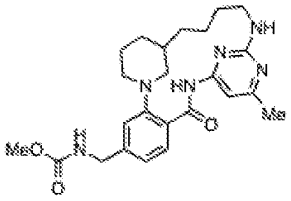
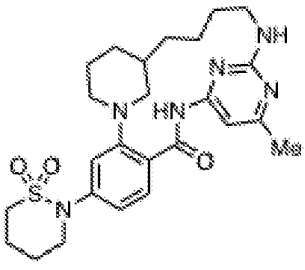
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
15		500.3	500.2320
16		500.3	500.2328
17		500.3	500.2328
18		515.3	515.2439
19		515.4	515.2430
20		515.4	515.2440
21		489.3	489.2286

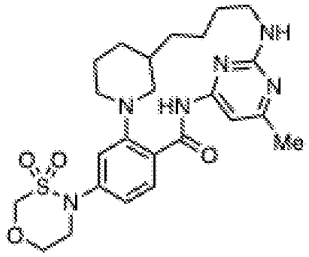
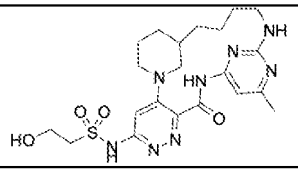
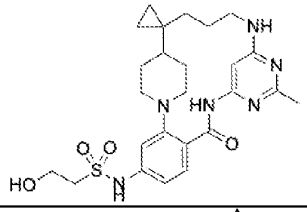
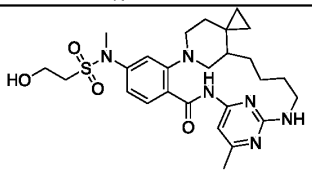
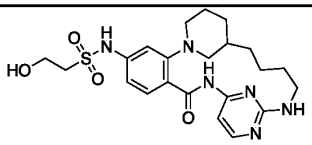
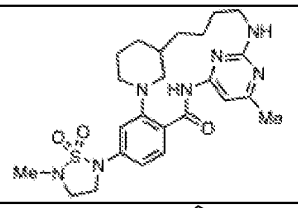
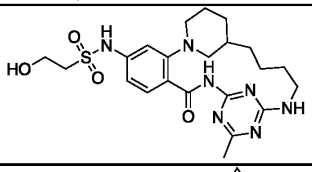
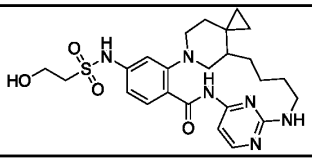
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
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23		503.2	503.2439
24		490.2	490.2235
25		504.3	504.2398
26		474.2	474.2284
27		531.3	531.2744
28		503.2	503.2427

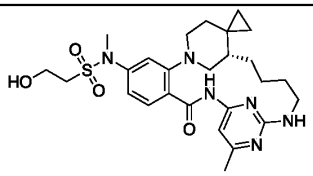
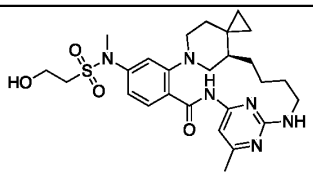
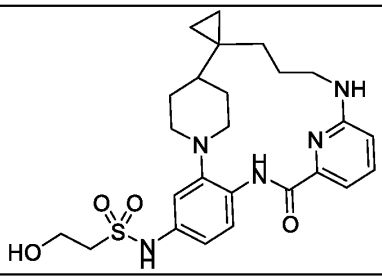
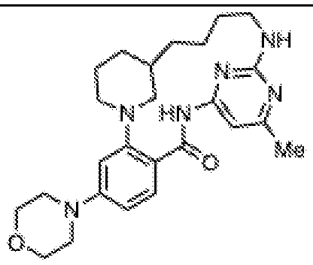
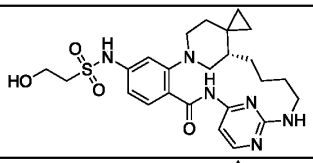
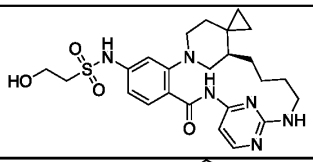
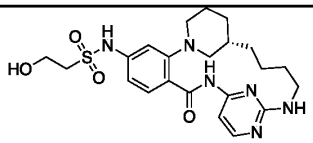
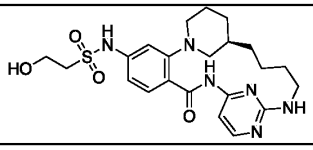
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
29		490.3	490.2236
30		490.3	490.2233
31		463.2	463.3176
32		485.1	485.2331
33		501.1	501.2274
34		516.2	516.2756

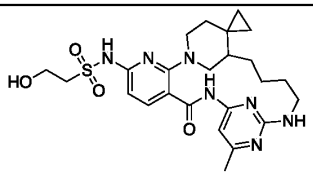
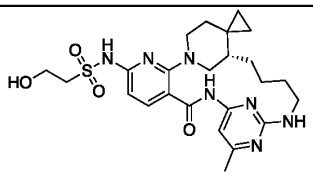
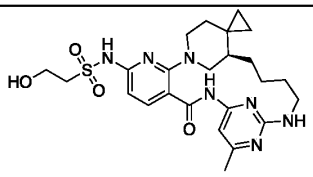
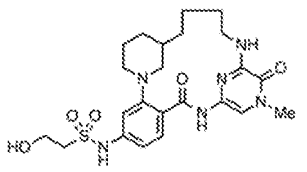
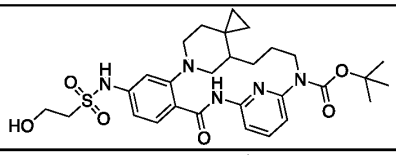
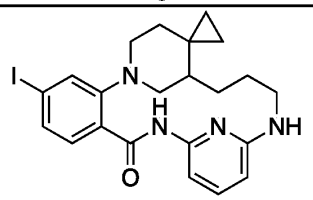
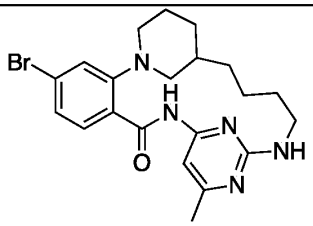
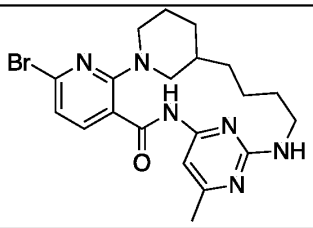
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
35		453.2	453.2972
36			366.2290
37		466.2	466.3289
38		463.1	463.1645
39		503.2	503.2438
40		462.2	462.2594
41		451.2	451.2448

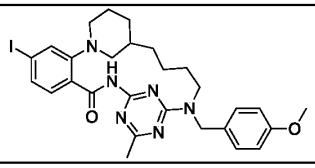
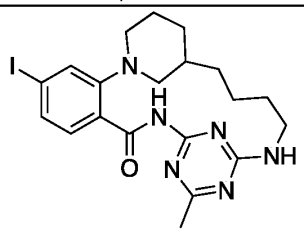
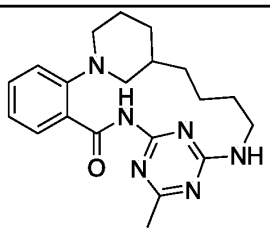
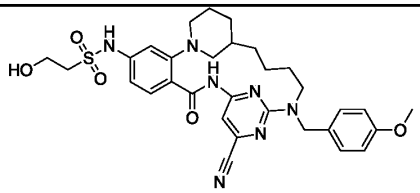
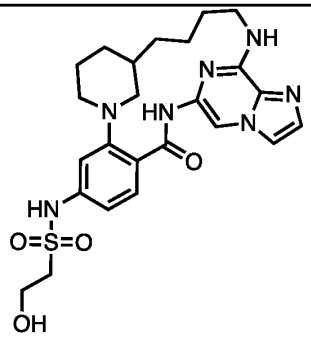
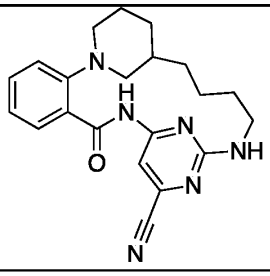
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
42		516.2	517.2601
43		459.1	459.2177
44		487.2	487.2487
45		473.1	473.2325
46		457.2	458.2332
47		488.2	488.2322
48		501.2	501.2275

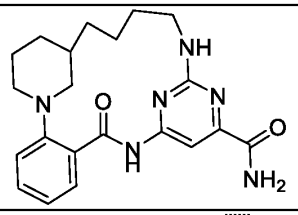
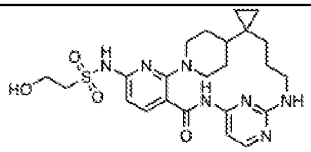
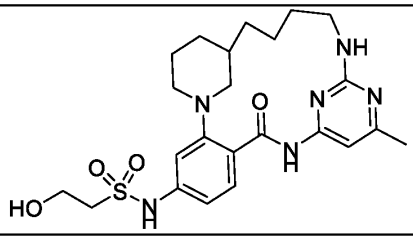
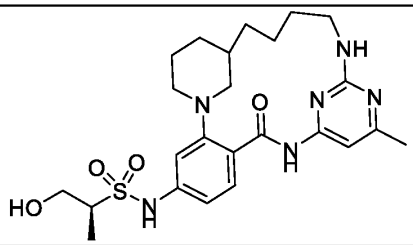
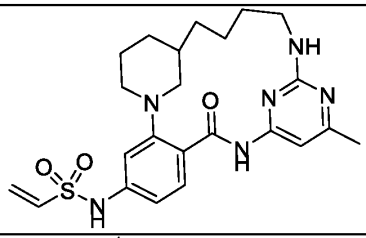
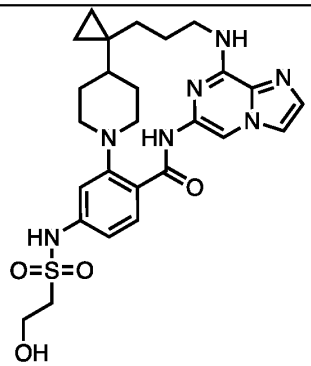
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
49		515.3	515.2436
50		503.2	503.2436
51		529.3	529.2595
52		461.1	461.1861
53		453.2	453.2613
54		499.2	499.2489

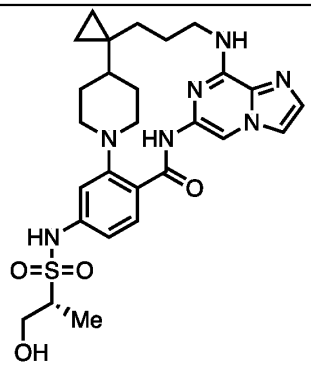
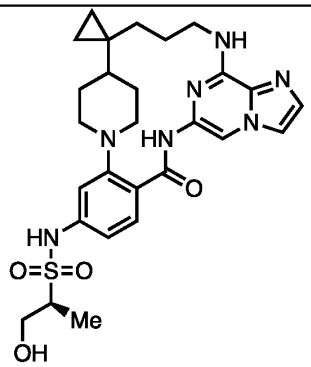
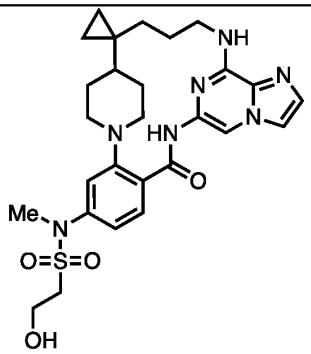
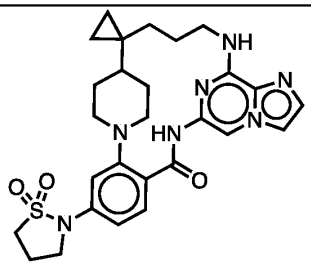
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
55		501.2	501.2283
56		491.2	491.2187
57		489.2	489.2283
58		529.4	529.2591
59		475.2	475.2127
60		500.2	500.2438
61		490.2	490.2236
62		501.3	501.2285

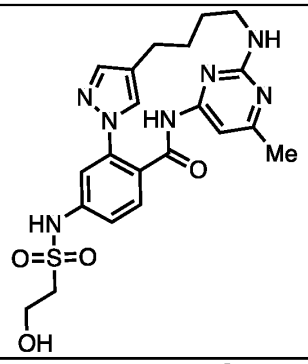
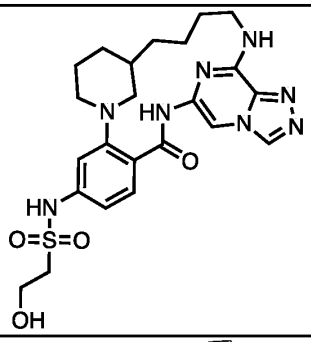
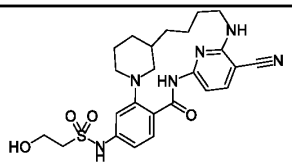
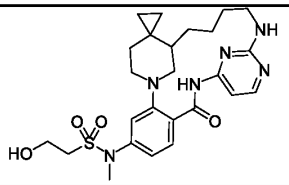
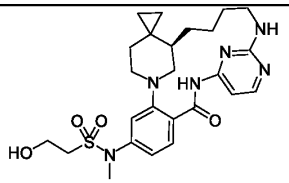
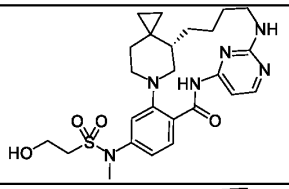
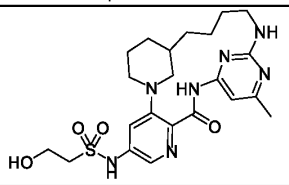
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
63		529.4	529.2595
64		529.4	529.2593
65			500.2330
66		451.3	451.2824
67		501.3	501.2287
68		501.4	501.2285
69		475.3	475.2128
70		475.3	475.2122

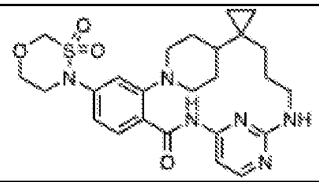
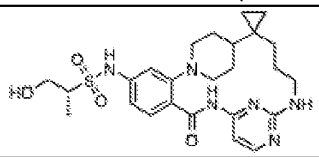
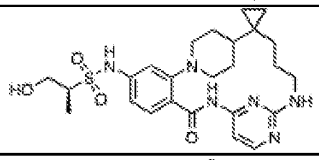
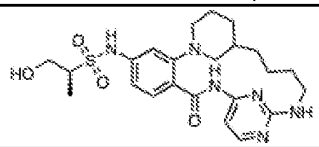
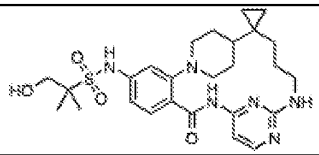
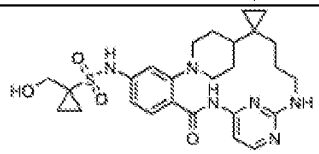
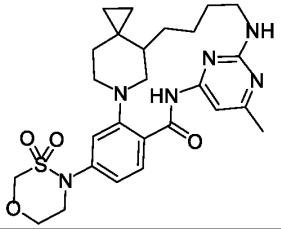
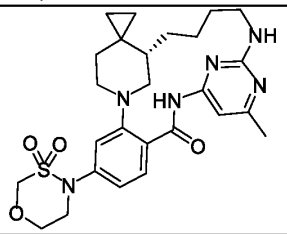
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
71		516.4	516.2393
72		516.4	516.2392
73		516.4	516.2391
74		505.2	505.2217
75		586.2	
76		489.1	
77		444.0	
78		446.1	

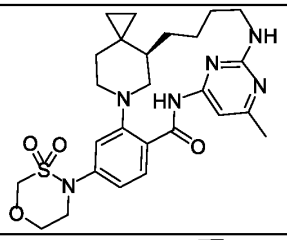
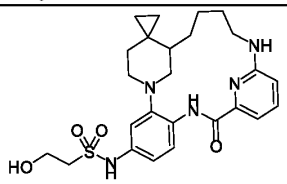
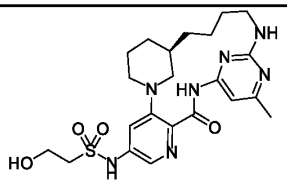
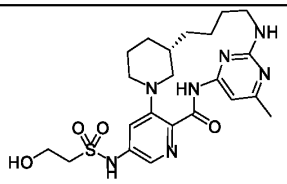
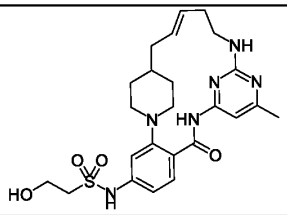
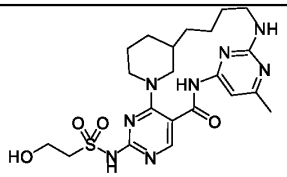
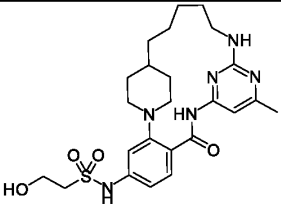
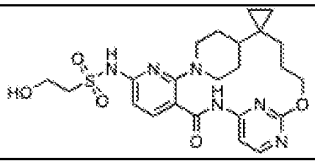
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
79		613.1	613.1788
80		493.1	493.1212
81		367.2	367.2249
82		620.2	
83		514.2	514.2235
84		377.1	377.2085

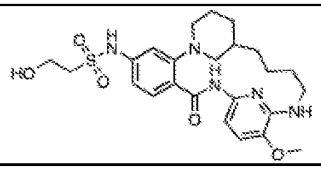
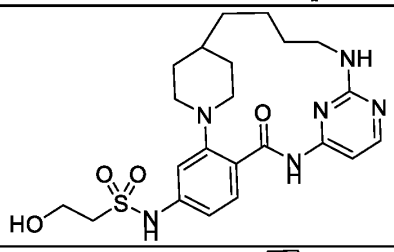
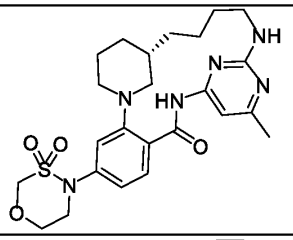
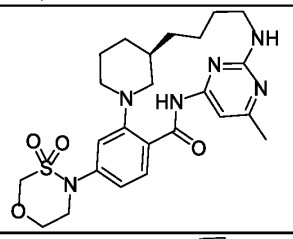
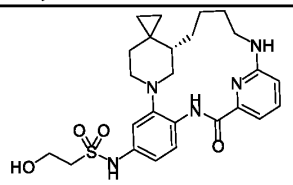
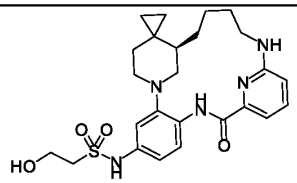
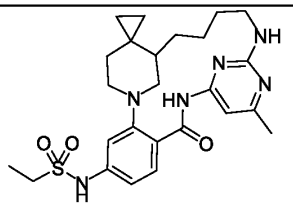
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
85		395.1	395.2188
86		502.2	502.2234
87		503.3	503.2437
88		503.3	503.2439
89		471.2	471.2172
90		540.1	540.2393

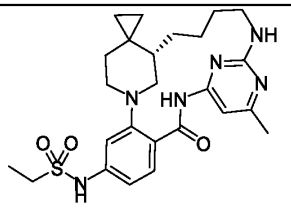
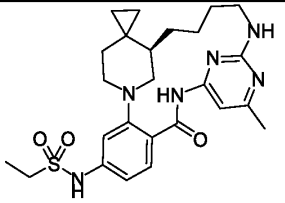
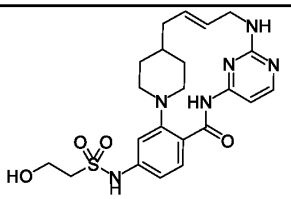
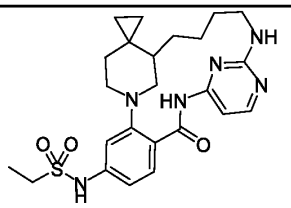
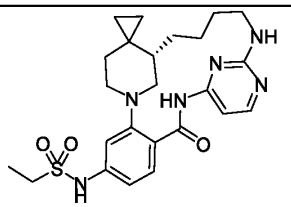
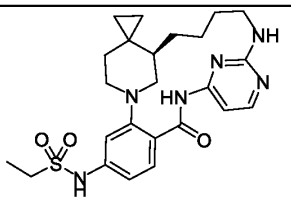
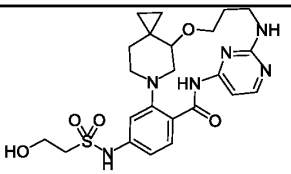
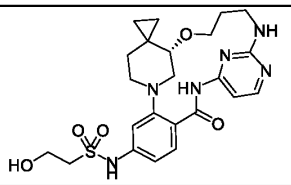
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
91		554.2	554.2541
92		554.2	554.2545
93		554.2	554.2549
94		536.2	536.2442

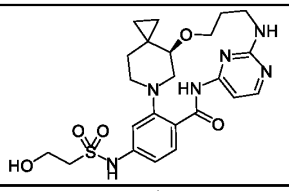
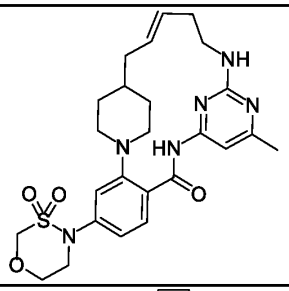
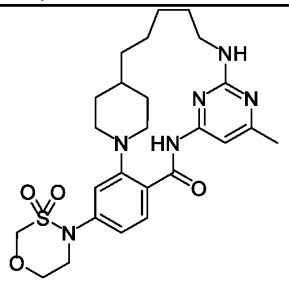
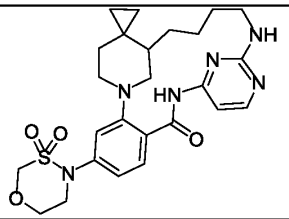
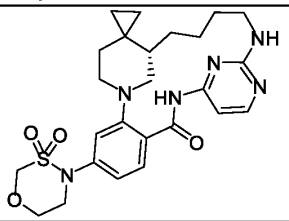
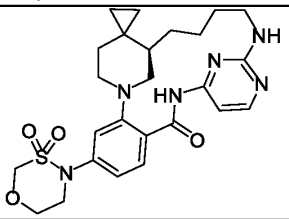
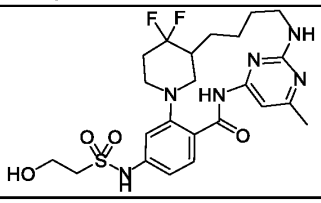
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
95		472.2	472.1766
96		515.3	515.2179
97		499.2	499.2128
98		515.2	515.2434
99		515.2	515.2438
100		515.2	515.2438
101		490.2	490.2236

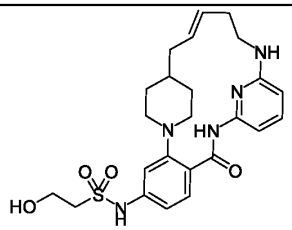
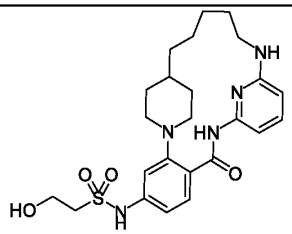
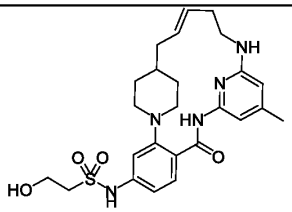
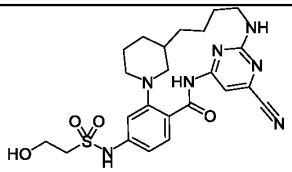
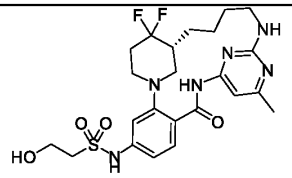
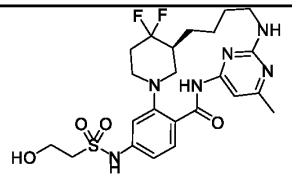
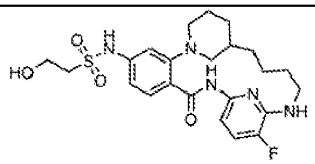
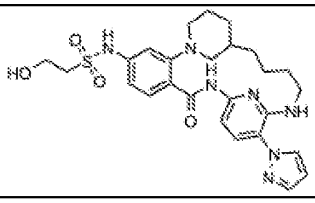
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
102		513.2	513.2283
103		515.2	515.2433
104		515.2	515.2435
105		489.2	489.2275
106		529.2	529.2595
107		527.2	527.2439
108		527.2	527.2435
109		527.2	527.2440

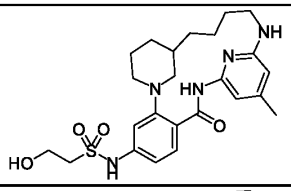
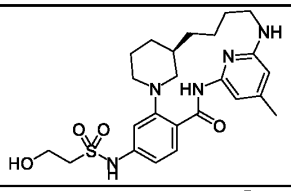
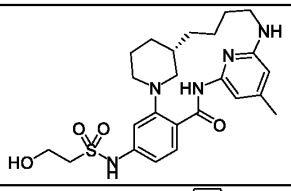
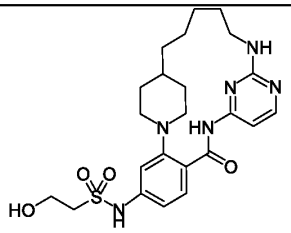
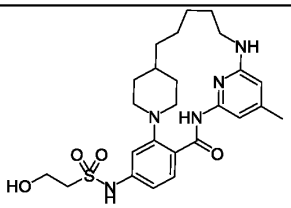
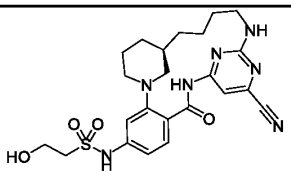
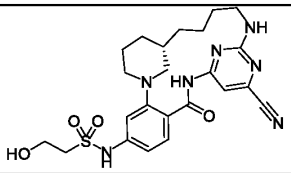
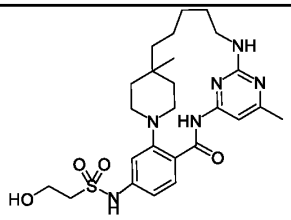
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
110		527.2	527.2435
111		500.3	500.2322
112		490.2	490.2232
113		490.2	490.2235
114		501.3	501.2286
115		491.2	491.2182
116		503.3	503.2434
117		503.1	503.2064

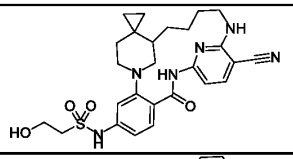
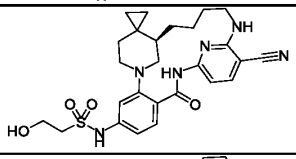
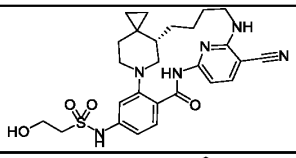
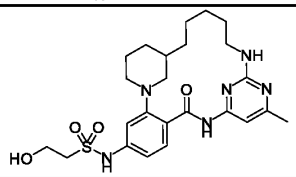
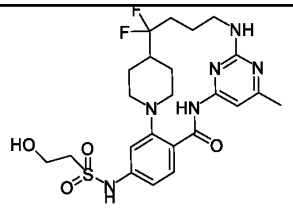
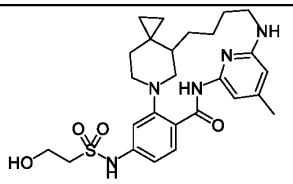
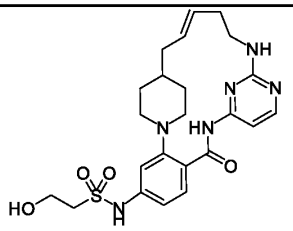
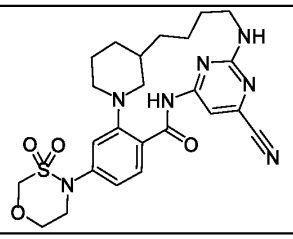
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
118		504.2	504.2273
119		475.3	475.2120
120		501.2	501.2275
121		501.2	501.2282
122		500.4	500.2325
123		500.3	500.2323
124		499.3	499.2487

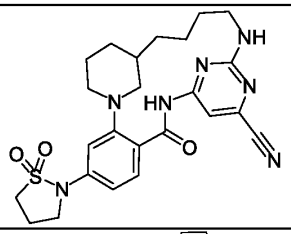
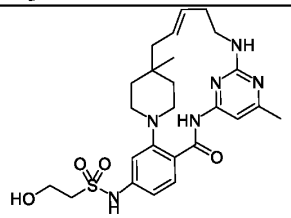
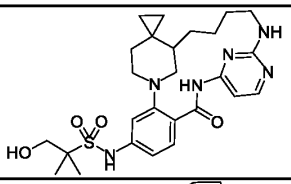
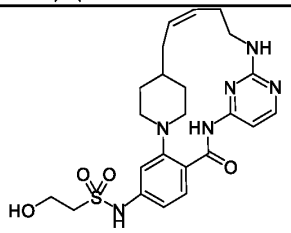
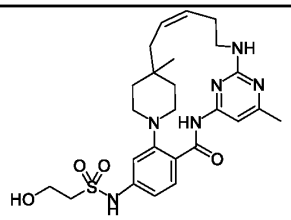
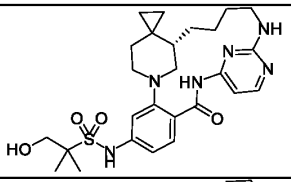
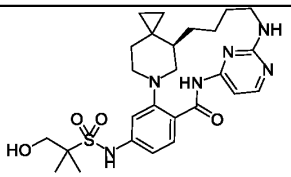
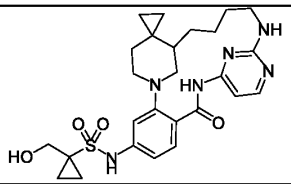
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
125		499.4	499.2483
126		499.4	499.2479
127		473.3	473.1969
128		485.2	485.2325
129		485.2	485.2330
130		485.2	485.2329
131		503.1	503.2073
132		503.1	503.2062

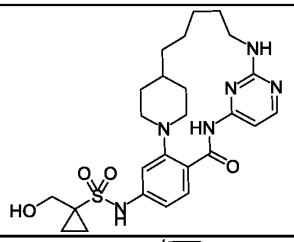
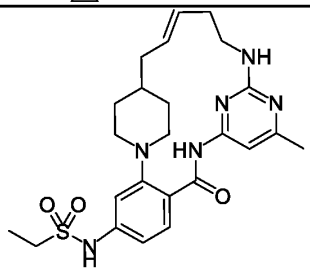
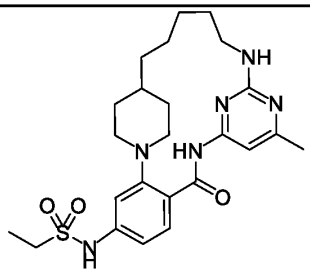
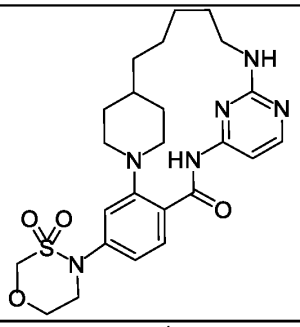
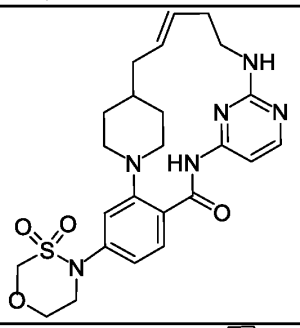
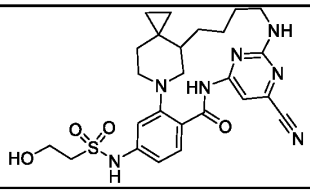
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
133		503.1	503.2069
134		513.2	513.2276
135		515.2	515.2432
136		513.1	513.2276
137		513.1	513.2278
138		513.1	513.2282
139		525.2	525.2089

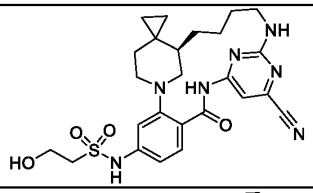
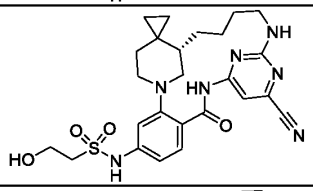
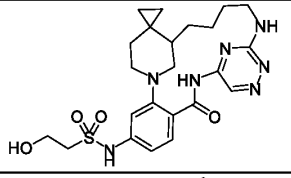
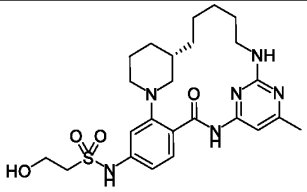
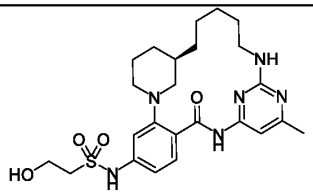
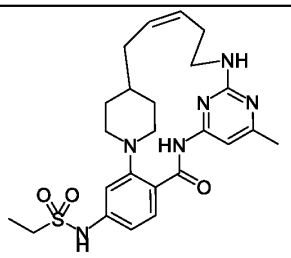
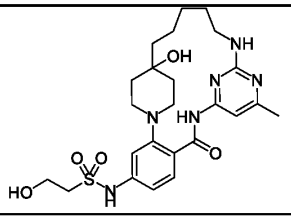
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
140		486.2	486.2171
141		488.2	488.2329
142		500.2	500.2325
143		500.1	500.2077
144		525.2	525.2087
145		525.1	525.2095
146		492.2	492.2071
147		540.2	540.2378

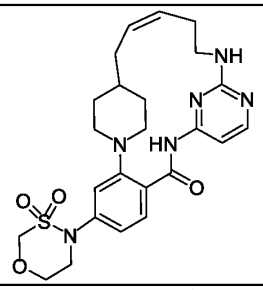
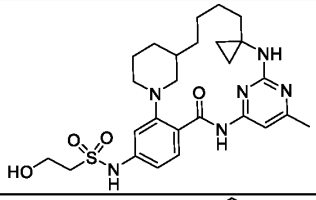
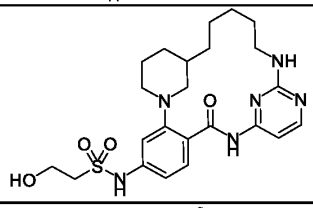
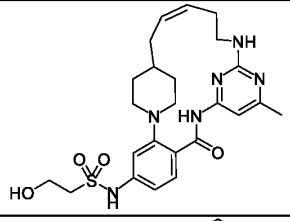
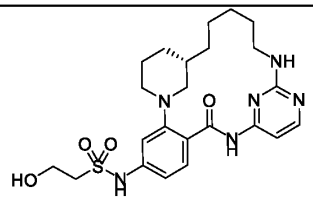
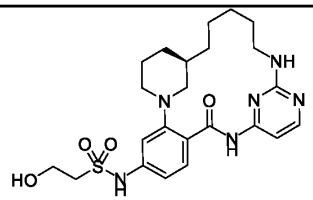
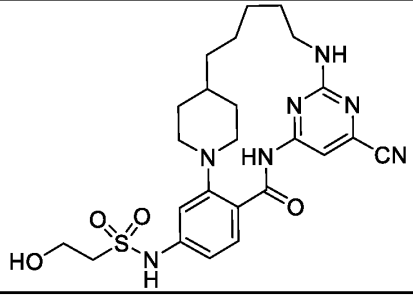
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
148		488.2	488.2328
149		488.2	488.2329
150		488.2	488.2327
151		489.1	489.2283
152		502.2	502.2487
153		500.1	500.2071
154		500.1	500.2070
155		517.3	517.2592

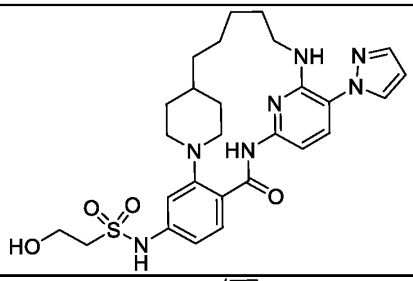
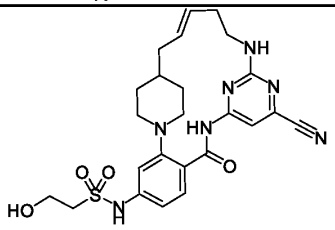
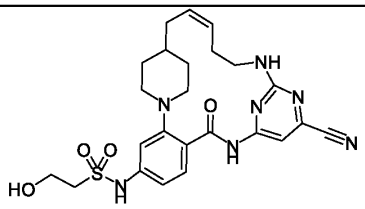
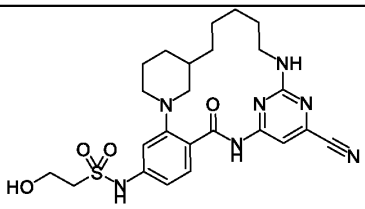
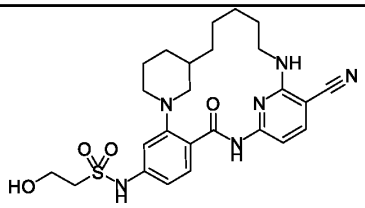
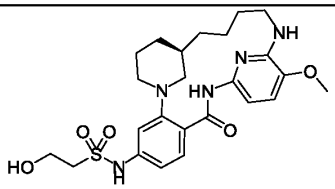
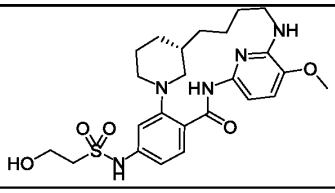
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
156		525.2	525.2278
157		525.2	525.2279
158		525.2	525.2274
159		503.2	503.2435
160		525.1	
161		514.2	514.2486
162		487.1	487.2119
163		512.1	512.2072

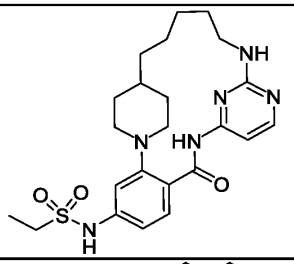
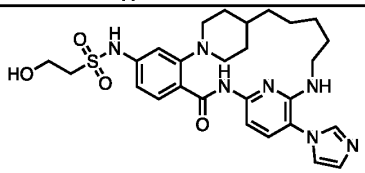
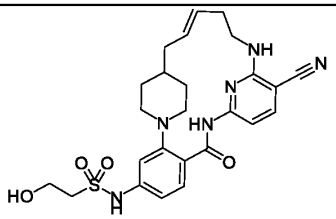
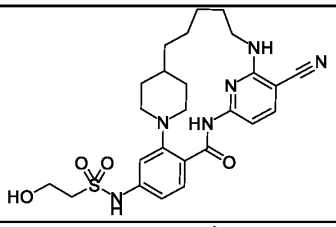
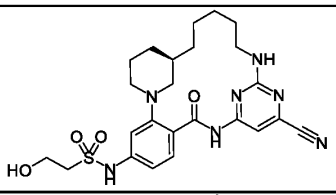
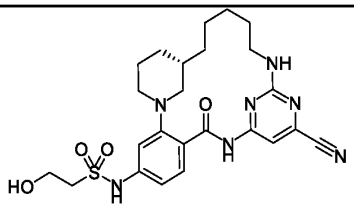
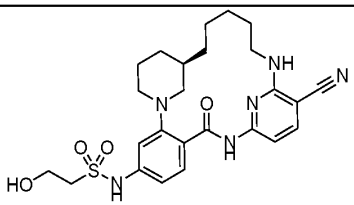
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
164		496.1	496.2121
165		515.2	515.2438
166		529.2	529.2595
167		487.1	487.2125
168		515.2	515.2435
169		529.2	529.2589
170		529.2	529.2595
171		527.2	527.2435

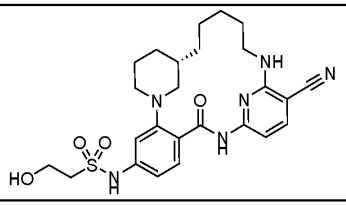
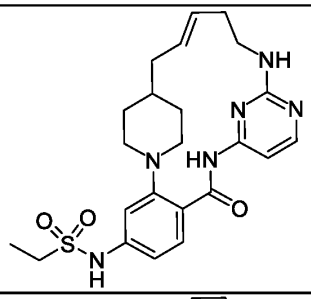
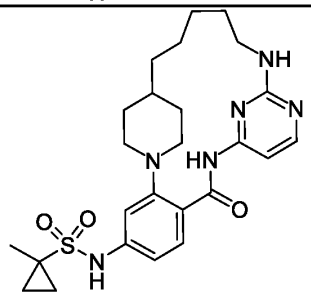
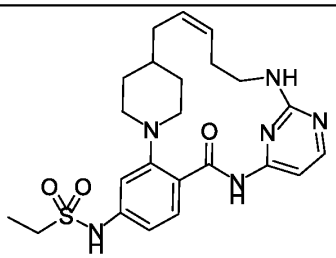
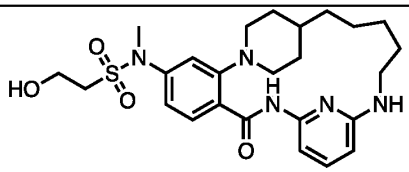
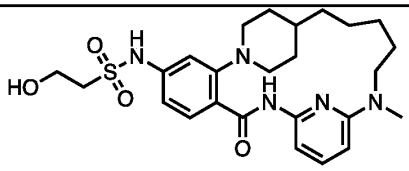
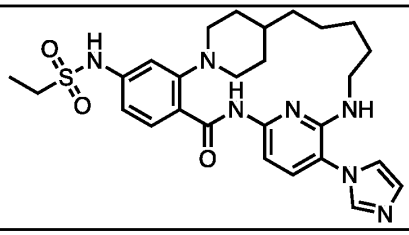
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
172		515.2	515.2440
173		485.1	485.2334
174		487.1	487.2489
175		501.2	501.2287
176		499.2	499.2125
177		526.2	526.2227

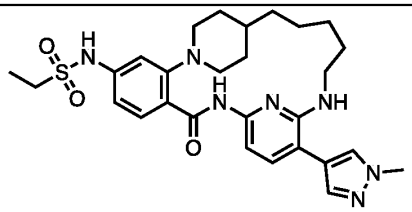
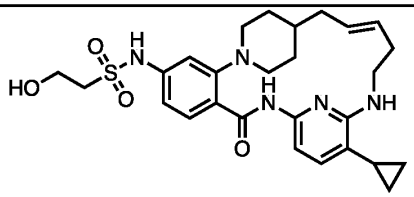
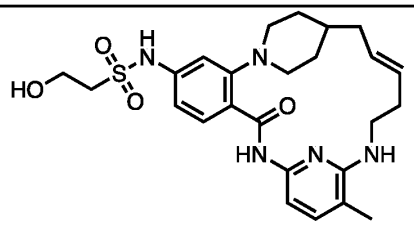
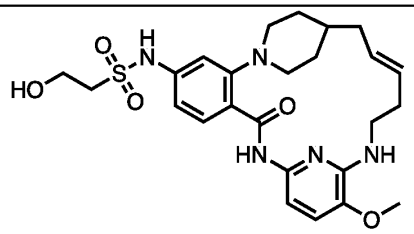
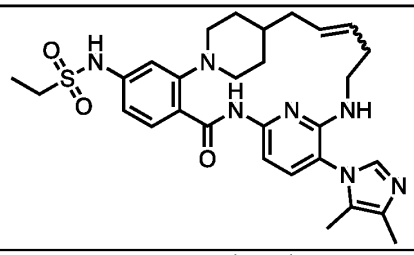
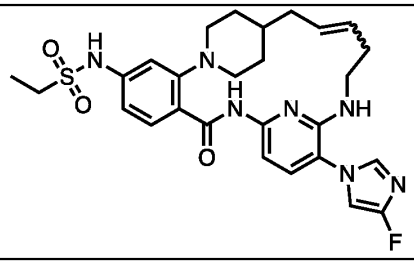
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
178		526.2	526.2238
179		526.2	526.2235
180		502.2	502.2232
181		503.2	503.2433
182		503.2	503.2435
183		485.1	485.2329
184		519.2	519.2389

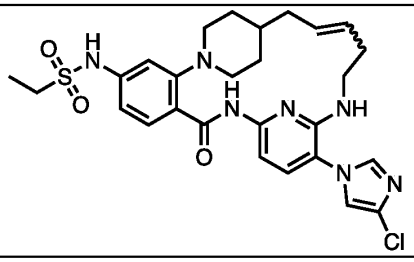
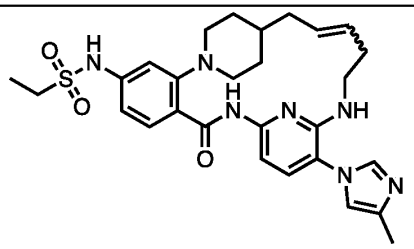
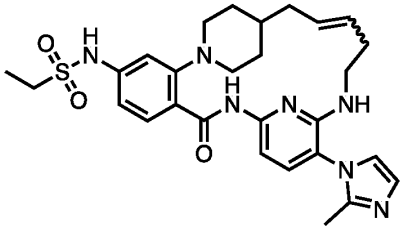
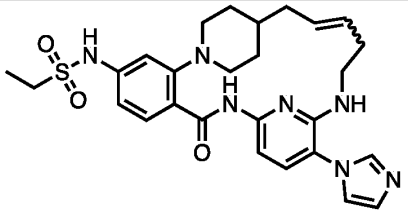
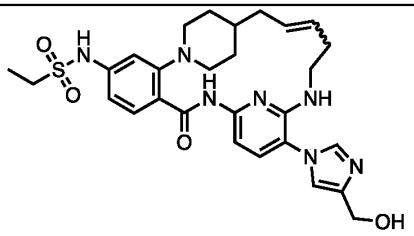
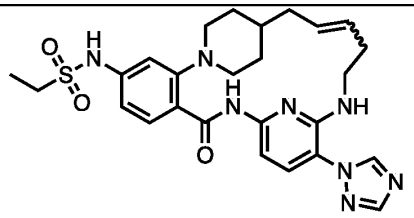
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
185		499.4	499.2126
186		529.3	529.2597
187		489.2	489.2281
188		501.2	501.2277
189		489.2	489.2279
190		489.2	489.2279
191		514.2	514.2235

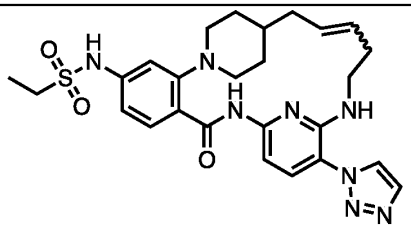
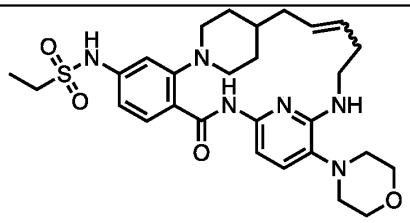
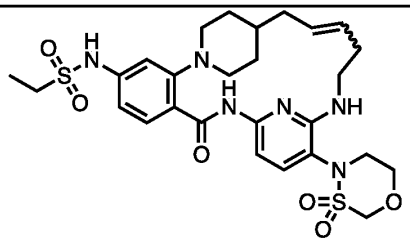
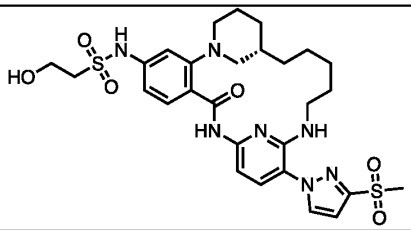
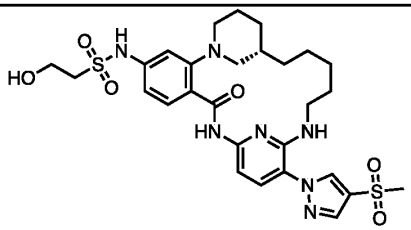
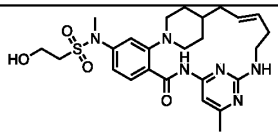
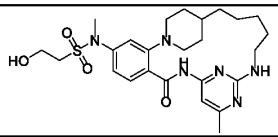
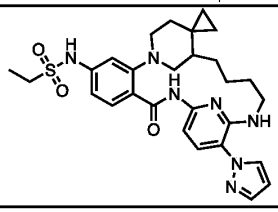
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
192		554.2	
193		512.2	512.2062
194		512.2	512.2063
195		514.2	514.2226
196		513.3	513.2261
197		504.2	504.2274
198		504.2	504.2264

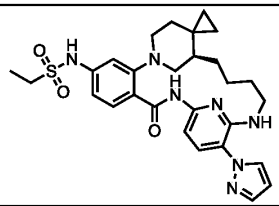
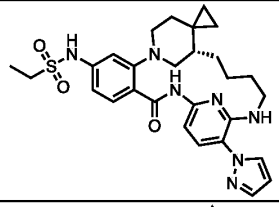
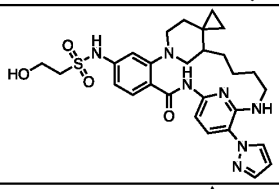
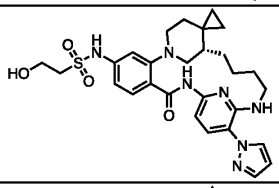
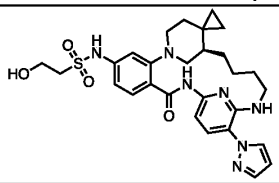
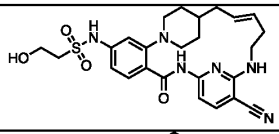
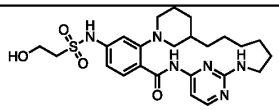
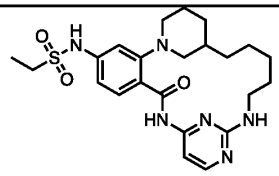
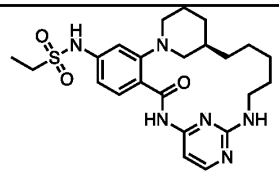
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
199		473.2	473.2325
200		554.2	554.2537
201		511.2	511.2106
202		513.2	
203		514.2	514.2222
204		514.2	514.2222
205		513.2	513.226

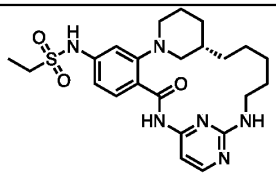
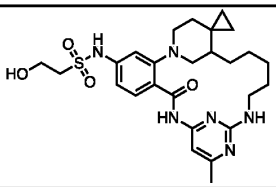
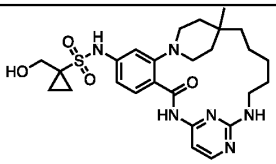
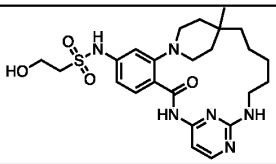
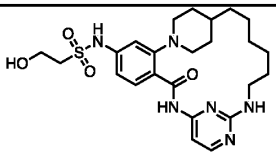
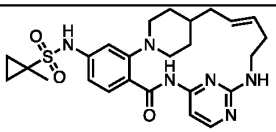
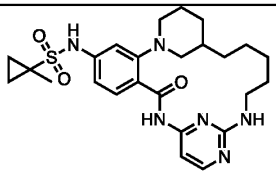
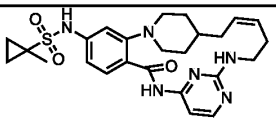
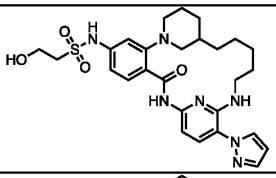
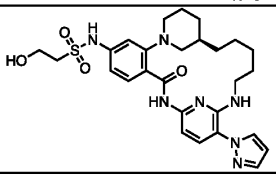
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
206		513.2	513.2266
207		471.1	471.2172
208		499.2	499.2482
209		471.1	471.2175
210		502.2	502.2482
211		502.2	502.248
212		538.2	538.2594

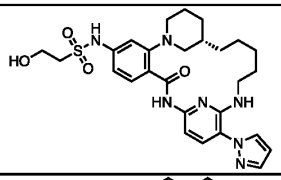
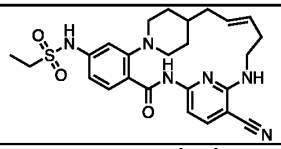
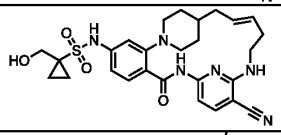
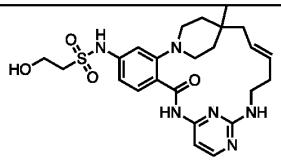
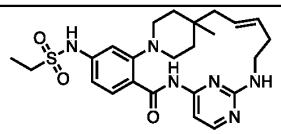
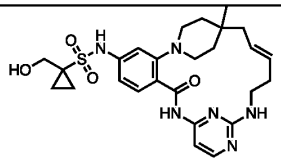
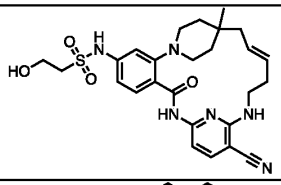
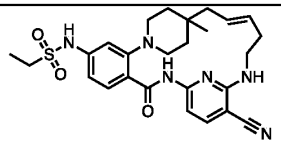
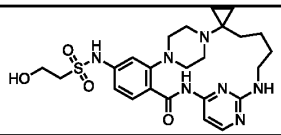
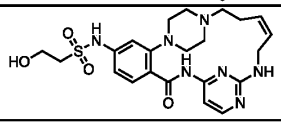
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
213		550.2	552.2741
214		526.2	526.2483
215		500.2	500.2324
216		516.2	516.227
217		564.2	564.275
218		554.2	#N/A

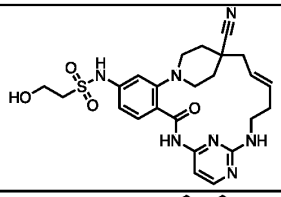
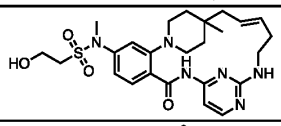
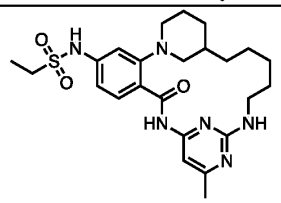
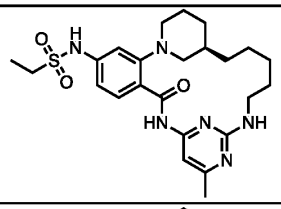
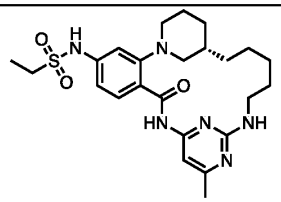
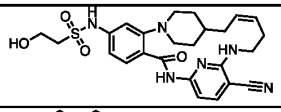
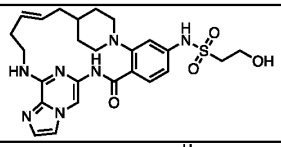
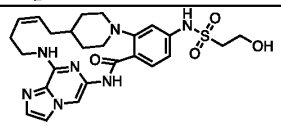
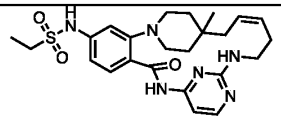
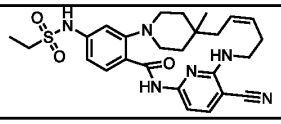
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
219		570.2	#N/A
220		550.3	#N/A
221		550.3	#N/A
222		536.2	#N/A
223		566.2	#N/A
224		537.2	#N/A

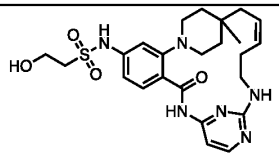
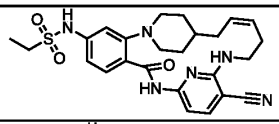
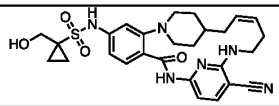
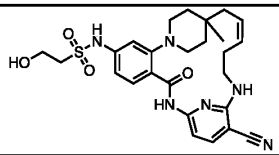
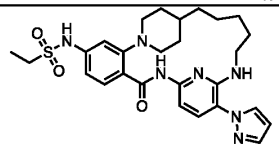
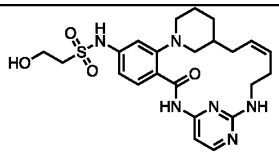
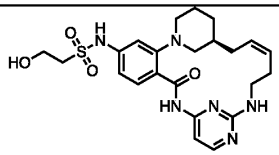
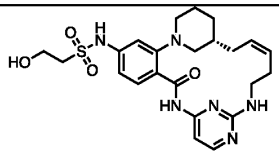
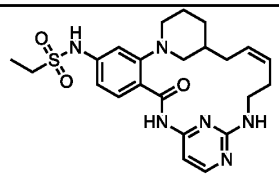
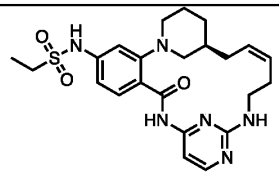
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
225		537.2	
226		555.2	555.2731
227		605.2	605.2196
228		632.2	632.2311
229		632.2	632.2304
230		515.2	515.2428
231		517.2	517.259
232		550.2	550.2587

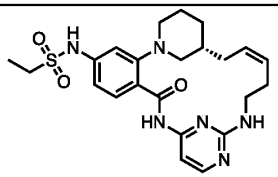
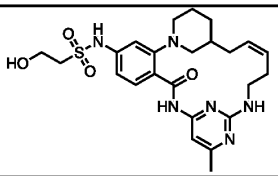
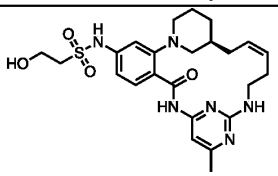
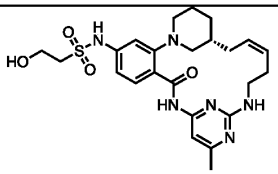
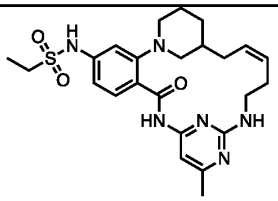
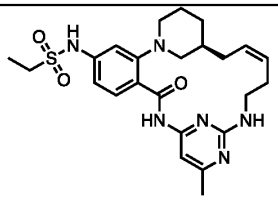
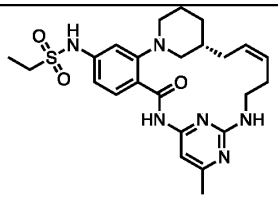
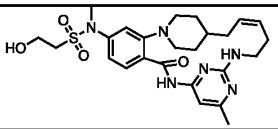
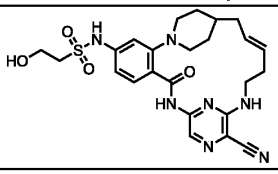
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
233		550.2	550.2596
234		550.2	550.2585
235		566.3	566.253
236		566.2	566.2525
237		566.3	566.2524
238		511.1	
239		503.1	503.2431
240		473.2	473.2322
241		473.2	473.2331

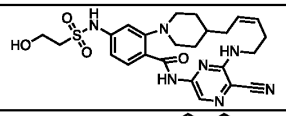
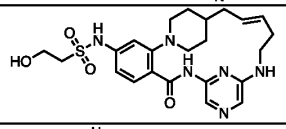
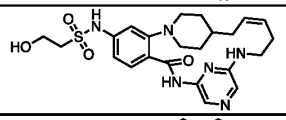
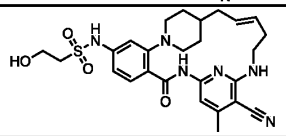
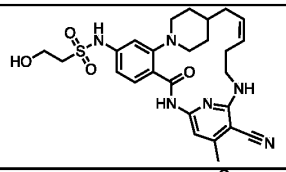
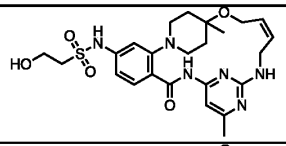
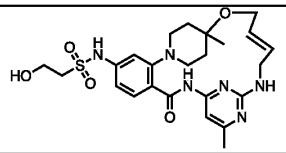
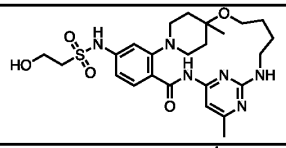
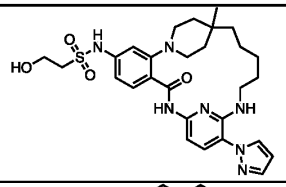
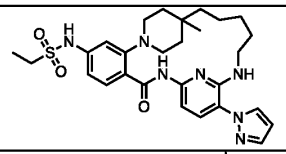
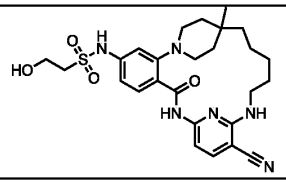
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
242		473.1	473.2328
243		529.2	529.2591
244		529.0	529.2590
245		503.1	503.2426
246		503.2	503.2419
247		497.1	497.2321
248		499.1	499.2482
249		497.1	497.2332
250		554.2	554.2546
251		554.2	

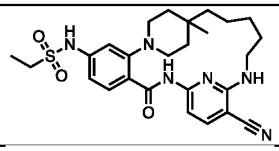
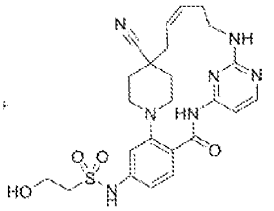
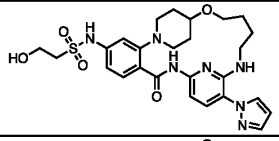
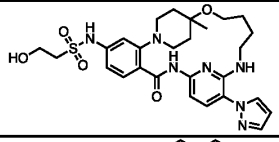
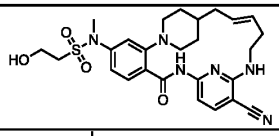
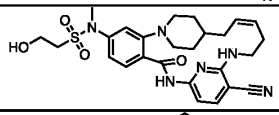
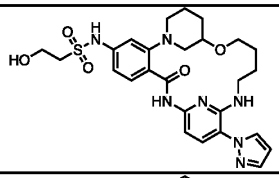
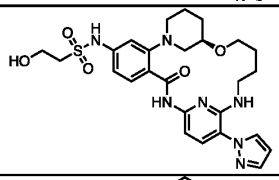
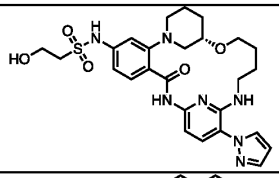
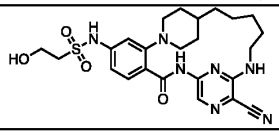
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
252		554.3	554.2543
253		495.2	495.2162
254		537.3	537.2267
255		501.1	501.2282
256		485.1	485.2334
257		527.0	527.2434
258		525.3	525.2269
259		509.2	509.2323
260		516.2	516.2367
261		488.2	488.2071

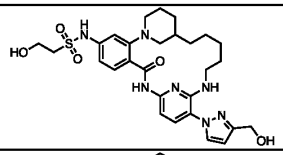
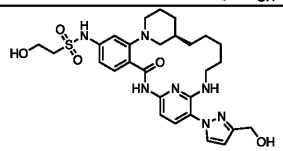
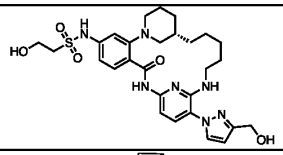
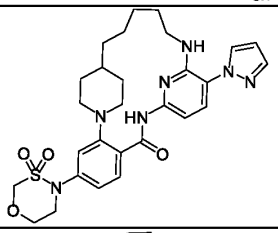
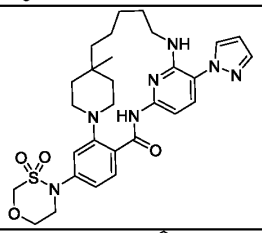
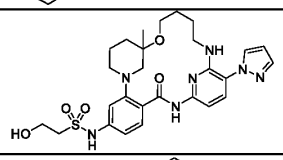
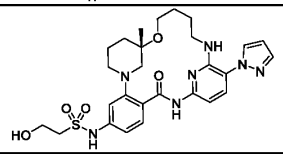
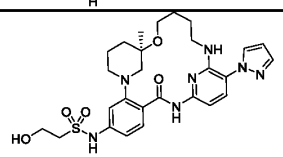
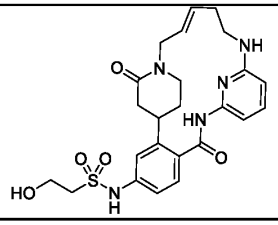
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
262		512.2	512.2075
263		515.2	515.2432
264		487.2	487.2485
265		487.3	487.2488
266		487.2	487.2487
267		511.2	511.2111
268		526.1	526.2235
269		526.0	526.2232
270		485.1	485.2332
271		509.2	509.2327

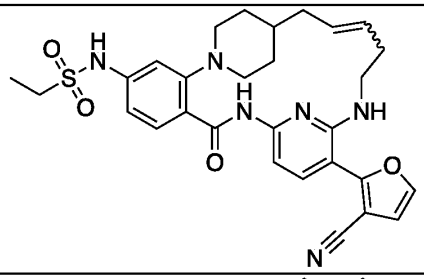
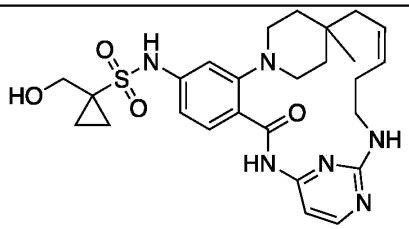
Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
272		501.1	501.2277
273		495.2	495.2162
274		537.3	537.2264
275		525.2	525.227
276		538.4	538.259
277		487.2	487.2127
278		487.1	487.2124
279		487.1	487.2124
280		471.2	471.2172
281		471.2	471.2175

Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
282		471.2	471.2173
283		501.2	501.2279
284		501.2	501.2278
285		501.2	501.2281
286		485.2	485.2331
287		485.2	485.2329
288		485.2	485.2326
289		515.1	515.2429
290		512.2	512.2068

Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
291		512.1	512.2067
292		487.2	487.2121
293		487.2	487.2127
294		525.2	525.2275
295		525.2	525.2274
296		517.2	517.2229
297		517.2	517.2233
298		519.2	519.2385
299		568.3	568.2687
300		552.2	
301		527.2	527.242

Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
302		511.3	511.2471
303		512.2	512.2072
304		556.3	
305		570.3	570.2479
306		525.3	525.2256
307		525.3	525.2272
308		556.2	556.2325
309		556.3	556.233
310		556.2	556.2334
317		514.2	514.2225

Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
318		584.3	584.2636
319		584.3	584.2637
320		584.3	584.2638
321			566.2531
322		580.3	580.2689
324		570.2	570.2484
325		570.2	570.2487
326		570.2	570.2488
327		500.4	

Cpd No.	Structure	Mass Spec. M+H/1	HRMS M+H/1
331		561.2	561.2275
332		527.0	

Characterization data of compounds in Table 1

Cpd No.	^{1}H NMR (ppm)
1	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (s, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.41-7.32 (m, 2H), 7.20 (s, 1H), 7.19-6.80 (m, 2H), 6.47 (s, 1H), 6.22 (d, J = 7.6 Hz, 1H), 4.94 (s, 1H), 3.75 (t, J = 6.4 Hz, 2H), 3.15-3.12 (m, 2H), 2.75-2.68 (m, 2H), 2.54 (s, 2H), 1.92-1.79 (m, 2H), 1.70-1.50 (m, 4H), 1.49-1.35 (m, 3H), 1.32-1.11 (m, 4H).
2	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (s, 1H), 10.11 (s, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.36 (t, J = 7.8 Hz, 1H), 7.19 (s, 1H), 7.02 (d, J = 10.4 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 6.79 (t, J = 5.6 Hz, 1H), 6.21 (d, J = 8.0 Hz, 1H), 4.92 (s, 1H), 3.75 (t, J = 6.6 Hz, 2H), 3.41- 3.17 (m, 4H), 3.14-3.01 (m, 2H), 2.99-2.91 (m, 2H), 2.35-2.29 (m, 1H), 1.90-1.71 (m, 3H), 1.64-1.46 (m, 2H), 1.29-1.05 (m, 3H).
3	^{1}H NMR (499 MHz, CHLOROFORM-d) δ 12.09-12.91 (m, 1 H) 9.48 (s, 1 H) 8.00 (br d, J = 7.1 Hz, 2 H) 7.63 (t, J = 7.9 Hz, 1 H) 7.13 (d, J = 1.9 Hz, 1 H) 6.98 (dd, J = 8.5, 2.2 Hz, 1 H) 6.86 (d, J = 7.7 Hz, 1 H) 4.82-5.49 (m, 7 H) 4.25 (br d, J = 13.4 Hz, 1 H) 4.07-4.19 (m, 2 H) 3.81 (t, J = 5.9 Hz, 2 H) 3.05-3.20 (m, 2 H) 2.88-3.04 (m, 3 H) 1.12-2.13 (m, 6 H)
5	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11-12.0 (m, 1H), 8.26-8.09 (m, 1H), 7.38-7.37 (m, 1H), 7.18 (s, 1H), 7.12-6.96 (m, 2H), 6.86 (s, 1H), 6.20-6.18 (m, 1H), 3.75-3.72 (m, 4H), 3.17-3.10 (m, 6H), 3.01-2.98(m, 3H), 1.94-1.05 (m, 6H), 0.37-0.35 (m, 3H), 0.11-0.10 (m,1H).
6	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12-12.1 (m, 1H), 8.26-8.08 (m, 1H), 7.38-7.36 (m, 1H), 7.18 (s, 1H), 7.12-6.96 (m, 2H), 6.85 (s, 1H), 6.20-6.17 (m, 1H), 3.75-3.70 (m, 4H), 3.17-3.10 (m, 6H), 3.01-2.98(m, 3H), 1.94-1.05 (m, 6H), 0.37-0.35 (m, 3H), 0.11-0.10 (m,1H).
7	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11-12.0 (m, 1H), 8.26-8.09 (m, 1H), 7.38-7.37 (m, 1H), 7.18 (s, 1H), 7.12-6.96 (m, 2H), 6.86 (s, 1H), 6.20-6.18 (m, 1H), 3.75-3.72 (m, 4H), 3.17-3.10 (m, 6H), 3.01-2.98(m, 3H), 1.94-1.05 (m, 6H), 0.37-0.35 (m, 3H), 0.11-0.10 (m,1H).

Cpd No.	^{1}H NMR (ppm)
10	^{1}H NMR (300 MHz, DMSO-d_6) δ 13.35 (s, 1H), 11.94 (s, 1H), 8.47-8.11 (m, 2H), 7.69-7.38 (m, 5H), 7.19-6.83 (m, 3H), 6.17 (s, 1H), 4.30-3.89 (m, 3H), 3.73-3.42 (m, 4H), 3.36-3.34 (m, 4H), 3.22-2.81 (m, 7H).
11	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.85 (s, 1H), 8.09 (d, J = 8.8 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.26 (s, 1H), 7.10 (d, J = 8.8 Hz, 1H), 6.42 (s, 1H), 6.23 (d, J = 8.0 Hz, 1H), 3.76 (t, J = 6.6 Hz, 2H), 3.55-3.45 (m, 3H), 3.18-2.97 (m, 4H), 2.70 (s, 1H), 2.59-2.52 (m, 2H), 2.30-2.10 (m, 2H), 2.09-1.92 (m, 1H), 1.91-1.79 (m, 1H), 1.73-1.59 (m, 1H), 1.58-1.41 (m, 1H), 1.20-1.09 (m, 1H).
13	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.20 (s, 1H), 10.20 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.36-7.32 (m, 1H), 7.14 (s, 1H), 7.07 (d, J = 8.8 Hz, 1H), 6.82 (t, J = 5.6 Hz, 1H), 6.17 (d, J = 8.0 Hz, 1H), 4.92 (s, 1H), 3.75 (t, J = 6.6 Hz, 2H), 3.35 (s, 2H), 3.18-3.16 (m, 2H), 3.13-3.08 (m, 2H), 2.67-2.61 (m, 2H), 2.49-2.43 (m, 2H), 1.90-1.79 (m, 2H), 1.78-1.72 (m, 2H), 1.31-1.26 (m, 2H), 0.83-0.67 (m, 1H), 0.27 (s, 4H).
14	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.61 (s, 1H), 9.55 (s, 1H), 8.63 (d, J = 8.9 Hz, 1H), 7.58-7.51 (m, 1H), 7.35 (d, J = 7.1 Hz, 1H), 7.22 (s, 1H), 7.03 (d, J = 2.5 Hz, 1H), 6.92-6.88 (m, 1H), 6.68 (d, J = 8.3 Hz, 1H), 4.91 (s, 1H), 3.73 (s, 3H), 3.69 (s, 1H), 3.55 (d, J = 12.0 Hz, 2H), 3.05 (d, J = 10.7 Hz, 1H), 2.98-2.85 (m, 2H), 2.35-2.23 (m, 1H), 2.13-2.02 (m, 2H), 1.90-1.75 (m, 1H), 1.74-1.66 (m, 2H), 1.43-1.30 (m, 2H), 1.26-1.17 (m, 2H).
15	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 10.14 (s, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.38-7.22 (m, 3H), 7.08 (d, J = 10.4 Hz, 1H), 6.82 (s, 1H), 6.18 (d, J = 8.0 Hz, 1H), 4.93 (t, J = 5.6 Hz, 1H), 3.78-3.73 (m, 2H), 3.41-3.36 (m, 1H), 3.35 (s, 2H), 3.18 (s, 2H), 3.04-3.02 (m, 1H), 2.92-2.89 (m, 1H), 2.67-2.61 (m, 1H), 2.33-2.31 (m, 1H),1.73 (s, 1H), 1.33-1.24 (m, 3H), 1.20-0.91 (m, 3H), 0.64-0.45 (m, 3H), 0.21 (s, 2H).
16	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.99 (s, 1H), 10.15 (s, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.38-7.29 (m, 2H), 7.21 (s, 1H), 7.08-7.06 (m, 1H), 6.84-6.81 (m, 1H), 6.18 (d, J = 7.6 Hz, 1H), 4.91 (s, 1H), 3.77-3.74 (m, 2H), 3.51-3.35 (m, 4H), 3.21-3.16 (m, 2H), 3.05-3.02 (m, 1H), 2.93-2.90 (m, 1H), 2.67-2.59 (m, 1H), 1.75-1.73 (m, 1H), 1.47-1.36 (m, 3H), 1.24-1.06 (m, 3H), 0.86-0.45 (m, 3H), 0.21-0.15 (m, 2H).
17	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.99 (s, 1H), 10.15 (s, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.38-7.29 (m, 2H), 7.22 (s, 1H), 7.09-7.06 (m, 1H), 6.84-6.81 (m, 1H), 6.18 (d, J = 7.6 Hz, 1H), 4.91 (s, 1H), 3.77-3.74 (m, 2H), 3.51-3.34 (m, 4H), 3.21-3.16 (m, 2H), 3.05-3.02 (m, 1H), 2.93-2.90 (m, 1H), 2.67-2.59 (m, 1H), 1.75-1.73 (m, 1H), 1.47-1.35 (m, 3H), 1.24-1.12 (m, 3H), 0.86-0.45 (m, 3H), 0.21-0.15 (m, 2H).
18	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.43 (s, 1H), 10.20 (s, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.27-7.10 (m, 4H), 4.96-4.93 (m, 1H), 3.77-3.74 (m, 2H), 3.51-3.35 (m, 3H), 3.19-3.03 (m, 2H), 3.00-2.91 (m, 2H), 2.91-2.89 (m, 1H), 2.68-2.60 (m, 1H), 2.49-2.44 (m, 1H), 2.24 (s, 3H), 1.77-1.71 (m, 1H), 1.45-1.23 (m, 3H), 1.18-1.05 (m, 2H), 0.70-0.57 (m, 2H), 0.48 (s, 1H), 0.22 (s, 2H).
19	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.42 (s, 1H), 10.19 (s, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.27-7.11 (m, 4H), 4.96-4.93 (m, 1H), 3.78-3.73 (m, 2H), 3.49-3.37 (m, 3H), 3.19-3.03 (m, 2H), 3.00-2.91 (m, 2H), 2.90-2.89 (m, 1H), 2.70-2.59 (m, 1H), 2.49-2.44 (m, 1H), 2.24 (s, 3H), 1.83-1.71 (m, 1H), 1.45-1.22 (m, 3H), 1.19-1.05 (m, 2H), 0.70-0.57 (m, 2H), 0.49 (s, 1H), 0.25 (s, 2H).

Cpd No.	^{1}H NMR (ppm)
20	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.42 (s, 1H), 10.19 (s, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.27-7.11 (m, 4H) 4.94 (s, 1H), 3.76-3.75 (m, 2H), 3.50-3.37 (m, 3H), 3.22-3.11 (m, 2H), 3.11-3.03 (m, 2H), 3.00-2.89 (m, 1H), 2.66-2.61 (m, 1H), 2.48-2.39 (m, 1H), 2.23 (s, 3H), 1.83-1.72 (m, 1H), 1.47-1.23 (m, 3H), 1.19-1.03 (m, 2H), 0.70-0.56 (m, 2H), 0.49 (s, 1H), 0.22 (s, 2H).
21	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.79-13.76(m, 1H),13.68-13.32(m, 1H), 8.10-7.90 (m, 1H), 7.70-7.65 (m, 1H), 7.26-6.98 (m, 2H), 5.09-4.99(m, 1H), 3.85-3.70 (m, 2H), 3.02-2.83 (m, 4H), 2.24 (s, 3H), 2.03-1.84 (m, 2H), 1.75-1.38 (m, 4H), 1.40- 0.95 (m, 8H), 0.90-0.71 (m, 2H).
22	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.91-13.69(m, 1H),13.60-13.31(m, 1H), 8.10-7.89 (m, 1H), 7.69-7.65 (m, 1H), 7.26-6.98 (m, 2H), 5.09-4.99(m, 1H), 3.85 – 3.70 (m, 2H), 3.02-2.85(m, 4H), 2.24 (s, 3H), 2.03-1.85 (m, 2H), 1.72-1.35 (m, 4H), 1.40- 0.95 (m, 8H), 0.90-0.73 (m, 2H).
23	^{1}H NMR (499 MHz, CHLOROFORM-d) δ 15.22-13.44 (m, 1 H) 10.34 (br d, J = 5.2 Hz, 1 H) 8.14-8.35 (m, 1 H) 7.42-7.59 (m, 1 H) 7.30-7.42 (m, 1 H) 6.99-7.13 (m, 1 H) 6.77-6.90 (m, 1 H) 3.85 (t, J = 5.2 Hz, 2 H) 3.42 (s, 4 H) 3.29 (br t, J = 5.5 Hz, 6 H) 2.60 (s, 1 H) 2.48-2.54 (m, 3 H) 1.68-2.24 (m, 6 H) 0.97-1.49 (m, 6 H)
32	^{1}H NMR (499 MHz, CHLOROFORM-d) δ 15.26 (s, 1 H) 13.52 (br s, 1 H) 10.05-10.20 (m, 1 H) 8.13-8.39 (m, 1 H) 7.41-7.59 (m, 1 H) 7.30-7.39 (m, 1 H) 6.90-7.05 (m, 1 H) 3.85 (t, J = 6.6 Hz, 2 H) 3.37-3.50 (m, 3 H) 3.15-3.30 (m, 2 H) 2.94 - 3.15 (m, 3 H) 2.57-2.65 (m, 3 H) 2.45-2.53 (m, 3 H) 0.99-2.37 (m, 10 H)
34	^{1}H NMR (499 MHz, THF-d_8) δ 14.96 (br s, 1 H) 13.15 (br dd, J = 6.6, 4.1 Hz, 1 H) 10.40 (br s, 1 H) 8.03-8.42 (m, 1 H) 7.31-7.68 (m, 2 H) 7.13-7.30 (m, 1 H) 2.95-3.57 (m, 11 H) 2.78 (s, 6 H) 2.60-2.71 (m, 1 H) 2.49 (s, 3 H) 1.82-2.28 (m, 4 H) 1.19 - 1.68 (m, 6 H)
38	1H NMR (499 MHz, DMSO-d6) δ ppm 12.71 (br dd, J=10.3, 3.1 Hz, 1 H) 10.15 (br s, 1 H) 7.80 - 7.96 (m, 1 H) 7.64 - 7.76 (m, 1 H) 7.34 (br dd, J=6.8, 2.2 Hz, 1 H) 7.12 (br s, 2 H) 6.51 (br d, J=4.1 Hz, 1 H) 4.26 - 4.58 (m, 2 H) 3.94 - 4.11 (m, 1 H) 3.59 - 3.82 (m, 4 H) 3.33 (br t, J=6.2 Hz, 2 H) 2.83 - 3.23 (m, 3 H) 2.65 - 2.80 (m, 1 H) 1.84 - 1.98 (m, 1 H) 1.75 (br s, 1 H) 1.47 - 1.62 (m, 1 H) 1.35 - 1.47 (m, 3 H)
40	^{1}H NMR (499 MHz, CHLOROFORM-d) δ 15.30-13.56 (m, 1 H) 10.24 (br d, J = 5.2 Hz, 1 H) 8.21-8.43 (m, 1 H) 7.83 (d, J = 2.7 Hz, 1 H) 7.69-7.77 (m, 1 H) 7.41 - 7.63 (m, 2 H) 6.00 (d, J = 2.5 Hz, 1 H) 4.01 (s, 3 H) 2.93 - 3.60 (m, 6 H) 2.61-2.73 (m, 2 H) 2.48-2.56 (m, 3 H) 1.01-2.25 (m, 10 H)
41	^{1}H NMR (499 MHz, CHLOROFORM-d) δ 15.36 (s, 1 H) 13.63 (br s, 1 H) 10.17-10.35 (m, 1 H) 8.22-8.37 (m, 1 H) 8.07 - 8.17 (m, 1 H) 7.44-7.61 (m, 1 H) 7.06-7.21 (m, 1 H) 4.48 - 4.62 (m, 2 H) 4.03-4.20 (m, 2 H) 2.90-3.59 (m, 6 H) 2.57 - 2.70 (m, 1 H) 2.47-2.56 (m, 3 H) 1.83-2.18 (m, 4 H) 1.05-1.49 (m, 6 H)
43	1H NMR (499 MHz, CHLOROFORM-d) δ ppm 15.13 - 13.36 (m, 1 H) 10.30 (br s, 1 H) 8.15 - 8.37 (m, 1 H) 7.42 - 7.59 (m, 1 H) 7.30 - 7.39 (m, 1 H) 7.03 - 7.15 (m, 1 H) 2.85 - 3.60 (m, 8 H) 2.55 - 2.66 (m, 1 H) 2.49 - 2.54 (m, 2 H) 0.99 - 2.22 (m, 14 H)
45	^{1}H NMR (499 MHz, CHLOROFORM-d) δ 15.28 (s, 1 H) 13.45 (br s, 1 H) 10.23 (br s, 1 H) 8.10-8.49 (m, 1 H) 7.40-7.61 (m, 2 H) 7.20-7.31 (m, 1 H) 3.34 - 3.56 (m, 4 H) 2.93-3.32 (m, 5 H) 2.88 (s, 3 H) 2.56-2.65 (m, 1 H) 2.47-2.55 (m, 3 H) 0.98-2.20 (m, 10 H)

Cpd No.	^{1}H NMR (ppm)
48	^{1}H NMR (499 MHz, THF-d8) δ 13.49 (s, 1 H) 9.39-9.83 (m, 1 H) 9.30 (br s, 1 H) 8.19 (d, J = 8.8 Hz, 1 H) 7.70-8.06 (m, 1 H) 7.33 (d, J = 2.2 Hz, 1 H) 7.14 (dd, J = 8.8, 2.2 Hz, 1 H) 3.92 (t, J = 6.2 Hz, 2 H) 3.25-3.35 (m, 6 H) 2.79 (br t, J = 11.1 Hz, 2 H) 2.50 (qd, J = 12.6, 3.6 Hz, 2 H) 1.98 (br d, J = 4.7 Hz, 2 H) 1.87 (br d, J = 12.3 Hz, 2 H) 1.41 (br t, J = 7.1 Hz, 2 H) 0.75-0.89 (m, 1 H) 0.28-0.43 (m, 4 H)
52	1H NMR (499 MHz, DMSO-d6) δ ppm 11.04 (br s, 1 H) 10.12 (s, 1 H) 7.92 (br d, J=5.5 Hz, 1 H) 7.72 (t, J=7.8 Hz, 1 H) 7.27 (br d, J=7.1 Hz, 1 H) 7.14 - 7.22 (m, 1 H) 7.01 (br d, J=8.2 Hz, 1 H) 6.54 (d, J=7.9 Hz, 1 H) 4.57 (m, 2.2 Hz, 2 H) 4.02 - 4.11 (m, 1 H) 3.75 (t, J=6.6 Hz, 2 H) 3.33 (t, J=6.6 Hz, 2 H) 3.23 (br d, J=11.0 Hz, 1 H) 2.81 - 3.15 (m, 3 H) 2.24 - 2.40 (m, 1 H) 1.58 - 1.99 (m, 5 H) 1.23 (br s, 2 H) 0.94 - 1.17 (m, 1 H)
53	1H NMR (499 MHz, CHLOROFORM-d) δ ppm 13.58 (br s, 1 H) 10.27 (br s, 1 H) 8.09 - 8.43 (m, 1 H) 7.40 - 7.64 (m, 1 H) 7.19 - 7.39 (m, 2 H) 5.11 (br s, 1 H) 4.43 (br d, J=5.7 Hz, 2 H) 3.74 (s, 3 H) 2.88 - 3.55 (m, 6 H) 2.56 - 2.70 (m, 1 H) 2.43 - 2.55 (m, 3 H) 0.96 - 2.25 (m, 11 H)
54	^{1}H NMR (499 MHz, CHLOROFORM-d) δ 15.34 (s, 1 H) 13.49 (br s, 1 H) 10.20 (br s, 1 H) 8.14-8.40 (m, 1 H) 7.45-7.60 (m, 1 H) 7.33-7.44 (m, 1 H) 7.18-7.32 (m, 1 H) 3.72-3.95 (m, 2 H) 3.35-3.57 (m, 1 H) 3.04 - 3.30 (m, 5 H) 2.91-3.04 (m, 2 H) 2.56-2.70 (m, 1 H) 2.48 - 2.55 (m, 3 H) 2.31-2.41 (m, 2 H) 1.71-2.19 (m, 5 H) 0.98-1.67 (m, 7 H)
55	^{1}H NMR (499 MHz, CHLOROFORM-d) δ 15.28 (s, 1 H) 13.40 (br s, 1 H) 10.19 (br d, J = 5.5 Hz, 1 H) 8.09-8.49 (m, 1 H) 7.45-7.62 (m, 1 H) 7.34-7.45 (m, 1 H) 7.17-7.33 (m, 1 H) 4.78 (s, 2 H) 4.09-4.16 (m, 2 H) 3.99 (br dd, J = 5.5, 3.3 Hz, 2 H) 3.34-3.57 (m, 1 H) 2.93-3.30 (m, 5 H) 2.57-2.66 (m, 1 H) 2.47-2.55 (m, 3 H) 1.78-2.45 (m, 4 H) 1.00-1.67 (m, 6 H)
56	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (s, 1H), 7.15-6.97 (m, 1H), 6.88 (s, 1H), 6.64 (s, 1H), 6.39 (s, 1H), 4.83 (s, 1H), 3.78-3.66 (m, 2H), 3.29-3.22 (m, 2H), 3.10-3.01 (m, 2H), 3.00-2.90 (m, 1H), 2.78-2.60 (m, 2H), 2.23 (s, 3H), 2.12 (s, 1H), 1.63-1.55 (m, 3H), 1.54-1.31 (m, 3H), 1.30-1.18 (m, 4H), 0.88-0.79 (m, 1H).
57	1H NMR (499 MHz, CHLOROFORM-d) δ ppm 7.35 (d, J=8.2 Hz, 1 H) 6.82 - 6.91 (m, 2 H) 6.75 (dd, J=8.1, 2.1 Hz, 1 H) 4.10 (t, J=5.3 Hz, 2 H) 3.50 (br d, J=11.5 Hz, 2 H) 3.19 - 3.37 (m, 4 H) 2.66 - 2.75 (m, 1 H) 2.36 - 2.46 (m, 3 H) 2.32 (br dd, J=12.6, 11.0 Hz, 1 H) 1.79 (br d, J=11.5 Hz, 3 H) 1.16 - 1.70 (m, 9 H) 0.98 - 1.13 (m, 3 H)
58	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.82 (s, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.92 (s, 1H), 7.48 (s, 1H), 7.37-7.36 (m, 2H), 3.76-3.72 (m, 3H), 3.44-3.35 (m, 3H), 3.32-3.17 (m, 2H), 3.04-3.01 (m, 1H), 2.93-2.91 (m, 1H), 2.73-2.67 (m, 2H), 2.48-2.36 (m, 4H), 1.81 (s, 1H), 1.53-1.04 (m, 7H), 0.64 (s, 2H), 0.49 (s, 1H), 0.39-0.21 (m, 2H).
59	^{1}H NMR (400 MHz, DMSO-d6) δ 14.52 (s, 1H), 10.34 (s, 1H), 8.26 (d, J = 6.0 Hz, 1H), 8.09 (s, 1H), 7.94 (s, 1H), 7.37 (s, 1H), 7.29 (s, 1H), 7.16 (d, J = 8.0 Hz, 1H), 3.78-3.75 (m, 3H), 3.69-3.58 (m, 4H), 3.09-2.89 (m, 5H), 1.89-1.80 (m, 2H), 1.79-1.39 (m, 4H), 1.33-1.18 (m, 3H).
60	^{1}H NMR (499 MHz, CHLOROFORM-d) δ ppm 15.21 (s, 1 H) 13.47 (br s, 1 H) 10.31 (br d, J=5.5 Hz, 1 H) 8.17 - 8.40 (m, 1 H) 7.41 - 7.61 (m, 1 H) 7.28 - 7.37 (m, 1 H) 6.90 - 7.03 (m, 1 H) 3.79 - 3.99 (m, 2 H) 3.55 (t, J=6.3 Hz, 2 H) 3.35 - 3.52 (m, 1 H) 2.93 - 3.32 (m, 5 H) 2.89 (s, 3 H) 2.58 - 2.69 (m, 1 H) 2.46 - 2.55 (m, 3 H) 1.00 - 2.17 (m, 10 H)).

Cpd No.	^{1}H NMR (ppm)
62	^{1}H NMR (400 MHz, DMSO-d6) δ 12.53 (s, 1H), 10.21 (s, 1H), 8.20 (d, *J* = 5.6 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 7.36-7.26 (m, 3H), 7.13 (d, *J* = 8.8 Hz, 1H), 4.95-4.93 (m, 1H), 3.78-3.74 (m, 2H), 3.59-3.44 (m, 1H), 3.37-3.34 (m, 2H), 3.32-3.22 (m, 1H), 3.21-3.11 (m, 1H), 3.05-3.02 (m, 1H), 2.92-2.89 (m, 1H), 2.67-2.64 (m, 1H), 2.49-2.44 (m, 1H), 1.80-1.78 (m, 1H), 1.51-1.36 (m, 3H), 1.23-1.12 (m, 2H), 0.64-0.59 (m, 2H), 0.49 (s, 1H), 0.23 (s, 2H).
63	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.80 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.88 (s, 1H), 7.48 (s, 1H), 7.37-7.26 (m, 2H), 5.70-4.70 (m, 1H), 3.75-3.73 (m, 3H), 3.71-3.56 (m, 4H), 3.22-3.16 (m, 2H), 3.04-2.99 (m, 1H), 2.98-2.91 (m, 1H), 2.80-2.62 (m, 1H), 2.41-2.19 (m, 4H), 1.81 (s, 1H), 1.52-1.01 (m, 6H), 0.85-0.36 (m, 3H), 0.35-0.12 (m, 2H).
64	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.55 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.46-7.43 (m, 2H), 7.36 (d, *J* = 8.0 Hz, 1H) 7.24 (s, 1H), 5.08 (s, 1H), 3.75-3.72 (m, 2H), 3.36-3.34 (m, 7H), 3.17-3.13 (m, 1H), 3.04-3.01 (m, 1H), 2.93-2.90 (m, 1H), 2.72-2.66 (m, 1H), 2.49-2.37 (m, 1H), 2.31 (s, 3H), 1.79 (s, 1H), 1.45-1.02 (m, 6H), 0.64-0.47 (m, 2H), 0.45 (s, 1H), 0.23 (s, 2H).
65	^{1}H NMR (400 MHz, DMSO-d6) δ 10.77 (s, 1H), 9.79-9.32 (m, 1H), 8.33 (d, J = 8.6 Hz, 1H), 7.55-7.53 (m, 1H), 7.27 (d, J = 7.1 Hz, 1H), 7.06-6.89 (m, 3H), 6.65 (d, J = 8.4 Hz, 1H), 5.08-4.60 (m, 1H), 3.95-3.69 (m, 4H), 3.21-3.18 (m, 2H), 3.04 (d, J = 10.9 Hz, 2H), 2.56 (d, J = 11.3 Hz, 2H), 2.22-2.04 (m, 2H), 1.69-1.67 (m 4H), 1.43-1.06 (m, 2H), 0.82-0.63 (m, 1H), 0.29 (s, 4H).
67	^{1}H NMR (400 MHz, DMSO-d6) δ 12.60 (s, 1H), 8.19 (d, *J* = 5.2 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.33-7.27 (m, 2H), 7.22 (s, 1H), 7.08-7.05 (m, 1H), 3.77-3.73 (m, 2H), 3.51 (s, 2H), 3.35-3.31 (m, 1H), 3.29-3.26 (m, 1H), 3.23-3.21 (m, 1H), 3.13-3.11 (m, 1H), 3.04-3.01 (m, 1H), 2.90-2.87 (m, 1H), 2.67-2.64 (m, 1H), 2.49-2.46 (m, 1H), 2.08 (s, 1H), 1.82 (s, 1H), 1.45-1.36 (m, 3H), 1.15-1.11 (m, 2H), 0.63-0.59 (m, 2H), 0.49 (s, 1H), 0.23 (s, 2H).
68	^{1}H NMR (400 MHz, DMSO-d6) δ 12.55 (s, 1H), 8.20 (d, *J* = 9.2 Hz, 1H), 7.99 (d, *J* = 8.8 Hz, 1H), 7.33-7.30 (m, 1H), 7.28-7.25 (m, 2H), 7.11-7.09 (m, 1H), 3.77-3.74 (m, 2H), 3.37-3.34 (m, 2H), 3.31-3.23 (m, 3H), 3.20-3.12 (m, 1H), 3.11-3.02 (m, 1H), 2.91-2.88 (m, 1H), 2.67-2.61 (m, 1H), 2.49-2.45 (m, 1H), 2.08 (s, 1H), 1.81 (s, 1H), 1.49-1.32 (m, 3H), 1.21-1.06 (m, 2H), 0.68-0.59 (m, 2H), 0.50 (s, 1H), 0.27 (s, 2H).
69	^{1}H NMR (400 MHz, DMSO-d6) δ 13.84-12.52 (m, 1H), 10.28 (s, 1H), 8.20 (s, 1H), 8.18 (s, 1H), 7.38-7.12 (m, 4H), 5.43-4.45 (m, 1H), 3.77-3.74 (m, 2H), 3.36-3.34 (m, 3H), 3.32-3.30 (m, 1H), 3.17-2.71 (m, 4H), 2.21-1.80 (m, 2H), 1.79-0.85 (m, 8H).
70	^{1}H NMR (400 MHz, DMSO-d6) δ 13.83-12.21 (m, 1H), 10.26 (s, 1H), 8.20 (s, 1H), 8.18-8.14 (m, 1H), 7.39-7.26 (m, 2H), 7.19-7.13 (m, 2H), 4.94 (s, 1H), 3.78-3.74 (m, 2H), 3.37-3.35 (m, 3H), 3.32 (s, 1H), 3.19-2.82 (m, 4H), 2.19-1.80 (m, 2H), 1.79-0.78 (m, 9H).
71	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.39 (s, 1H), 7.97-7.95 (m, 1H), 7.75 (s, 1H), 7.27-7.05 (m, 1H), 6.51 (d, J = 8.6 Hz, 1H), 3.92-3.90 (m, 2H), 3.73-3.60 (m, 2H), 3.44 (s, 4H), 2.98-2.97 (m, 2H), 2.87-2.80 (m, 2H). 2.23 (s, 3H), 1.78 (s, 2H), 1.51-1.26 (m, 3H), 1.33-1.24 (m, 2H), 0.95 (s, 1H), 0.61 (s, 2H), 0.45 (s, 1H), 0.21-0.14 (m, 2H).

Cpd No.	^{1}H NMR (ppm)
72	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.98 (s, 1H), 8.07 (s, 1H), 7.17-7.15 (m, 1H), 7.09 (s, 1H), 6.63-6.60 (m, 1H), 3.77-3.75 (m, 2H), 3.63-3.60 (m, 2H), 3.08-3.05 (m, 4H), 2.84-2.75 (m, 2H), 2.33-2.31 (m, 2H), 2.23 (s, 3H), 1.74 (s, 2H), 1.48-1.26 (m, 3H), 1.22-1.20 (m, 2H), 1.08 (s, 1H), 0.59-0.57 (m, 2H), 0.44-0.42 (m, 1H), 0.19-0.15 (m, 2H).
73	^{1}H NMR (400 MHz, DMSO-d6) δ 11.72 (s, 1H), 10.94 (s, 1H), 8.14 (s, 1H), 7.19 (s, 1H), 7.06 (s, 1H), 6.71 (s, 1H), 3.77-3.75 (m, 2H), 3.27 (s, 1H), 3.17-3.15 (m, 2H), 3.08 (s, 4H), 2.81-2.72 (m, 2H), 2.35-2.27 (m, 2H), 2.24 (s, 3H), 1.72 (s, 2H), 1.49-1.29 (m, 3H), 1.24-1.22 (m, 1H), 1.08 (s, 1H), 0.60-0.58 (m, 1H), 0.43-0.41 (m, 1H), 0.19-0.15 (m, 2H).
75	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.49 (s, 1H), 7.79-7.44 (m, 3H), 7.28 (s, 1H), 6.79 (s, 3H), 6.66 (dd, J = 8.7, 2.0 Hz, 1H), 5.00 (s, 1H), 4.22 (t, J = 6.6 Hz, 1H), 3.87-3.53 (m, 4H), 3.29-3.06 (m, 2H), 2.93 (t, J = 6.7 Hz, 2H), 2.23-1.92 (m, 2H), 1.67 (d, J = 17.3 Hz, 2H), 1.50 (s, 9H), 1.24 (s, 3H), 0.99-0.79 (m, 2H), 0.61 – 0.11 (m, 2H).
76	^{1}H NMR (400 MHz, Chloroform-d) δ 12.27 (s, 1H), 8.00-7.88 (s, 1H), 7.61 (s, 2H), 7.45-7.42 (m, 1H), 6.21-6.20 (m, 1H), 4.96-4.6 (m, 1H), 3.99-3.81 (m, 2H), 3.51-2.82 (m, 6H), 2.56-1.81(m, 3H)1.28-1.88 (m, 3H), 0.99-0.80(m, 3H),0.33-0.31 (m, 1H).
79	^{1}H NMR (499 MHz, DMSO-d$_6$) δ = 12.74 - 12.47 (m, 1H), 7.70 - 7.66 (m, 1H), 7.66 - 7.56 (m, 2H), 7.24 (d, J = 8.8 Hz, 2H), 6.93 - 6.86 (m, 2H), 4.87 - 4.63 (m, 3H), 3.73 (s, 3H), 3.47 - 3.34 (m, 2H), 3.12 (br d, J = 8.2 Hz, 1H), 3.02 - 2.93 (m, 1H), 2.93 - 2.84 (m, 1H), 2.63 - 2.54 (m, 1H), 2.36 (s, 3H), 1.82 - 1.69 (m, 2H), 1.60 - 1.50 (m, 1H), 1.49 - 1.32 (m, 2H), 1.31 - 1.11 (m, 5H)
87	^{1}H NMR (499 MHz, DMSO-d$_6$) δ = 10.25 (s, 1H), 8.24 - 7.89 (m, 1H), 7.41 - 6.99 (m, 4H), 5.12 - 4.92 (m, 1H), 3.93 - 3.75 (m, 1H), 3.51 - 3.44 (m, 1H), 3.31 - 3.22 (m, 4H), 2.98 (br d, J = 3.3 Hz, 4H), 2.25 (s, 3H), 2.15 - 0.87 (m, 14H)
88	^{1}H NMR (499 MHz, DMSO-d$_6$) δ = 10.36 - 10.15 (m, 1H), 8.26 - 7.91 (m, 1H), 7.47 - 6.98 (m, 4H), 5.02 (br s, 1H), 3.89 - 3.76 (m, 1H), 3.54 - 3.45 (m, 1H), 3.31 - 3.19 (m, 4H), 3.12 - 2.82 (m, 4H), 2.25 (s, 3H), 2.18 - 0.84 (m, 14H)
97	^{1}H NMR (400 MHz, DMSO- d6) δ 13.94 (s, 1H), 8.06 (s, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.41 (s, 2H), 7.21 (s, 1H), 7.09 (d, J = 8.8 Hz, 1H), 4.97 (s, 1H), 3.75 (t, J = 6.5 Hz, 2H), 3.38 (s, 1H), 3.11-2.97 (m, 5H), 2.08-0.86 (m, 13H).
98	^{1}H NMR (400 MHz, DMSO-d6) δ 12.48 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.46 (s, 1H), 7.36-7.32 (m, 2H), 7.26 (d, J = 4.0 Hz, 1H), 5.05 (m, 1H), 3.76-3.72 (m, 2H), 3.49-3.32(m, 6H), 3.14-3.08 (m, 1H), 3.05-2.90 (m, 2H), 2.72-2.66 (m, 1H), 2.49 (s, 2H), 2.46-2.35 (m, 1H), 1.84-1.73 (m, 1H), 1.46-1.35 (m, 3H), 1.19-1.05 (m, 2H), 0.67-0.59 (m, 2H), 0.47 (s, 1H),0.25-0.21 (m, 2H).
99	^{1}H NMR (400 MHz, DMSO-d6) δ 12.49 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 4.0 Hz, 1H), 7.36-7.32 (m, 2H), 7.27 (d, J = 4.0 Hz, 1H), 5.06-5.03 (m, 1H), 3.76-3.72 (m, 2H), 3.49-3.39 (m, 2H), 3.37-3.35 (m, 4H), 3.15-3.10 (m, 1H), 3.02-2.90 (m, 2H), 2.72-2.66 (m, 1H), 2.49-2.40(m, 2H), 2.40-2.30 (m, 1H), 1.78 (s, 1H), 1.46-1.35 (m, 3H), 1.15-1.02 (m, 2H), 0.66-0.62 (m, 2H), 0.47 (s, 1H), 0.23 (d, J = 8.0 Hz, 2H).

Cpd No.	^{1}H NMR (ppm)
100	^{1}H NMR (400 MHz, DMSO-d6) δ 12.49 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 12.0 Hz, 1H), 7.46 (d, J = 4.0 Hz, 1H), 7.36-7.32 (m, 2H), 7.27 (d, J = 4.0 Hz, 1H), 5.06-5.03 (m, 1H), 3.74-3.71 (m, 2H), 3.49-3.37 (m, 2H), 3.35-3.34 (m, 5H), 3.14-3.08 (m, 1H), 3.04-2.90 (m, 2H), 2.72-2.66 (m, 1H), 2.41 (s, 2H), 1.78 (s, 1H), 1.46-1.35 (m, 3H), 1.23-1.15 (m, 2H), 0.67-0.62 (m, 2H), 0.47 (s, 1H), 0.25-0.22 (m, 2H).
101	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.28 (s, 1H), 8.15 (d, J = 2.2 Hz, 1H), 7.44 (s, 1H), 7.10 (t, J = 6.4 Hz, 1H), 7.02 (s, 1H), 4.91 (s, 1H), 3.75 (t, J = 6.4 Hz, 2H), 3.29-3.22 (m, 2H), 3.09-2.90 (m, 3H), 2.80-2.61 (m, 3H), 2.76 (s, 3H), 1.79-1.62 (m, 2H), 1.57-1.38 (m, 4H), 1.37-1.15 (m, 5H).
102	1H NMR (499 MHz, CHLOROFORM-d) δ ppm 13.96 (s, 1 H) 10.23 - 10.31 (m, 1 H) 8.29 (d, J=8.5 Hz, 1 H) 7.92 (d, J=6.8 Hz, 1 H) 7.84 (d, J=7.1 Hz, 1 H) 7.33 (d, J=2.2 Hz, 1 H) 7.21 (dd, J=8.5, 2.2 Hz, 1 H) 4.77 (s, 2 H) 4.07 - 4.19 (m, 4 H) 3.96 - 4.02 (m, 3 H) 3.29 - 3.39 (m, 2 H) 3.25 (br d, J=11.5 Hz, 2 H) 2.74 - 2.87 (m, 2 H) 2.28 - 2.44 (m, 2 H) 1.86 - 1.97 (m, 2 H) 1.34 (br t, J=7.5 Hz, 2 H) 0.71 - 0.84 (m, 1 H) 0.24 - 0.41 (m, 4 H)
103	1H NMR (499 MHz, DMSO-d6) δ ppm 13.35 (br s, 1 H) 10.35 (s, 1 H) 8.26 (d, J=6.3 Hz, 1 H) 8.05 (d, J=8.5 Hz, 1 H) 8.01 (br s, 1 H) 7.57 (d, J=6.3 Hz, 1 H) 7.23 (d, J=2.2 Hz, 1 H) 7.14 (dd, J=8.8, 2.2 Hz, 1 H) 3.83 (dd, J=11.1, 4.5 Hz, 1 H) 3.49 (dd, J=11.1, 7.5 Hz, 1 H) 3.29 (td, J=7.1, 4.4 Hz, 1 H) 3.17 (br d, J=10.4 Hz, 4 H) 2.66 (br t, J=11.8 Hz, 2 H) 2.24 - 2.38 (m, 2 H) 1.72 - 1.87 (m, 4 H) 1.29 (d, J=6.8 Hz, 5 H) 0.78 (br s, 1 H) 0.29 (s, 4 H)
104	1H NMR (499 MHz, DMSO-d6) δ ppm 13.34 (br s, 1 H) 10.34 (s, 1 H) 8.26 (d, J=6.3 Hz, 1 H) 8.04 - 8.08 (m, 1 H) 8.00 (br s, 1 H) 7.56 (d, J=6.3 Hz, 1 H) 7.23 (d, J=2.2 Hz, 1 H) 7.09 - 7.19 (m, 1 H) 3.83 (dd, J=11.2, 4.4 Hz, 1 H) 3.49 (dd, J=11.2, 7.7 Hz, 1 H) 3.29 (quind, J=7.0, 7.0, 7.0, 7.0, 4.7 Hz, 1 H) 3.16 (br d, J=9.6 Hz, 4 H) 2.66 (br t, J=11.5 Hz, 2 H) 2.24 - 2.35 (m, 2 H) 1.72 - 1.87 (m, 4 H) 1.24 - 1.35 (m, 5 H) 0.73 - 0.82 (m, 1 H) 0.29 (s, 4 H)
105	1H NMR (499 MHz, DMSO-d6) δ ppm 10.36 (s, 1 H) 8.29 (d, J=6.6 Hz, 2 H) 8.09 (br d, J=4.1 Hz, 1 H) 7.44 (br s, 1 H) 7.32 (br s, 1 H) 7.19 (br d, J=5.2 Hz, 1 H) 3.83 (ddd, J=11.1, 4.5, 0.8 Hz, 3 H) 3.50 (ddd, J=11.1, 7.5, 5.2 Hz, 2 H) 2.85 - 3.42 (m, 9 H) 1.88 (m, 2 H) 1.09 - 1.41 (m, 8 H)
106	1H NMR (499 MHz, DMSO-d6) δ ppm 13.35 (br s, 1 H) 10.11 (s, 1 H) 8.25 (d, J=6.3 Hz, 1 H) 8.02 (d, J=8.8 Hz, 1 H) 7.90 (br d, J=1.4 Hz, 1 H) 7.54 (d, J=6.3 Hz, 1 H) 7.36 (d, J=1.9 Hz, 1 H) 7.17 (dd, J=8.8, 2.2 Hz, 1 H) 3.55 (s, 2 H) 3.15 (br d, J=11.0 Hz, 4 H) 2.61 - 2.70 (m, 2 H) 2.31 (qd, J=12.5, 3.6 Hz, 2 H) 1.72 - 1.88 (m, 4 H) 1.28 (br t, J=7.4 Hz, 2 H) 1.24 (s, 6 H) 0.73 - 0.83 (m, 1 H) 0.29 (s, 4 H)
107	1H NMR (499 MHz, DMSO-d6) δ ppm 13.39 (br s, 1 H) 10.27 (s, 1 H) 8.26 (d, J=6.3 Hz, 1 H) 8.04 (d, J=8.5 Hz, 1 H) 7.97 (br s, 1 H) 7.56 (d, J=6.3 Hz, 1 H) 7.27 (d, J=1.9 Hz, 1 H) 7.13 (dd, J=8.8, 2.2 Hz, 1 H) 3.74 (s, 2 H) 3.16 (br d, J=11.0 Hz, 4 H) 2.61 - 2.70 (m, 2 H) 2.24 - 2.38 (m, 2 H) 1.73 - 1.87 (m, 4 H) 1.29 (br t, J=7.4 Hz, 2 H) 1.12 - 1.18 (m, 2 H) 0.96 - 1.03 (m, 2 H) 0.72 - 0.85 (m, 1 H) 0.29 (s, 4 H)
108	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.37 (s, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.36-7.26 (m, 2H), 7.25-7.15 (m, 2H), 5.03 (s, 2H), 4.12-4.04 (m, 2H), 4.01-3.91 (m, 2H), 3.58-3.44 (m, 3H), 3.15-2.98 (m, 2H), 2.90 (d, J = 10.6 Hz, 1H), 2.74-2.63 (m, 1H), 2.44-2.31 (m, 1H), 2.25 (s, 3H), 1.84-1.70 (m, 1H), 1.50-1.26 (m, 3H), 1.24-1.02 (m, 2H), 0.69-0.54 (m, 2H), 0.51-0.43 (m, 1H), 0.28-0.19 (m, 2H).

Cpd No.	^{1}H NMR (ppm)
109	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.38 (s, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.36-7.27 (m, 2H), 7.25-7.15 (m, 2H), 5.03 (s, 2H), 4.12-4.04 (m, 2H), 4.01-3.91 (m, 2H), 3.59-3.40 (m, 3H), 3.15-2.98 (m, 2H), 2.90 (d, J = 10.6 Hz, 1H), 2.74-2.63 (m, 1H), 2.44-2.31 (m, 1H), 2.25 (s, 3H), 1.84-1.70 (m, 1H), 1.50-1.26 (m, 3H), 1.24-1.02 (m, 2H), 0.69-0.54 (m, 2H), 0.51-0.43 (m, 1H), 0.28-0.19 (m, 2H).
110	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.38 (s, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.36-7.27 (m, 2H), 7.25-7.15 (m, 2H), 5.03 (s, 2H), 4.12-4.04 (m, 2H), 4.01-3.91 (m, 2H), 3.59-3.40 (m, 3H), 3.15-2.98 (m, 2H), 2.90 (d, J = 10.6 Hz, 1H), 2.74-2.63 (m, 1H), 2.44-2.31 (m, 1H), 2.25 (s, 3H), 1.84-1.70 (m, 1H), 1.50-1.26 (m, 3H), 1.24-1.02 (m, 2H), 0.69-0.54 (m, 2H), 0.51-0.43 (m, 1H), 0.28-0.19 (m, 2H).
111	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 9.59 (s, 1H), 8.30 (d, J = 8.0 Hz, 1H), 7.56-7.52 (m, 1H), 7.30-7.28 (m, 1H), 7.15 (d, J = 4.0 Hz, 1H), 7.02-6.99 (m, 1H), 6.95 (s, 1H), 6.70-6.68 (m, 1H), 4.92 (s, 1H), 3.74 (d, J = 8.0 Hz, 2H), 3.71-3.57 (m, 2H), 3.23-3.20 (m, 3H), 3.04 (d, J = 8.0 Hz, 2H), 2.79-2.77 (m, 1H), 2.68-2.62 (m, 2H), 2.33-2.31 (m, 1H), 2.10-2.18 (m, 1H),1.79 (s, 1H), 1.55 (s, 1H), 1.37 (s, 2H), 1.23-1.14 (m, 1H), 0.55 (s, 1H), 0.41 (s, 1H), 0.24 (d, J = 8.0 Hz, 2H).
112	^{1}H NMR (300 MHz, DMSO-d6) δ 12.02 (s, 1H), 10.46 (s, 1H), 8.24 (d, J = 2.1 Hz, 1H), 7.51 (d, J = 2.3 Hz, 1H), 7.10 (t, J = 6.4 Hz, 1H), 7.00 (s, 1H), 4.97 (s, 1H), 3.77 (t, J = 6.3 Hz, 2H), 3.09-2.88 (m, 4H), 2.81-2.64 (m, 3H), 2.24 (s, 3H), 1.76-1.60 (m, 2H), 1.55-1.38 (m, 4H), 1.33-1.19 (m, 6H).
113	^{1}H NMR (400 MHz, DMSO-d6) δ 12.02 (s, 1H), 8.24 (d, J = 2.1 Hz, 1H), 7.51 (d, J = 2.3 Hz, 1H), 7.44-7.7.29 (m, 1H), 7.10 (t, J = 6.4 Hz, 1H), 7.00 (s, 1H), 4.97 (s, 1H), 3.77 (t, J = 6.3 Hz, 2H), 3.09-2.88 (m, 4H), 2.81-2.64 (m, 3H), 2.24 (s, 3H), 1.76-1.60 (m, 2H), 1.55-1.38 (m, 4H), 1.33-1.19 (m, 6H).
114	^{1}H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.32 (s, 1H), 7.02-6.96 (m, 3H), 5.75-5.42 (m, 2H), 3.75-3.72 (m, 2H), 3.58-3.49 (m, 5H), 3.14-3.11 (m, 3H), 2.68-2.62 (m, 2H), 2.22 (s, 3H), 2.13-2.05 (m, 4H), 1.80-1.77 (m, 2H), 1.69-1.57 (m, 1H), 1.55-1.43 (m, 2H).
115	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H), 7.07-7.02 (m, 1H), 7.01 (s, 1H), 6.90-6.86 (m, 2H), 6.38 (s, 1H), 4.62-4.54 (m, 1H), 3.93-3.77 (m, 2H), 3.32-3.12 (m, 4H), 3.11-3.01 (m, 1H), 2.79-2.64 (m, 2H), 2.27-2.12 (m, 4H), 1.41-1.31 (m, 3H), 1.30-1.25 (m, 3H), 1.24-1.19 (m, 4H).
116	^{1}H NMR (400 MHz, DMSO-d6) δ 11.28 (s, 1H), 8.17 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.37 (s, 1H), 7.10 (s, 1H), 7.04 (d, J = 8.8 Hz, 1H), 6.93-6.90 (m, 1H), 3.77-3.74 (m, 2H), 3.39-3.36 (m, 4H), 3.16-3.14 (m, 2H), 2.70-2.65 (m, 2H), 2.21 (s, 3H), 1.99-1.91 (m, 2H), 1.72-1.59 (m, 1H), 1.55-1.31 (m, 10H).
118	1H NMR (499 MHz, DMSO-d6) δ ppm 10.16 (s, 1 H) 8.07 (br s, 1 H) 7.22 (br s, 1 H) 7.05 - 7.17 (m, 2 H) 6.96 - 7.04 (m, 1 H) 6.42 (br d, J=3.3 Hz, 1 H) 3.69 - 3.81 (m, 6 H) 3.34 (br t, J=6.4 Hz, 3 H) 2.87 - 3.18 (m, 5 H) 0.89 - 2.07 (m, 11 H)
119	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (s, 1H), 8.18 (d, J = 5.5 Hz, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.42-7.31 (m, 1H), 7.31-7.21 (m, 1H), 7.18 (d, J = 2.3 Hz, 1H), 7.10-7.08 (m, 1H), 3.76-3.75 (m, 2H), 3.14-3.15 (m, 2H), 3.08-3.05 (m, 3H), 2.73-2.70 (m, 3H), 2.26-2.20 (m, 4H), 1.75-1.72 (m, 3H), 1.59-1.56 (m, 4H), 1.41-1.39 (m, 2H).
120	^{1}H NMR (400 MHz, DMSO- d6) δ 8.14 (s, 1H), 7.40-7.33 (m, 2H), 7.21 (s, 1H), 7.12 (s, 1H), 5.03 (s, 2H), 4.08 (d, J = 4.5 Hz, 2H), 3.98 (d, J = 5.0 Hz, 2H), 3.06-3.03 (m, 5H), 2.25 (s, 3H), 1.91-1.24 (m, 12H).

Cpd No.	^{1}H NMR (ppm)
121	^{1}H NMR (400 MHz, DMSO- d6) δ 8.13 (s, 1H), 7.40-7.32 (m, 2H), 7.19-7.12 (m, 2H), 5.03 (s, 2H), 4.07 (d, *J* = 4.5 Hz, 2H), 3.97 (d, *J* = 5.0 Hz, 2H), 3.32-3.17 (m, 5H), 2.25 (s, 3H), 1.89-1.24 (m, 12H).
122	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 9.57 (s, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 7.56-7.52 (m, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.15 (s, 1H), 7.02-6.96 (m, 2H), 6.69 (d, *J* = 8.0 Hz, 1H), 5.00 (s, 1H), 3.76-3.72 (m, 2H), 3.58-3.52 (m, 2H), 3.23-3.20 (m, 3H), 3.05 (d, *J* = 8.0 Hz, 1H), 2.77 (s, 1H), 2.66-2.63 (m, 2H), 2.14 (s, 1H), 1.79 (s, 1H), 1.56 (s, 1H), 1.38-1.25 (m, 2H), 1.24 (s, 1H), 1.04 (s, 1H), 0.63-0.55 (m, 2H), 0.41 (s, 1H), 0.25 (d, *J* = 8.0 Hz, 2H).
123	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.39 (s, 1H), 9.60 (s, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 7.56-7.52 (m, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 4.0 Hz, 1H), 7.02-6.95 (m, 2H), 6.69 (d, *J* = 8.0 Hz, 1H), 4.94 (s, 1H), 3.76-3.73 (m, 2H), 3.58-3.52 (m, 3H), 3.23-3.20 (m, 2H), 3.05 (d, *J* = 8.0 Hz, 1H), 2.80-2.77 (m, 1H), 2.67-2.63 (m, 2H), 2.14 (s, 1H), 1.79 (s, 1H), 1.58-1.55 (m, 1H), 1.37 (s, 2H), 1.24 (s, 1H) , 1.03 (s, 1H) , 0.63-0.53 (m, 2H) , 0.41 (s, 1H) , 0.24 (d, *J* = 8.0 Hz, 2H).
124	^{1}H NMR (400 MHz, DMSO- d_6) δ 12.20 (s, 1H), 10.20 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.36-7.32 (m, 1H), 7.14 (s, 1H), 7.07 (d, J = 8.8 Hz, 1H), 6.82 (t, *J* = 5.6 Hz, 1H), 6.17 (d, *J* = 8.0 Hz, 1H), 4.92 (s, 1H), 3.75 (t, *J* = 6.6 Hz, 2H), 3.35 (s, 2H), 3.18-3.16 (m, 2H), 3.13-3.08 (m, 2H), 2.67-2.61 (m, 2H), 2.49-2.43 (m, 2H), 1.90-1.79 (m, 2H), 1.78-1.72 (m, 2H), 1.31-1.26 (m, 2H), 0.83-0.67 (m, 1H), 0.27 (s, 4H).
125	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.41 (br s, 1 H) 10.25 (s, 1 H) 8.00 (d, J=8.5 Hz, 1 H) 7.28 (d, J=1.8 Hz, 1 H) 7.20 - 7.25 (m, 1 H) 7.18 (s, 1 H) 7.13 (dd, J=8.8, 1.8 Hz, 1 H) 3.43 - 3.62 (m, 1 H) 3.16 - 3.26 (m, 3 H) 3.07 - 3.15 (m, 1 H) 2.98 - 3.06 (m, 1 H) 2.87 - 2.96 (m, 1 H) 2.56 - 2.66 (m, 1 H) 2.44 (br dd, J=5.1, 2.1 Hz, 1 H) 2.25 (s, 3 H) 1.67 - 1.87 (m, 1 H) 1.28 - 1.52 (m, 3 H) 1.01 - 1.25 (m, 6 H) 0.55 - 0.70 (m, 2 H) 0.41 - 0.54 (m, 1 H) 0.22 (br d, J=4.0 Hz, 2 H)
126	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 12.40 (s, 1 H) 10.25 (s, 1 H) 7.99 (d, J=8.5 Hz, 1 H) 7.28 (d, J=2.0 Hz, 1 H) 7.23 (br t, J=5.6 Hz, 1 H) 7.18 (s, 1 H) 7.13 (dd, J=8.5, 2.0 Hz, 1 H) 3.43 - 3.63 (m, 1 H) 3.16 - 3.27 (m, 4 H) 3.07 - 3.15 (m, 1 H) 2.99 - 3.06 (m, 1 H) 2.87 - 2.95 (m, 3 H) 2.57 - 2.65 (m, 1 H) 2.25 (s, 3 H) 1.67 - 1.89 (m, 1 H) 1.28 - 1.51 (m, 3 H) 1.03 - 1.21 (m, 4 H) 0.54 - 0.70 (m, 2 H) 0.42 - 0.52 (m, 1 H) 0.16 - 0.31 (m, 2 H)
127	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 11.59 (s, 1 H) 8.18 (d, J=5.5 Hz, 1 H) 7.87 - 8.10 (m, 1 H) 7.53 (d, J=5.5 Hz, 1 H) 7.24 - 7.42 (m, 1 H) 6.95 - 7.19 (m, 2 H) 5.38 - 5.67 (m, 1 H) 5.14 - 5.36 (m, 1 H) 3.63 - 3.86 (m, 4 H) 3.33 - 3.59 (m, 2 H) 3.09 (br d, J=10.0 Hz, 2 H) 2.54 - 2.86 (m, 3 H) 1.87 - 2.39 (m, 5 H) 1.66 - 1.85 (m, 1 H) 1.48 (br d, J=10.8 Hz, 2 H)
128	^{1}H NMR (400 MHz, DMSO- d6) δ 12.51 (s, 1H), 10.26 (s, 1H), 8.20 (d, *J* = 5.5 Hz, 1H), 8.01 (d, *J* = 8.7 Hz, 1H), 7.33-7.26 (m, 3H), 7.13 (d, *J* = 8.5 Hz, 1H), 3.52 (s, 1H), 3.25-2.91 (m, 6H), 2.68-2.64 (m, 2H), 2.08 (s, 1H), 1.80 (s, 1H), 1.41-1.13 (m, 8H), 0.64 (s, 2H), 0.49 (s, 1H), 0.24 (s, 2H).
129	^{1}H NMR (400 MHz, DMSO- d6) δ 12.51 (s, 1H), 10.26 (s, 1H), 8.20 (d, *J* = 5.4 Hz, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.34-7.26 (m, 3H), 7.13 (dd, *J* = 8.5, 2.0 Hz, 1H), 3.50 (s, 1H), 3.25-2.90 (m, 5H), 2.68-2.61 (m, 1H), 2.55 (s, 3H), 1.80 (s, 1H), 1.46-1.13 (m, 8H), 0.65 (d, *J* = 8.7 Hz, 2H), 0.48 (s, 1H), 0.24 (s, 2H).

Cpd No.	^{1}H NMR (ppm)
130	^{1}H NMR (400 MHz, DMSO- d6) δ 12.52 (s, 1H), 10.26 (s, 1H), 8.20 (d, *J* = 5.4 Hz, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.51-7.21 (m, 3H), 7.13 (dd, *J* = 8.6, 2.0 Hz, 1H), 3.50 (s, 1H), 3.36 (s, 1H), 3.27-2.83 (m, 6H), 2.74-2.59 (m, 1H), 2.46 (s, 1H), 1.80 (s, 1H), 1.49-1.28 (m, 3H), 1.21 (t, *J* = 7.3 Hz, 3H), 1.14 (d, *J* = 10.8 Hz, 2H), 0.64 (s, 2H), 0.49 (s, 1H), 0.24 (s, 2H).
131	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.26 (s, 1H), 8.18 (d, *J* = 5.5Hz, 1H), 8.09 (d, *J* = 8.6Hz, 1H), 7.34-7.21 (m, 3H), 7.14 (m, 1H), 3.86-3.72 (m, 2H), 3.69-3.47 (m, 3H), 3.40-3.32 (m, 2H), 3.15-2.95 (m, 6H), 2.80-2.65 (m, 1H), 1.86-1.52 (m, 2H), 1.00-0.84 (m, 1H), 0.75-0.63 (m, 1H), 0.61-0.53 (m, 1H), 0.38-0.25 (m, 2H).
132	^{1}H NMR (400 MHz, DMSO-d6) δ 13.26 (s, 1H), 8.18 (d, J = 5.4 Hz, 1H), 8.09 (d, J = 8.6 Hz, 1H), 7.34-7.19 (m, 3H), 7.18-77.08 (m, 1H), 3.84-3.70 (m, 2H), 3.69-3.44 (m, 3H), 3.43-3.35 (m, 2H), 3.25-2.91 (m, 6H), 2.77-2.63 (m, 1H), 1.83-1.54 (m, 2H), 0.98-0.78 (m, 1H), 0.76-0.64 (m, 1H), 0.63-0.48 (m, 1H), 0.41-0.24 (m, 2H).
133	^{1}H NMR (400 MHz, DMSO-d6) δ 13.26 (s, 1H), 10.24 (br s, 1H), 8.18 (d, J = 5.4 Hz, 1H), 8.09 (d, J = 8.7 Hz, 1H), 7.32-7.21 (m, 3H), 7.17-7.10 (m, 1H), 4.94 (br s, 1H), 3.82-3.70 (m, 2H), 3.69-3.46 (m, 3H), 3.41-3.34 (m, 2H), 3.25-2.87 (m, 6H), 2.76-2.65 (m, 1H), 1.81-1.55 (m, 2H), 0.91-0.81 (m, 1H), 0.76-0.64 (m, 1H), 0.63-0.53 (m, 1H), 0.41-0.26 (m, 2H).
134	^{1}H NMR (400 MHz, DMSO-d6) δ 10.93 (s, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.34 (s, 1H), 7.19 (dd, J = 8.4, 2.1 Hz, 1H), 7.13 (d, J = 2.1 Hz, 1H), 7.02 (s, 1H), 5.62-5.46 (m, 2H), 5.02 (s, 2H), 4.08 (dd, J = 5.6, 3.4 Hz, 2H), 3.95 (dd, J = 5.5, 3.6 Hz, 2H), 3.52 (s, 2H), 3.15 (d, J = 11.2 Hz, 2H), 2.74 (t, J = 11.6 Hz, 2H), 2.24 (s, 3H), 2.13 (d, J = 4.4 Hz, 2H), 2.07 (dt, J = 7.4, 3.0 Hz, 2H), 1.76 (q, J = 11.9 Hz, 2H), 1.64 (d, J = 12.2 Hz, 1H), 1.50 (d, J = 12.3 Hz, 2H).
135	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 11.30 (s, 1 H) 7.95 (d, J=8.5 Hz, 1 H) 7.38 (s, 1 H) 7.13 - 7.28 (m, 2 H) 6.95 (t, J=6.5 Hz, 1 H) 5.02 (s, 2 H) 4.05 - 4.11 (m, 2 H) 3.93 - 3.99 (m, 2 H) 3.36 - 3.45 (m, 2 H) 3.17 (d, J=11.0 Hz, 2 H) 2.77 (t, J=11.5 Hz, 2 H) 2.23 (s, 3 H) 1.86 - 2.04 (m, 2 H) 1.61 - 1.75 (m, 1 H) 1.41 - 1.59 (m, 8 H) 1.37 (d, J=4.8 Hz, 2 H)
136	^{1}H NMR (400 MHz, DMSO- d_6) δ 8.21 (d, *J* = 5.4 Hz, 1H), 8.06 (d, *J* = 8.3 Hz, 1H), 7.37-7.23 (m, 4H), 5.02 (s, 2H), 4.81 (s, 3H), 4.65 (s, 1H), 4.04 (s, 2H), 3.97 (s, 4H), 3.91-3.82 (m, 3H), 3.62-3.55 (m, 3H), 1.24 (s, 1H), 0.64 (s, 2H), 0.24 (s, 4H).
137	^{1}H NMR (400 MHz, DMSO- d_6) δ 8.21 (d, *J* = 5.4 Hz, 1H), 8.06 (d, *J* = 8.3 Hz, 1H), 7.37-7.23 (m, 4H), 5.03 (s, 2H), 4.82 (s, 3H), 4.69 (s, 1H), 4.08 (s, 2H), 3.97 (s, 4H), 3.90-3.83 (m, 3H), 3.62-3.55 (m, 3H), 1.24 (s, 1H), 0.64 (s, 2H), 0.24 (s, 4H).
138	^{1}H NMR (400 MHz, DMSO- d_6) δ 8.21 (d, *J* = 5.4 Hz, 2H), 8.06 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 12.8 Hz, 6H), 7.31-7.23 (m, 3H), 6.52 (s, 1H), 5.03 (s, 4H), 4.08 (s, 4H), 3.97 (s, 3H), 1.24 (s, 1H), 0.64 (s, 2H),0.24 (s, 4H).
139	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.12 (s, 1H), 8.11 (d, *J* = 8.8 Hz, 1H), 7.27 (s, 1H), 7.22-7.19 (m, 2H), 7.17-7.10 (m, 1H), 4.97 (s, 1H), 4.11-3.82 (m, 1H), 3.77-3.74 (m, 2H), 3.37-3.35 (m, 3H), 3.22-3.01 (m, 3H), 3.00-2.89 (m, 1H), 2.80-2.60 (m, 1H), 2.40-2.31 (m, 1H), 2.24 (s, 3H), 2.22-2.08 (m, 1H), 2.00-1.72 (m, 1H), 1.70-1.49 (m, 2H), 1.45-1.29 (m, 2H), 1.28-0.99 (m, 1H).

Cpd No.	^{1}H NMR (ppm)
140	^{1}H NMR (400 MHz, DMSO- d6) δ 10.73 (s, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.05 (d, *J* = 2.1 Hz, 1H), 6.99 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.52 (t, *J* = 6.6 Hz, 1H), 6.17 (d, *J* = 8.1 Hz, 1H), 5.69-5.40 (m, 2H), 3.75 (t, *J* = 6.5 Hz, 2H), 3.54 (s, 2H), 3.34 (s, 1H), 3.17 (d, *J* = 11.2 Hz, 2H), 2.65 (t, *J* = 11.3 Hz, 2H), 2.13 (s, 2H), 2.09-2.01 (m, 3H), 1.86-1.48 (m, 5H).
141	^{1}H NMR (400 MHz, DMSO-d6) δ 11.19 (s, 1H),10.11 (s, 1H), 7.93 (d, *J* = 8.6 Hz, 1H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.10 (s, 1H), 7.06-6.99 (m, 1H), 6.50 (t, *J* = 6.6 Hz, 1H), 6.17 (d, *J* = 8.1 Hz, 1H), 3.75 (t, *J* = 6.5 Hz, 3H), 3.63 (s, 2H), 3.43 (d, *J* = 6.0 Hz, 2H), 3.17 (d, *J* = 11.0 Hz, 2H), 2.76-2.62 (m, 2H), 2.01 (d, *J* = 12.3 Hz, 2H), 1.68-1.24 (m, 11H).
142	^{1}H NMR (400 MHz, DMSO-d6) δ 10.67 (s, 1H), 10.12 (s, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.35 (d, *J* = 1.2 Hz, 1H), 7.10-6.97 (m, 2H), 6.41 (t, *J* = 6.6 Hz, 1H), 6.00 (s, 1H), 5.68-5.39 (m, 2H), 4.93 (s, 1H), 3.75 (t, *J* = 6.5 Hz, 2H), 3.53 (d, *J* = 9.3 Hz, 2H), 3.35-3.33 (m, 2H), 3.16 (d, *J* = 11.0 Hz, 2H), 2.65 (t, *J* = 11.4 Hz, 2H), 2.20-1.94 (m, 7H), 1.81 (q, *J* = 12.4, 11.9 Hz, 2H), 1.63 (s, 1H), 1.49 (d, *J* = 12.4 Hz, 2H).
143	^{1}H NMR (400 MHz, DMSO-d6) δ 14.50 (s, 1H), 10.26 (s, 1H), 8.03 (d, J = 4.6 Hz, 2H), 7.56 (s, 1H), 7.28 (s, 1H), 7.16 (d, J = 8.7 Hz, 1H), 5.01 (s, 1H), 3.83-3.71 (m, 2H), 3.44-3.35 (m, 4H), 3.30-3.22 (m, 1H), 3.12-2.87 (m, 4H), 2.08-1.85 (m, 2H), 1.82-1.40 (m, 3H), 1.39-0.98 (m, 5H).
144	^{1}H NMR (400 MHz, DMSO-d6) δ 13.15 (s, 1H), 8.86 (s, 1H), 8.41 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.28-7.23 (m, 2H), 7.20-7.12 (m, 2H), 4.20-3.82 (m, 1H), 3.81-3.68 (m, 2H), 3.29-3.26 (m, 2H), 3.24-3.01 (m, 3H), 3.00-2.85 (m, 1H), 2.33-2.13 (m, 4H), 2.11-2.09 (m, 1H), 2.07-1.76 (m, 1H), 1.75-1.30 (m, 5H), 1.29-0.97 (m, 2H).
145	^{1}H NMR (400 MHz, DMSO-d6) δ 13.21 (s, 1H), 8.84 (s, 1H), 8.48 (m, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.28-7.04 (m, 4H), 4.97 (s, 1H), 3.80-3.72 (m, 2H), 3.24-3.21 (m, 2H), 3.20-3.00 (m, 3H), 2.99-2.88 (m, 1H), 2.28-2.20 (m, 4H), 2.12-2.10 (m, 1H), 2.00-1.79 (m, 1H), 1.76-1.34 (m, 5H), 1.28-1.24 (m, 1H), 1.22-1.03 (m, 1H).
147	1H NMR (499 MHz, CHLOROFORM-d) δ ppm 8.16 (br d, J=11.0 Hz, 1 H) 7.72 - 7.86 (m, 2 H) 7.27 - 7.68 (m, 3 H) 6.95 - 7.14 (m, 1 H) 6.51 (br d, J=1.9 Hz, 1 H) 4.08 (br t, J=4.7 Hz, 2 H) 3.25 - 3.52 (m, 7 H) 2.68 (br d, J=8.8 Hz, 1 H) 1.66 - 2.22 (m, 6 H) 1.08 - 1.58 (m, 8 H)
148	^{1}H NMR (400 MHz, DMSO- d6) δ 13.07 (s, 1H), 10.18 (s, 1H), 8.05 (s, 1H), 7.21 (s, 1H), 7.10 (d, J = 9.2 Hz, 2H), 6.69 (s, 1H), 6.02 (t, J = 1.1 Hz, 1H), 4.96 (s, 1H), 3.76 (t, J = 6.5 Hz, 2H), 3.33 (s, 3H), 2.99 (s, 4H), 2.50 (m, 2H), 2.16 (s, 3H), 1.92 (s, 2H), 1.42 (m, 8H).
149	^{1}H NMR (400 MHz, DMSO- d6) δ 13.06 (s, 1H), 10.18 (s, 1H), 8.06 (s, 1H), 7.22 (s, 1H), 7.10 (d, J = 9.3 Hz, 2H), 6.69 (s, 1H), 6.02 (s, 1H), 4.94 (s, 1H), 3.76 (t, J = 6.5 Hz, 2H), 3.35 (s, 3H), 2.99 (s, 4H), 2.16 (s, 4H), 1.42 (s, 9H).
150	^{1}H NMR (400 MHz, DMSO- d6) δ 13.09 (s, 1H), 10.17 (s, 1H), 8.06 (s, 1H), 7.22 (s, 1H), 7.10 (d, J = 9.0 Hz, 2H), 6.69 (s, 1H), 6.02 (s, 1H), 4.93 (s, 1H), 3.76 (t, J = 6.5 Hz, 2H), 3.35 (s, 3H), 2.99 (s, 4H), 2.16 (s, 4H), 1.92 (s, 2H), 1.43 (s, 9H).
151	^{1}H NMR (400 MHz, DMSO-d6) δ 11.43 (s, 1H), 8.15 (d, J = 5.5 Hz, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.44 (d, J = 5.5 Hz, 1H), 7.08 (d, J = 2.1 Hz, 1H), 7.05-6.94 (m, 2H), 3.80-3.69 (m, 4H), 3.43-3.35 (m, 2H), 3.22-3.10 (m, 2H), 2.76-2.62 (m, 2H), 2.04-1.85 (m, 2H), 1.75-1.61 (m, 1H), 1.60-1.31 (m, 11H).

Cpd No.	^{1}H NMR (ppm)
152	^{1}H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 7.91 (d, J = 8.6 Hz, 1H), 7.35 (d, J = 1.2 Hz, 1H), 7.07 (d, J = 2.1 Hz, 1H), 7.01 (dd, J = 8.6, 2.0 Hz, 1H), 6.37 (t, J = 6.5 Hz, 1H), 6.00 (s, 1H), 3.75 (t, J = 6.5 Hz, 2H), 3.42 (d, J = 6.2 Hz, 2H), 3.31-3.29 (m, 2H), 3.16 (d, J = 11.1 Hz, 2H), 2.75-2.61 (m, 2H), 2.14 (s, 3H), 2.00 (q, J = 12.2 Hz, 2H), 1.67 (s, 1H), 1.56 (d, J = 12.5 Hz, 2H), 1.42 (d, J = 26.9 Hz, 9H).
153	^{1}H NMR (400 MHz, DMSO-d6) δ 14.48 (s, 1H), 10.33 (s, 1H), 8.03 (d, J = 43.6 Hz, 2H), 7.56 (s, 1H), 7.28 (s, 1H), 7.16 (d, J = 8.4 Hz, 1H), 5.08 (s, 1H), 3.83-3.70 (m, 2H), 3.44-3.34 (m, 2H), 3.30-3.22 (m, 2H), 3.12-2.74 (m, 4H), 2.17-1.82 (m, 2H), 1.81-0.90 (m, 9H).
154	^{1}H NMR (400 MHz, DMSO-d6) δ 14.42 (s, 1H), 8.03 (d, J = 42.8 Hz, 2H), 7.56 (s, 1H), 7.28 (s, 1H), 7.15 (d, J = 8.4 Hz, 1H), 3.78-3.75 (m, 2H), 3.45-3.34 (m, 2H), 3.30-3.17 (m, 2H), 3.13-2.86 (m, 4H), 2.20-1.83 (m, 2H), 1.82-0.91 (m, 9H).
155	^{1}H NMR (400 MHz, DMSO-d6) δ 11.20 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.35 (s, 1H), 7.11 (s, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 7.00-6.92 (m, 1H), 3.78-3.74 (m, 2H), 3.46-3.41 (m, 2H), 3.36-3.34 (m, 2H), 3.00-2.97 (m, 2H), 2.86-2.81 (m, 2H), 2.22 (s, 3H), 2.15-2.05 (m, 2H), 1.58-1.44 (m, 4H), 1.22-1.17 (m, 6H), 0.97 (s, 3H).
156	^{1}H NMR (400 MHz, DMSO-d6) δ 12.31 (s, 1H), 7.97 (d, J = 8.6 Hz, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.51-7.37 (m, 2H), 7.22 (s, 1H), 7.08 (d, J = 8.6 Hz, 1H), 3.76 (t, J = 6.5 Hz, 2H), 3.49 (d, J = 8.8 Hz, 1H), 3.21 (d, J = 10.4 Hz, 2H), 3.03 (d, J = 11.2 Hz, 1H), 2.93 (d, J = 10.4 Hz, 1H), 2.70-2.58 (m, 1H), 2.41-2.23 (m, 3H), 1.79 (s, 1H), 1.52-1.03 (m, 6H), 0.70-0.55 (m, 2H), 0.48 (s, 1H), 0.22 (s, 2H).
157	^{1}H NMR (400 MHz, DMSO-d6) δ 12.41 (s, 1H), 8.32 (s, 1H), 7.93 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.41 (t, J = 5.9 Hz, 1H), 7.14 (s, 1H), 7.00 (s, 1H), 3.74 (t, J = 6.5 Hz, 2H), 3.54-3.42 (m, 1H), 3.27-3.25 (m, 3H), 3.02 (d, J = 11.3 Hz, 1H), 2.90 (d, J = 10.7 Hz, 1H), 2.70-2.58 (m, 1H),2.40-2.38 (m, 1H), 1.80 (s, 1H), 1.52-1.30 (m, 3H), 1.26-1.15 (m, 5H), 0.72-0.53 (m, 2H), 0.48 (s, 1H), 0.23 (s, 2H).
158	^{1}H NMR (400 MHz, DMSO-d6) δ 12.33 (s, 1H), 7.97 (d, *J* = 8.6 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.43 (t, *J* = 5.9 Hz, 1H), 7.21 (d, *J* = 2.2 Hz, 1H), 7.07 (dd, *J* = 8.6, 2.0 Hz, 1H), 3.76 (t, *J* = 6.5 Hz, 2H), 3.49 (dd, *J* = 14.0, 6.9 Hz, 1H), 3.21 (d, *J* = 10.3 Hz, 2H), 3.03 (d, *J* = 11.2 Hz, 1H), 2.92 (d, *J* = 10.5 Hz, 1H), 2.71-2.57 (m, 1H), 2.44-2.27 (m, 1H), 1.79 (s, 1H), 1.50-1.29 (m, 4H), 1.24-1.13 (m, 3H), 0.86 (t, *J* = 7.3 Hz, 1H), 0.63 (d, *J* = 21.4 Hz, 2H), 0.48 (s, 1H), 0.22 (s, 2H).
159	^{1}H NMR (400 MHz, DMSO-d_6) δ12.05 (s, 1H), 10.15 (s, 1H), 8.01 (d, *J* = 8.7 Hz, 1H), 7.34 (s, 1H), 7.19 (d, *J* = 2.1 Hz, 1H), 7.14 (t, *J* = 5.9 Hz, 1H), 7.06 (s, 1H), 4.90 (s, 1H), 3.75 (t, *J* = 6.5 Hz, 2H), 3.42 (s, 1H), 3.33 (t, *J* = 6.5 Hz, 2H), 3.16 (s, 1H), 3.09 (d, *J* = 11.6 Hz, 1H), 2.96 (d, *J* = 10.9 Hz, 1H), 2.75 (s, 3H), 2.33 (p, *J* = 1.9 Hz, 0H), 2.22 (s, 3H), 2.17 (d, *J* = 13.3 Hz, 1H), 1.98 (s, 2H), 1.81 (s, 1H), 1.64-1.52 (m, 1H), 1.47 (d, *J* = 10.3 Hz, 4H), 1.12 (t, *J* = 12.9 Hz, 1H). δ 13.35 (s, 1H), 11.94 (s, 1H).
160	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.79 (s, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.29 (d, *J* = 9.3 Hz, 2H), 7.18-6.99 (m, 2H), 3.75 (t, *J* = 6.5 Hz, 2H), 3.19 (d, *J* = 11.8 Hz, 6H), 2.79 (t, *J* = 11.0 Hz, 2H), 2.24 (s, 6H), 2.08 (s, 1H), 1.92-1.90 (m, 6H).

Cpd No.	^{1}H NMR (ppm)
161	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 7.95 (d, J = 8.5 Hz, 1H), 7.19 (s, 2H), 7.06 (d, J = 8.4 Hz, 1H), 6.68 (t, J = 6.0 Hz, 1H), 6.01 (s, 1H), 3.75 (t, J = 6.5 Hz, 2H), 3.51 (s, 1H), 3.34 (s, 5H), 3.20 (d, J = 10.6 Hz, 2H), 3.14 (s, 1H), 2.90 (d, J = 10.4 Hz, 2H), 2.60 (d, J = 12.5 Hz, 1H), 2.16 (s, 1H), 1.72 (s, 1H), 1.49–1.39 (m, 3H), 1.34–1.11 (m, 3H), 0.57 (s, 1H), 0.45 (s, 1H), 0.21 (s,2H).
162	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.01 (s, 1H), 10.21 (s, 1H), 8.15 (d, J = 5.5 Hz, 1H), 7.85 (d, J = 8.6 Hz, 1H), 7.40 (d, J = 5.5 Hz, 1H), 7.16-6.97 (m, 3H), 5.65-5.44 (m, 2H), 3.84-3.70 (m, 2H), 3.60-3.46 (m, 2H), 3.40-3.34 (m, 2H), 3.24-3.07 (m, 3H), 2.76-2.60 (m, 2H), 2.23-1.95 (m, 4H), 1.85-1.58 (m, 3H), 1.57-1.43 (m, 2H).
163	^{1}H NMR (400 MHz, DMSO-d6) δ 14.50 (s, 1H), 8.33-7.90 (m, 2H), 7.56 (s, 1H), 7.52-7.22 (m, 2H), 5.03 (s, 2H), 4.22-3.80 (m, 4H), 3.30-3.19 (m, 2H), 3.16-2.81 (m, 5H), 2.00-0.93 (m, 10H).
164	^{1}H NMR (400 MHz, DMSO-*d6*) δ 14.50 (s, 1H), 8.05 (d, J = 70.4 Hz, 2H), 7.56 (s, 1H), 7.30-7.07 (m, 2H), 3.94-3.74 (m, 2H), 3.66-3.54 (m, 2H) 3.20-3.14 (m, 1H), 3.11-2.81 (m, 4H), 2.47-2.37 (m, 2H), 2.20-0.83 (m, 12H).
165	^{1}H NMR (400 MHz, DMSO-d6) δ 10.86 (s, 1H), 10.13 (s, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.31 (s, 1H), 7.13 (s, 1H), 7.02-6.99 (m, 2H), 5.68-5.62 (m, 1H), 5.53-5.48 (m, 1H), 4.91 (s, 1H), 3.77-3.74 (m, 2H), 3.53-3.47 (m, 2H), 3.37-3.35 (m, 2H), 2.99-2.89 (m, 2H), 2.86-2.83 (m, 2H), 2.22 (s, 3H), 2.19-2.14 (m, 2H), 2.07-1.87 (m, 4H), 1.23-1.12 (m, 2H), 0.98 (s, 3H).
166	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.63 (s, 1H), 8.19 (d, J = 5.4 Hz, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.41 (s, 1H), 7.27-7.12 (m, 3H), 4.01-3.62 (m, 2H), 3.61-3.40 (m, 2H), 3.26-2.75 (m, 3H), 2.71-2.57 (m, 1H), 2.46-2.21 (m, 4H), 1.81 (s, 1H), 1.52-0.92 (m, 11H), 0.71-0.27 (m, 3H), 0.24 (s, 2H).
167	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.93 (s, 1H), 10.24 (s, 1H), 8.19 (d, J = 5.4 Hz, 1H), 8.08 (d, J = 8.7 Hz, 1H), 7.36-7.20 (m, 3H), 7.18-7.08 (m, 1H), 5.57-5.44 (m, 2H), 3.84-3.70 (m, 2H), 3.40-3.34 (m, 2H), 3.31-3.20 (m, 2H), 3.14-3.00 (m, 2H), 2.83-2.70 (m, 2H), 2.31-2.11 (m, 4H), 2.01-1.85 (m, 2H), 1.83-1.66 (m, 3H).
168	^{1}H NMR (400 MHz, DMSO-d6) δ 12.81 (s, 1H), 10.18 (s, 1H), 8.09 (d, J = 8.8 Hz, 1H), 7.32 (s, 1H), 7.19-7.14 (m, 3H), 5.63-5.51 (m, 2H), 4.92 (s, 1H), 3.78-3.75 (m, 2H), 3.37-3.34 (m, 2H), 3.29-3.24 (m, 3H), 2.93-2.91 (m, 4H), 2.49-2.23 (m, 4H), 2.19-2.2.07 (m, 4H), 1.50-1.46 (m, 2H), 1.12 (s, 3H).
169	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.63 (s, 1H), 8.20 (d, J = 5.5 Hz, 1H), 7.99 (d, J = 8.6 Hz, 1H), 7.42 (s, 1H), 7.37-7.24 (m, 2H), 7.22-7.12 (m, 1H), 3.65-3.42 (m, 3H), 3.26-2.96 (m, 3H), 2.92-2.77 (m, 1H), 2.71-2.57 (m, 1H), 2.48-2.35 (m, 4H), 1.82 (s, 1H), 1.56-0.97 (m, 11H), 0.71-0.40 (m, 3H), 0.25 (s, 2H).
170	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.63 (s, 1H), 8.20 (d, J = 5.4 Hz, 1H), 7.99 (d, J = 8.7 Hz, 1H), 7.42 (s, 1H), 7.38-7.23 (m, 2H), 7.22-7.12 (m, 1H), 3.66-3.43 (m, 3H), 3.26-2.96 (m, 3H), 2.94-2.79 (m, 1H), 2.72-2.57 (m, 1H), 2.45-2.32 (m, 4H), 1.80 (s, 1H), 1.62-0.97 (m, 11H), 0.72-0.38 (m, 3H), 0.25 (s, 2H).
171	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.64 (s, 1H), 8.20 (d, J = 5.4 Hz, 1H), 8.00 (d, J = 8.6 Hz, 1H), 7.41-7.23 (m, 3H), 7.17-7.09 (m, 1H), 3.75 (s, 2H), 3.52 (s, 1H), 3.26-2.98 (m, 3H), 2.92-2.82 (m, 1H), 2.72-2.56 (m, 1H), 2.45-2.32 (m, 4H), 1.80 (s, 1H), 1.52-1.27 (m, 3H), 1.22-1.04 (m, 4H), 1.03-0.89 (m, 2H), 0.70-0.56 (m, 2H), 0.55-0.41 (m, 1H), 0.34-0.14 (m, 2H).

Cpd No.	^{1}H NMR (ppm)
172	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.47 (s, 1H), 8.15 (d, *J* = 5.5 Hz, 1H), 7.90 (d, *J* = 8.6 Hz, 1H), 7.44 (d, *J* = 5.5 Hz, 1H), 7.16 (s, 1H), 7.10-6.94 (m, 2H), 4.26-3.53 (m, 3H), 3.46-3.35 (m, 2H), 3.20-3.06 (m, 2H), 2.75-2.62 (m, 2H), 2.05-1.87 (m, 2H), 1.75-1.62 (m, 1H), 1.61-1.29 (m, 11H), 1.15-1.08 (m, 2H), 1.04-0.90 (m, 2H).
173	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.94 (s, 1H), 10.22 (s, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.33 (s, 1H), 7.08 (s, 1H), 7.07-6.93 (m, 2H), 5.63-5.48 (m, 2H), 3.54-3.46 (m, 2H), 3.21 (q, *J* = 7.2 Hz, 2H), 3.16-3.13 (m, 2H), 2.69-2.64 (m, 2H), 2.23 (s, 3H), 2.18-2.14 (m, 2H), 2.13-2.06 (m, 2H), 1.82-1.71 (m, 2H), 1.70-1.59 (m, 1H), 1.57-1.47 (m, 2H), 1.25-1.18 (m, 3H).
174	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.27 (s, 1H), 10.24 (s, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.37 (s, 1H), 7.11 (s, 1H), 7.05 (d, *J* = 8.8 Hz, 1H), 6.94-6.91 (m, 1H), 3.40-3.38 (m, 2H), 3.22 (q, *J* = 7.2 Hz, 2H), 3.19-3.14 (m, 2H), 2.71-2.65 (m, 2H), 2.22 (s, 3H), 2.02-1.91 (m, 2H), 1.73-1.61 (m, 1H), 1.60-1.51 (m, 2H), 1.50-1.42 (m, 6H), 1.41-1.30 (m, 2H), 1.28-1.17 (m, 3H).
175	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.40 (s, 1H), 8.16 (d, *J* = 5.5 Hz, 1H), 7.96 (d, *J* = 8.5 Hz, 1H), 7.44 (d, *J* = 5.5 Hz, 1H), 7.24-7.16 (m, 2H), 7.03 (t, *J* = 6.7 Hz, 1H), 5.02 (s, 2H), 4.08 (dd, *J* = 5.7, 3.5 Hz, 2H), 3.95 (dd, *J* = 5.5, 3.6 Hz, 2H), 3.40 (d, *J* = 6.0 Hz, 2H), 3.17 (d, *J* = 11.1 Hz, 2H), 2.77 (t, *J* = 11.7 Hz, 2H), 2.31 (s, 1H), 1.98-1.88 (m, 2H), 1.54 (d, *J* = 14.8 Hz, 2H), 1.49-1.44 (m, 5H), 1.40-1.34 (m, 2H).
176	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 8.17 (d, *J* = 5.5 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 5.5 Hz, 1H), 7.18 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.13 (d, *J* = 2.1 Hz, 1H), 7.09 (s, 1H), 5.55 (dtd, *J* = 21.8, 15.4, 8.0 Hz, 2H), 5.02 (s, 2H), 4.07 (dd, *J* = 5.6, 3.5 Hz, 2H), 3.95 (dd, *J* = 5.6, 3.5 Hz, 2H), 3.50 (d, *J* = 8.8 Hz, 2H), 3.15 (d, *J* = 11.3 Hz, 2H), 2.74 (t, *J* = 11.6 Hz, 2H), 2.14 (s, 2H), 2.06 (dd, *J* = 7.5, 3.6 Hz, 2H), 1.77 (s, 1H), 1.73 (d, *J* = 11.9 Hz, 1H), 1.64 (d, *J* = 12.6 Hz, 1H), 1.51 (d, *J* = 12.3 Hz, 2H).
177	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.11 (s, 1H), 8.03 (d, *J* =8.4 Hz, 2H), 7.64 (s, 1H), 7.31 (s, 1H), 7.15 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 3.77 (t, *J* = 6.4 Hz, 2H), 3.38-3.35 (m, 4H), 3.24-3.21 (m, 1H), 3.14-3.12 (m, 1H), 3.06-3.03 (m, 1H), 2.91-2.88 (m, 1H), 2.68-2.63 (m, 1H), 2.49-2.32 (m, 1H), 1.89-1.76 (m, 1H), 1.49-1.28 (m, 3H), 1.18-1.02 (m, 2H), 0.73-0.61 (m, 2H), 0.60-0.46 (m, 1H), 0.33-0.21 (m, 2H).
178	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.11 (s, 1H), 10.30 (s, 1H), 8.04 (d, *J* =8.4 Hz, 2H), 7.64 (s, 1H), 7.31 (s, 1H), 7.15 (dd, *J* = 8.8 Hz, 1.6 Hz, 1H), 4.92 (s, 1H), 3.76 (t, *J* = 6.8 Hz, 2H), 3.38-3.35 (m, 3H), 3.24-3.21 (m, 1H), 3.14-3.12 (m, 1H), 3.06-3.03 (m, 1H), 2.92-2.89 (m, 1H), 2.68-2.63 (m, 1H), 2.49-2.32 (m, 1H), 1.89-1.74 (m, 1H), 1.45-1.31 (m, 3H), 1.17-1.03(m, 2H), 0.70-0.59 (m, 2H), 0.57-0.47 (m, 1H), 0.32-0.21 (m, 2H).
179	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.12 (s, 1H), 10.26 (s, 1H), 8.04 (d, *J* =8.4 Hz, 2H), 7.64 (s, 1H), 7.31 (s, 1H), 7.15 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 4.94 (s, 1H), 3.76 (t, J = 6.4 Hz, 2H), 3.36 (t, *J* = 6.4 Hz, 3H), 3.24-3.22 (m, 1H), 3.14-3.12 (m, 1H), 3.06-3.03 (m, 1H), 2.92-2.89 (m, 1H), 2.68-2.63 (m, 1H), 2.49-2.33 (m, 1H), 1.91-1.76 (m, 1H), 1.45-1.30 (m, 3H), 1.18-1.05 (m, 2H), 0.69-0.60 (m, 2H), 0.58-0.45 (m, 1H), 0.31-0.21 (m, 2H).

Cpd No.	^{1}H NMR (ppm)
181	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 10.27 (s, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.34 (s, 1H), 7.21-7.18 (m, 2H), 7.09 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 4.92 (br, 1H), 3.76 (t, J = 6.4 Hz, 2H), 3.37-3.18 (m, 4H), 3.17-3.15 (m, 1H), 3.14-3.11 (m, 1H), 3.08-2.96 (m, 1H), 2.74-2.67 (m, 2H), 2.45-2.41 (m, 1H), 2.32 (s, 1H), 2.23 (s, 3H), 2.21-2.17 (m, 1H), 2.03-1.97 (m, 2H), 1.81-1.73 (m, 1H), 1.69-1.46 (m, 3H), 1.34-1.24 (m, 2H), 1.18-1.09 (m, 1H).
182	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.06 (s, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.34 (s, 1H), 7.19-7.16 (m, 2H), 7.07 (d, J = 8.4 Hz 1H), 3.75 (t, J = 6.4 Hz, 2H), 3.42-3.32 (m, 3H), 3.18-3.15 (m, 1H), 3.14-3.11 (m, 1H), 3.08-2.98 (m, 1H), 2.86-2.70 (m, 2H), 2.46-2.41 (m, 1H), 2.32 (s, 1H), 2.23 (s, 3H), 2.23-2.19 (m, 1H), 2.10-1.88 (m, 3H), 1.83-1.73 (m, 1H), 1.69-1.46 (m, 2H), 1.36-1.34 (m, 2H), 1.32-1.24 (m, 2H).
183	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.81 (s, 1H), 10.29 (s, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.24-7.21 (m, 1H), 7.19-7.16 (m, 1H), 7.15-7.14 (m, 2H), 5.51-5.48 (m, 2H), 3.29-3.19 (m, 2H), 3.09-3.06 (m, 2H), 2.77 (t, J = 11.6 Hz, 2H), 2.27-2.15 (m, 7H), 0.96-0.87 (m, 2H), 0.83-0.71 (m, 3H), 0.24-0.14 (m, 4H).
185	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.07 (s, 1H), 8.20 (d, J = 5.4 Hz, 1H), 8.16 (d, J = 8.6 Hz, 1H), 7.39 (d, J = 2.3 Hz, 1H), 7.36-7.29 (m, 2H), 7.25 (d, J = 5.3 Hz, 1H), 5.65 -5.35 (m, 2H), 5.02 (s, 2H), 4.08 (dd, J = 5.7, 3.3 Hz, 2H), 3.97 (dd, J = 5.6, 3.5 Hz, 2H), 3.26 (s, 1H), 3.06 (d, J = 11.2 Hz, 2H), 2.90 (t, J = 11.4 Hz, 2H), 2.24 (d, J = 9.8 Hz, 2H), 2.18 (t, J = 6.9 Hz, 2H), 1.97-1.85 (m, 3H), 1.77 (d, J = 12.4 Hz, 2H), 1.23 (s, 1H).
186	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.72 (s, 1H), 7.94 (d, J = 8.6 Hz, 1H), 7.35 (s, 1H), 7.26 (s, 1H), 7.16 (d, J = 2.2 Hz, 1H), 7.05 (dd, J = 8.6, 2.0 Hz, 1H), 3.75 (t, J = 6.5 Hz, 2H), 3.12-2.95 (m, 2H), 2.75-2.68 (m, 2H), 2.31 (s, 1H), 2.22 (s, 3H), 2.11 (s, 3H), 1.93 (s, 2H), 1.63 (s, 1H), 1.52 (s, 2H), 1.35-1.24 (m, 5H), 1.07 (s, 1H), 0.73-0.68 (m, 2H), 0.55 (s, 2H).
187	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (s, 1H), 8.17 (d, J = 5.4 Hz, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 5.5 Hz, 1H), 7.27 (t, J = 5.9 Hz, 1H), 7.20 (s, 1H), 7.07 (d, J = 8.7 Hz, 1H), 3.76 (t, J = 6.5 Hz, 2H), 3.14 (dd, J = 26.3, 10.6 Hz, 3H), 2.97 (d, J = 10.8 Hz, 1H), 2.76 (s, 3H), 2.31 (s, 1H), 2.17 (d, J = 14.3 Hz, 2H), 1.98 (s, 2H), 1.82 (s, 1H), 1.56 (s, 3H), 1.47 (s, 3H), 1.27 (s, 2H), 1.12 (d, J = 13.5 Hz, 1H).
188	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.83 (s, 1H), 10.22 (s, 1H), 8.06 (d, J = 8.7 Hz, 1H), 7.30-7.06 (m, 4H), 5.55-5.43 (m, 2H), 4.94 (s, 1H), 3.76 (t, J = 6.5 Hz, 2H), 3.35 (d, J = 6.4 Hz, 2H), 3.26 (dt, J = 11.6, 6.7 Hz, 2H), 3.07 (d, J = 11.0 Hz, 2H), 2.77 (t, J = 11.5 Hz, 2H), 2.37-2.04 (m, 7H), 1.99-1.83 (m, 2H), 1.77 (d, J = 12.5 Hz, 3H).
189	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (s, 1H), 8.17 (d, J = 5.5 Hz, 1H), 8.06-7.99 (m, 1H), 7.42 (d, J = 5.5 Hz, 1H), 7.27 (t, J = 5.8 Hz, 1H), 7.20 (s, 1H), 7.07 (d, J = 9.0 Hz, 1H), 3.75 (t, J = 6.5 Hz, 2H), 3.34 (s, 2H), 3.13 (dd, J = 25.2, 10.2 Hz, 2H), 2.97 (d, J = 11.0 Hz, 1H), 2.76 (s, 2H), 2.31 (s, 1H), 2.18 (s, 2H), 1.98 (s, 2H), 1.82 (s, 1H), 1.57 (d, J = 16.5 Hz, 2H), 1.47 (s, 3H), 1.25 (d, J = 11.9 Hz, 3H), 1.13 (t, J = 12.8 Hz, 1H).

Cpd No.	^{1}H NMR (ppm)
190	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (s, 1H), 8.17 (d, J = 5.5 Hz, 1H), 8.02 (d, J = 8.6 Hz, 1H), 7.42 (d, J = 5.5 Hz, 1H), 7.27 (t, J = 6.0 Hz, 1H), 7.20 (d, J = 2.2 Hz, 1H), 7.07 (dd, J = 8.6, 2.1 Hz, 1H), 3.75 (t, J = 6.5 Hz, 2H), 3.35 (t, J = 6.6 Hz, 2H), 3.16 (dd, J = 11.0, 3.3 Hz, 1H), 3.10 (d, J = 11.5 Hz, 1H), 2.97 (d, J = 10.9 Hz, 1H), 2.76 (s, 3H), 2.45 (d, J = 11.1 Hz, 1H), 2.17 (d, J = 12.2 Hz, 1H), 1.99 (s, 2H), 1.81 (s, 1H), 1.65 -1.53 (m, 1H), 1.48 (d, J = 11.9 Hz, 4H), 1.26 (t, J = 10.2 Hz, 2H), 1.13 (t, J = 13.0 Hz, 1H).
191	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 7.91 (d, J = 9.2 Hz, 1H), 7.80 (s, 1H), 7.74 (s, 1H), 7.11 (s, 1H), 7.04 (d, J = 9.2 Hz, 1H), 3.75 (t, J = 6.0 Hz, 2H), 3.40-3.36 (m, 2H), 3.35 (s, 2H), 3.32 (s, 2H), 3.17-3.14 (m, 2H), 2.70-2.67 (m, 2H), 2.33 (s, 1H), 1.90-1.87 (m, 2H), 1.69-1.64 (m, 1H), 1.57-1.53 (m, 2H), 1.49-1.40 (m, 4H), 1.39-1.35 (m, 2H).
192	^{1}H NMR (499 MHz, DMSO-d6) δ ppm 11.42 (s, 1 H) 10.17 (s, 1 H) 8.16 (d, J=2.5 Hz, 1 H) 7.96 (d, J=8.5 Hz, 1 H) 7.79 (d, J=1.6 Hz, 1 H) 7.63 (s, 2 H) 7.13 (d, J=1.9 Hz, 1 H) 7.05 (dd, J=8.6, 2.1 Hz, 1 H) 6.86 - 7.01 (m, 1 H) 6.54 (t, J=2.2 Hz, 1 H) 3.76 (t, J=6.4 Hz, 2 H) 3.55 (br t, J=5.7 Hz, 2 H) 3.35 (t, J=6.6 Hz, 2 H) 3.19 (br d, J=11.0 Hz, 2 H) 2.70 (br t, J=11.4 Hz, 2 H) 1.92 - 2.07 (m, 2 H) 1.69 (br s, 1 H) 1.61 (br d, J=11.5 Hz, 2 H) 1.38 - 1.55 (m, 9 H)
193	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.46 (s, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.79-7.76 (m, 2H), 7.07 (s, 1H), 7.02 (d, J = 8.4 Hz, 1H), 5.58-5.51 (m, 2H), 3.75 (t, J = 6.8 Hz, 2H), 3.51 (s, 2H), 3.36-3.34 (m, 2H), 3.15-3.12 (m, 2H), 2.68 (t, J = 10.8 Hz, 2H), 2.15-2.10 (m, 2H), 2.09-2.05 (m, 2H), 1.71-1.66 (m, 3H), 1.53-1.50 (m, 2H).
194	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.58 (s, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.96 (t, J = 6.4 Hz, 1H), 7.62 (s, 1H), 7.18 (s, 1H), 7.11 (d, J = 8.8 Hz, 1H), 5.50 (s, 2H), 3.75 (t, J = 6.4 Hz, 2H), 3.35 (s, 1H), 3.31-3.29 (m, 2H), 3.07-3.05 (m, 2H), 2.78 (t, J = 11.2 Hz, 2H), 2.24-2.22 (m, 2H), 2.17-2.07 (m, 2H), 1.85-1.68 (m, 6H).
195	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.60 (s, 1H), 10.32 (br, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.98 (s, 1H), 7.78 (s, 1H), 7.24 (s, 1H), 7.11 (d, J = 7.6,1H), 4.96-4.85 (br, 1H), 3.76 (s, 2H), 3.37 (s, 3H), 3.19-3.09 (m, 2H), 3.03-2.95 (m, 1H), 2.89-2.67 (m, 2H), 2.09-1.97 (m, 2H), 1.94-1.75 (m, 2H), 1.67-1.34 (m, 6H), 1.32-1.19 (m, 2H), 1.18-1.09 (m, 1H).
196	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.95 (s, 1H), 8.02 (d, J = 8.6 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.34 (t, J = 5.7 Hz, 1H), 7.19 (s, 1H), 7.07 (d, J = 8.7 Hz, 1H), 3.75 (t, J = 6.4 Hz, 2H), 3.54 (s, 1H), 3.13 (t, J = 15.1 Hz, 2H), 2.98 (d, J = 10.8 Hz, 1H), 2.90 (s, 1H), 2.32 (s, 1H), 2.14 (d, J = 17.8 Hz, 1H), 2.08 (s, 1H), 1.97 (s, 2H), 1.80 (s, 1H), 1.49 (d, J = 10.9 Hz, 2H), 1.31 (s, 5H), 1.26 (d, J = 14.4 Hz, 3H), 1.17 (d, J = 13.3 Hz, 1H).
197	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.94-12.79 (br, 1H), 10.15 (s, 1H), 8.08 (s, 1H), 7.23 (s, 1H), 7.11 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.0 Hz, 1H), 6.41 (s, 1H), 4.93 (s, 1H), 3.76 (s, 5H), 3.35-3.34 (m, 7H), 3.12-2.88 (m, 4H), 1.99-1.87 (m, 1H), 1.72-1.38 (m, 4H), 1.36-1.20 (m, 3H).
198	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.06 (s, 1H), 7.23 (s, 1H), 7.11 (d, J = 7.6 Hz, 2H), 7.01 (d, J = 8.4 Hz, 1H), 6.41 (s, 1H), 4.93 (s, 1H), 3.76 (s, 5H), 3.36-3.34 (m, 5H), 3.17-2.90 (m, 4H), 2.09-1.81 (m, 2H), 1.73-1.1.11 (m, 8H).

Cpd No.	^{1}H NMR (ppm)
199	^{1}H NMR (400 MHz, DMSO-d6) δ 11.42 (s, 1H), 10.20 (s, 1H), 8.14 (s, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.44 (s, 1H), 7.05 (d, J = 30.0 Hz, 3H), 3.17 (s, 3H), 2.68 (s, 3H), 2.31-2.32 (m, 2H), 1.97-1.96 (m, 1H), 1.67 (s, 1H), 1.42-1.40 (m,11H), 1.20 (s, 3H).
201	1H NMR (400 MHz, DMSO-d6) δ 11.00 (s, 1 H) 7.86 (dd, J=8.5, 3.3 Hz, 2 H) 7.62 (d, J=8.3 Hz, 1 H) 6.93 - 7.13 (m, 3 H) 5.41 - 5.63 (m, 2 H) 3.75 (t, J=6.5 Hz, 2 H) 3.54 - 3.69 (m, 2 H) 3.15 (m, 4 H) 2.67 (br t, J=11.0 Hz, 2 H) 2.16 - 2.26 (m, 2 H) 2.05 (br dd, J=7.3, 2.5 Hz, 2 H) 1.58 - 1.81 (m, 3 H) 1.51 (br d, J=10.5 Hz, 2 H)
202	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96-7.72 (m, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.23 (t, J = 7.7 Hz, 2H), 6.93 (dd, J = 30.8, 8.7 Hz, 2H), 5.33 (s, 1H), 3.85-3.77 (m, 1H), 3.73 (t, J = 6.5 Hz, 1H), 3.50 (d, J = 6.7 Hz, 1H), 3.38 (s, 1H), 3.23-3.09 (m, 2H), 2.71 (s, 1H), 2.13-1.82 (m, 3H), 1.77-1.35 (m, 7H), 1.24-1.19(m, 7H) 0.85 (d, J = 6.6 Hz, 1H).
203	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.61 (s, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.98 (s, 1H), 7.78 (s, 1H), 7.23 (s, 1H), 7.11 (dd, J = 8.4 Hz, 1.6 Hz,1H), 3.75 (t, J = 6.4 Hz, 2H), 3.35-3.40 (m, 3H), 3.22-3.19 (m, 1H), 3.17-3.11 (m, 1H), 3.08-2.95 (m, 1H), 2.83-2.67 (m, 2H), 2.49 (s, 1H), 2.10-2.07 (m, 1H), 2.03-1.88 (m, 2H), 1.87-1.74 (m, 1H), 1.65-1.38 (m, 5H), 1.32-1.20 (m, 2H), 1.19-1.06 (m, 1H).
204	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.61 (s, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.98 (s, 1H), 7.78 (s, 1H), 7.22 (s, 1H), 7.09 (d, J = 8.4 Hz, 1H), 3.75 (t, J = 6.4 Hz, 2H), 3.45-3.28 (m, 5H), 3.22-3.14 (m, 1H), 3.13-3.06 (m, 1H), 3.01-2.88 (m, 1H), 2.86-2.60 (m, 2H), 2.49-2.45 (m, 1H), 2.15-1.72 (m, 4H), 1.64-1.37 (m, 5H), 1.36-1.19 (m, 2H), 1.18-1.07 (m, 1H).
205	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.95 (s, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8.5 Hz, 1H), 7.34 (d, J = 6.4 Hz, 1H), 7.19 (s, 1H), 7.07 (d, J = 8.6 Hz, 1H), 3.75 (t, J = 6.4 Hz, 2H), 3.52 (s, 1H), 3.39-3.31 (m, 3H), 3.19-3.07 (m, 2H), 2.98 (d, J = 10.7 Hz, 1H), 2.89 (s, 1H), 2.30 (s, 1H), 2.12 (s, 1H), 1.97 (s, 3H), 1.80 (s, 1H), 1.55 (s, 2H), 1.48 (d, J = 11.9 Hz, 3H), 1.30 (s, 2H), 1.26 (d, J = 14.5 Hz, 1H), 1.15 (s, 1H).
206	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.95 (s, 1H), 10.22 (s, 1H), 8.02 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.34 (t, J = 5.7 Hz, 1H), 7.19 (d, J = 2.1 Hz, 1H), 7.07 (dd, J = 8.6, 2.1 Hz, 1H), 4.94 (s, 2H), 3.75 (t, J = 6.5 Hz, 2H), 3.53 (s, 1H), 3.35 (t, J = 6.6 Hz, 2H), 3.19- 3.07 (m, 2H), 2.98 (d, J = 10.7 Hz, 1H), 2.89 (s, 1H), 2.32 (s, 1H), 2.13 (d, J = 13.1 Hz, 1H), 1.97 (s, 3H), 1.80 (s, 1H), 1.56 (d, J = 11.0 Hz, 1H), 1.51- 1.44 (m, 3H), 1.33-1.21 (m, 1H), 1.15 (t, J = 12.6 Hz, 1H).
207	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (s, 1H), 8.15 (d, J = 5.5 Hz, 1H), 7.83 (d, J = 8.5 Hz, 1H), 7.40 (d, J = 5.5 Hz, 1H), 7.18 -6.92 (m, 3H), 5.55-5.53 (m, 2H), 3.51 (s, 2H), 3.24-2.99 (m, 3H), 2.67-2.65 (m, 3H), 2.32 (s, 1H), 2.14 (s, 2H), 2.06-2.00 (m, 2H), 1.75-1.73 (m, 2H), 1.65-1.62 (m, 1H), 1.51-1.49 (m, 2H), 1.20-1.19 (m, 4H).
208	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.45 (s, 1H), 10.23 (s, 1H), 8.15 (d, J = 5.4 Hz, 1H), 7.92 (d, J = 8.6 Hz, 1H), 7.44 (d, J = 5.5 Hz, 1H), 7.19 (d, J = 2.1 Hz, 1H), 7.13-6.94 (m, 2H), 3.40-3.36 (m, 2H), 3.15-3.12 (m, 2H), 2.68-2.65 (m, 2H), 2.32 (s, 1H), 1.96-1.94 (m, 2H), 1.68 (s, 1H), 1.56-1.52 (m, 2H), 1.47 (s, 6H), 1.40 (s, 4H), 1.25-1.17 (m, 2H), 0.90-0.76 (m, 2H).

Cpd No.	^{1}H NMR (ppm)
209	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.96 (s, 1H), 8.38 (s, 1H), 8.17 (d, J = 5.3 Hz, 1H), 8.03 (d, J = 8.3 Hz, 1H), 7.25 (d, J = 5.4 Hz, 2H), 7.19-7.04 (m, 2H), 5.50 (d, J = 5.8 Hz, 2H), 3.24 (s, 1H), 3.20-3.03 (m, 3H), 2.77-2.75 (m, 3H), 2.31 (s, 1H), 2.24 (s, 2H), 2.18 (s, 2H), 1.91-1.89 (m, 2H), 1.77-1.75 (m, 2H), 1.23-1.09 (m, 4H).
210	1H NMR (499 MHz, DMSO-d6) δ ppm 11.23 (s, 1 H) 7.97 (d, J=8.5 Hz, 1 H) 7.45 (d, J=7.4 Hz, 1 H) 7.30 - 7.35 (m, 2 H) 7.26 (dd, J=8.5, 2.2 Hz, 1 H) 6.52 (br s, 1 H) 6.18 (d, J=7.7 Hz, 1 H) 5.05 (br s, 1 H) 3.74 (t, J=6.3 Hz, 2 H) 3.43 (br d, J=4.9 Hz, 3 H) 3.29 - 3.34 (m, 3 H) 3.11 - 3.24 (m, 3 H) 2.76 (br t, J=11.1 Hz, 2 H) 1.94 - 2.05 (m, 2 H) 1.68 (br s, 1 H) 1.57 (br d, J=12.0 Hz, 2 H) 1.44 - 1.51 (m, 6 H) 1.36 - 1.43 (m, 2 H).
211	1H NMR (499 MHz, DMSO-d6) δ ppm 11.35 (s, 1 H) 10.15 (s, 1 H) 7.95 (d, J=8.8 Hz, 1 H) 7.55 - 7.60 (m, 1 H) 7.48 - 7.54 (m, 1 H) 7.12 (d, J=2.2 Hz, 1 H) 7.04 (dd, J=8.6, 2.1 Hz, 1 H) 6.32 (d, J=7.9 Hz, 1 H) 4.94 (br t, J=5.2 Hz, 1 H) 3.72 - 3.79 (m, 2 H) 3.66 (t, J=6.3 Hz, 2 H) 3.33 - 3.36 (m, 2 H) 3.16 (br d, J=11.2 Hz, 2 H) 2.84 (s, 3 H) 2.63 - 2.74 (m, 2 H) 1.91 - 2.06 (m, 2 H) 1.70 (br s, 1 H) 1.53 - 1.62 (m, 4 H) 1.37 - 1.50 (m, 6 H).
213	1H NMR (499 MHz, DMSO-d6) δ ppm 11.24 (s, 1 H) 10.19 (s, 1 H) 7.95 (d, J=8.8 Hz, 1 H) 7.90 (s, 1 H) 7.59 (d, J=0.5 Hz, 1 H) 7.54 (d, J=8.2 Hz, 1 H) 7.36 (d, J=7.9 Hz, 1 H) 7.13 (d, J=2.2 Hz, 1 H) 7.04 (dd, J=8.6, 2.1 Hz, 1 H) 5.72 (br s, 1 H) 3.87 (s, 3 H) 3.39 - 3.65 (m, 8 H) 3.16 - 3.19 (m, 2 H) 2.69 (br t, J=11.2 Hz, 2 H) 1.94 - 2.07 (m, 2 H) 1.69 (br s, 1 H) 1.60 (br d, J=12.6 Hz, 2 H) 1.52 (br t, J=6.0 Hz, 2 H) 1.36 - 1.49 (m, 6 H).
214	1H NMR (499 MHz, DMSO-d6) δ ppm 10.65 (s, 1 H) 10.10 (s, 1 H) 7.84 (d, J=8.5 Hz, 1 H) 7.44 (d, J=7.9 Hz, 1 H) 7.13 (d, J=7.9 Hz, 1 H) 7.05 (d, J=2.2 Hz, 1 H) 6.98 (dd, J=8.5, 2.2 Hz, 1 H) 6.04 - 6.29 (m, 1 H) 5.42 - 5.63 (m, 2 H) 3.74 (t, J=6.4 Hz, 2 H) 3.67 (br s, 2 H) 3.33 (t, J=6.4 Hz, 2 H) 3.16 (br d, J=11.2 Hz, 2 H) 2.64 (br t, J=11.4 Hz, 2 H) 2.13 - 2.28 (m, 2 H) 2.04 (dd, J=7.5, 3.7 Hz, 2 H) 1.79 (qd, J=12.1, 3.0 Hz, 2 H) 1.53 - 1.68 (m, 2 H) 1.49 (br d, J=10.7 Hz, 2 H) 1.03 - 1.20 (m, 1 H) 0.82 - 0.98 (m, 3 H) 0.44 - 0.54 (m, 2 H).
215	1H NMR (499 MHz, DMSO-d6) δ ppm 10.60 (s, 1 H) 10.10 (br s, 1 H) 7.85 (d, J=8.5 Hz, 1 H) 7.44 (d, J=7.9 Hz, 1 H) 7.20 (d, J=7.9 Hz, 1 H) 7.06 (d, J=1.9 Hz, 1 H) 6.99 (dd, J=8.5, 2.2 Hz, 1 H) 5.95 (t, J=6.7 Hz, 1 H) 5.43 - 5.64 (m, 2 H) 4.93 (br s, 1 H) 3.75 (br d, J=3.0 Hz, 2 H) 3.56 - 3.69 (m, 2 H) 3.30 - 3.36 (m, 2 H) 3.16 (br d, J=11.2 Hz, 2 H) 2.64 (br t, J=11.2 Hz, 2 H) 2.15 - 2.24 (m, 2 H) 2.00 - 2.05 (m, 5 H) 1.80 (qd, J=12.5, 3.4 Hz, 2 H) 1.57 - 1.69 (m, 1 H) 1.48 (br d, J=11.0 Hz, 2 H).
216	1H NMR (499 MHz, DMSO-d6) δ ppm 10.63 (s, 1 H) 10.09 (br s, 1 H) 7.85 (d, J=8.5 Hz, 1 H) 7.46 (d, J=8.2 Hz, 1 H) 7.05 (d, J=1.9 Hz, 1 H) 6.96 - 7.01 (m, 2 H) 6.17 (t, J=6.8 Hz, 1 H) 5.44 - 5.62 (m, 2 H) 4.93 (br s, 1 H) 3.78 (s, 3 H) 3.75 (t, J=6.6 Hz, 2 H) 3.55 - 3.61 (m, 2 H) 3.29 - 3.36 (m, 2 H) 3.16 (br d, J=11.5 Hz, 2 H) 2.64 (br t, J=11.2 Hz, 2 H) 2.13 - 2.21 (m, 2 H) 2.03 (dd, J=7.3, 3.7 Hz, 2 H) 1.80 (qd, J=12.4, 3.3 Hz, 2 H) 1.62 (tt, J=11.9, 3.7 Hz, 1 H) 1.48 (br d, J=11.2 Hz, 2 H).

Cpd No.	^{1}H NMR (ppm)
228	1H NMR (499 MHz, DMSO-d6) δ ppm 11.78 (br s, 1 H) 10.21 (s, 1 H) 8.28 (d, J=2.5 Hz, 1 H) 8.04 (d, J=8.8 Hz, 1 H) 7.66 - 7.72 (m, 1 H) 7.60 - 7.66 (m, 1 H) 7.20 (d, J=1.9 Hz, 1 H) 7.08 (dd, J=8.6, 2.1 Hz, 1 H) 7.03 (d, J=2.5 Hz, 1 H) 6.65 (br s, 1 H) 3.76 (t, J=6.6 Hz, 2 H) 3.49 - 3.64 (m, 1 H) 3.49 - 3.51 (m, 1 H) 3.34 - 3.38 (m, 2 H) 3.34 (s, 3 H) 3.09 - 3.22 (m, 2 H) 3.01 (br d, J=10.4 Hz, 1 H) 2.66 - 2.94 (m, 2 H) 2.13 - 2.31 (m, 1 H) 1.93 - 2.11 (m, 2 H) 1.82 (br d, J=6.3 Hz, 1 H) 1.40 - 1.67 (m, 5 H) 1.29 (br dd, J=12.2, 9.7 Hz, 2 H) 1.19 (br t, J=13.3 Hz, 1 H).
229	1H NMR (499 MHz, DMSO-d6) δ ppm 11.66 - 11.90 (m, 1 H) 10.20 (s, 1 H) 8.73 (s, 1 H) 8.20 (s, 1 H) 8.04 (d, J=8.5 Hz, 1 H) 7.62 - 7.71 (m, 2 H) 7.20 (d, J=2.2 Hz, 1 H) 7.08 (dd, J=8.6, 2.1 Hz, 1 H) 6.74 (br d, J=4.1 Hz, 1 H) 3.76 (t, J=6.4 Hz, 2 H) 3.49 - 3.64 (m, 1 H) 3.32 - 3.40 (m, 2 H) 3.28 (s, 3 H) 3.10 - 3.20 (m, 2 H) 2.96 - 3.06 (m, 1 H) 2.83 - 2.94 (m, 1 H) 2.66 - 2.81 (m, 1 H) 2.43 - 2.49 (m, 1 H) 2.12 - 2.29 (m, 1 H) 1.93 - 2.11 (m, 2 H) 1.71 - 1.90 (m, 1 H) 1.39 - 1.67 (m, 5 H) 1.23 - 1.37 (m, 2 H) 1.13 - 1.22 (m, 1 H).
230	^{1}HNMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.33 (s, 1H), 7.29 – 7.20 (m, 2H), 7.00 (s, 1H), 5.70 – 5.42 (m, 2H), 5.06 (s, 1H), 3.74 (t, J = 6.2 Hz, 2H), 3.32 (d, J = 7.5 Hz, 5H), 2.79 – 2.69 (m, 2H), 2.51 (p, J = 1.8 Hz, 4H), 2.23 (s, 3H), 2.09 (ddd, J = 26.4, 8.8, 4.6 Hz, 4H), 1.76 (tt, J = 12.4, 6.0 Hz, 2H), 1.63 (dt, J = 11.9, 3.5 Hz, 1H), 1.58 – 1.40 (m, 2H).
231	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.34 (br s, 1 H) 8.31 (br s, 1 H) 7.94 (d, J=8.3 Hz, 1 H) 7.38 (s, 1 H) 7.21 - 7.33 (m, 2 H) 6.95 (br t, J=5.4 Hz, 1 H) 3.74 (br t, J=6.1 Hz, 2 H) 3.32 - 3.42 (m, 5 H) 3.17 (br d, J=10.3 Hz, 3 H) 2.77 (br t, J=11.3 Hz, 2 H) 2.23 (s, 3 H) 1.86 - 2.02 (m, 2 H) 1.62 - 1.73 (m, 1 H) 1.30 - 1.60 (m, 11 H)
232	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.04 - 12.43 (m, 1 H) 10.16 (br s, 1 H) 8.19 (d, J=2.3 Hz, 1 H) 8.01 (br d, J=8.5 Hz, 1 H) 7.79 (s, 1 H) 7.69 (d, J=8.3 Hz, 1 H) 7.51 (br d, J=8.0 Hz, 1 H) 7.17 - 7.33 (m, 2 H) 7.01 - 7.16 (m, 1 H) 6.55 (s, 1 H) 3.45 - 3.57 (m, 4 H) 3.14 - 3.26 (m, 4 H) 3.03 - 3.11 (m, 1 H) 2.90 - 3.00 (m, 2 H) 1.74 - 1.87 (m, 1 H) 1.07 - 1.58 (m, 8 H) 0.56 - 0.74 (m, 1 H) 0.48 (br dd, J=6.4, 2.9 Hz, 1 H) 0.18 - 0.31 (m, 2 H)
233	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (s, 1H), 10.31 (s, 1H), 8.19 (d, J = 2.4 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.79 (d, J = 1.8 Hz, 1H), 7.69 (d, J = 8.3 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.26 (d, J = 6.4 Hz, 2H), 7.10 (dd, J = 8.7, 2.0 Hz, 1H), 6.55 (t, J = 2.2 Hz, 1H), 3.53 (dt, J = 13.8, 7.3 Hz, 1H), 3.21 (q, J = 7.5 Hz, 3H), 3.07 (d, J = 11.1 Hz, 1H), 2.95 (d, J = 10.3 Hz, 1H), 2.63 (d, J = 11.6 Hz, 1H), 2.39 (s, 3H), 2.33 (s, 1H), 1.79 (s, 1H), 1.47 (d, J = 9.4 Hz, 2H), 1.36 (s, 1H), 1.21 (t, J = 7.3 Hz, 3H), 0.67 (s, 1H), 0.62 (s, 2H), 0.48 (s, 2H), 0.23 (s, 2H).
234	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.22 (br s, 1 H) 10.12 - 10.66 (m, 1 H) 8.19 (d, J=2.5 Hz, 1 H) 8.01 (d, J=8.3 Hz, 1 H) 7.74 - 7.84 (m, 1 H) 7.69 (d, J=8.3 Hz, 1 H) 7.51 (d, J=8.5 Hz, 1 H) 7.19 - 7.32 (m, 2 H) 7.09 (br d, J=8.5 Hz, 1 H) 6.55 (t, J=1.8 Hz, 1 H) 3.33 - 3.60 (m, 5 H) 3.14 - 3.24 (m, 3 H) 3.02 - 3.11 (m, 1 H) 2.89 - 2.99 (m, 1 H) 2.58 - 2.70 (m, 2 H) 1.72 - 1.87 (m, 1 H) 1.29 - 1.55 (m, 3 H) 1.22 - 1.28 (m, 2 H) 1.07 - 1.16 (m, 1 H) 0.41 - 0.74 (m, 3 H) 0.15 - 0.32 (m, 2 H)

Cpd No.	^{1}H NMR (ppm)
235	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 (br s, 1 H) 8.19 (d, *J*=2.5 Hz, 1 H) 7.96 - 8.04 (m, 1 H) 7.79 (d, *J*=1.3 Hz, 1 H) 7.69 (d, *J*=8.5 Hz, 1 H) 7.52 (d, *J*=8.3 Hz, 1 H) 7.17 - 7.30 (m, 2 H) 7.03 - 7.11 (m, 1 H) 6.54 (t, *J*=2.1 Hz, 1 H) 3.76 (t, *J*=6.5 Hz, 2 H) 3.42 - 3.58 (m, 2 H) 3.18 - 3.26 (m, 2 H) 3.03 - 3.12 (m, 1 H) 2.89 - 2.99 (m, 1 H) 2.60 - 2.67 (m, 1 H) 2.29 - 2.35 (m, 2 H) 1.73 - 1.88 (m, 1 H) 1.06 - 1.55 (m, 6 H) 0.54 - 0.73 (m, 2 H) 0.43 - 0.53 (m, 1 H) 0.19 - 0.30 (m, 2 H)
237	^{1}H NMR (400 MHz, DMSO-d_6) δ12.20 (s, 1H), 8.19 (s, 1H), 7.99 (s, 1H), 7.79 (s, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 16.8 Hz, 3H), 7.09 (s, 1H), 6.54 (s, 1H), 3.76 (t, *J* = 6.5 Hz, 2H), 3.51 (s, 3H), 3.07 (d, *J* = 10.6 Hz, 1H), 2.95 (s, 2H), 2.64 (s, 2H), 2.30 (s, 3H), 1.47 (s, 2H), 1.37 (s, 4H), 1.24 (s, 2H), 0.23 (s, 2H).
238	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (s, 1H), 7.85 (dd, *J* = 8.5, 6.1 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.13 – 6.94 (m, 2H), 5.52 (tdd, *J* = 22.3, 15.2, 7.2 Hz, 2H), 3.75 (t, *J* = 6.5 Hz, 2H), 3.62 (s, 2H), 3.16 – 3.05 (m, 3H), 2.66 (t, *J* = 11.3 Hz, 2H), 2.27 – 2.14 (m, 2H), 2.09 – 1.99 (m, 2H), 1.79 – 1.68 (m, 3H), 1.51 (d, *J* = 11.7 Hz, 2H), 1.24 (s, 1H), 1.06 (t, *J* = 7.0 Hz, 1H).
240	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (br s, 1 H) 10.29 (br s, 1 H) 8.18 (d, *J*=5.5 Hz, 1 H) 8.03 (d, *J*=8.8 Hz, 1 H) 7.42 (d, *J*=5.5 Hz, 1 H) 7.27 (br t, *J*=5.8 Hz, 1 H) 7.22 (s, 1 H) 7.06 - 7.12 (m, 1 H) 3.36 - 3.51 (m, 1 H) 3.06 - 3.28 (m, 4 H) 2.93 - 3.04 (m, 1 H) 2.70 - 2.87 (m, 2 H) 2.09 - 2.26 (m, 1 H) 1.89 - 2.08 (m, 2 H) 1.73 - 1.88 (m, 1 H) 1.37 - 1.69 (m, 5 H) 1.16 - 1.35 (m, 6 H) 1.07 - 1.16 (m, 1 H)
241	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (br s, 1 H) 10.31 (br s, 1 H) 8.18 (d, *J*=5.5 Hz, 1 H) 8.03 (d, *J*=8.8 Hz, 1 H) 7.42 (d, *J*=5.5 Hz, 1 H) 7.25 - 7.31 (m, 1 H) 7.22 (d, *J*=2.0 Hz, 1 H) 7.09 (dd, *J*=8.6, 1.9 Hz, 1 H) 3.38 - 3.50 (m, 1 H) 3.05 - 3.27 (m, 5 H) 2.94 - 3.03 (m, 1 H) 2.70 - 2.86 (m, 2 H) 2.08 - 2.27 (m, 1 H) 1.89 - 2.06 (m, 2 H) 1.75 - 1.88 (m, 1 H) 1.37 - 1.70 (m, 5 H) 1.09 - 1.35 (m, 6 H)
242	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.97 - 12.21 (m, 1 H) 10.36 (s, 1 H) 8.18 (d, *J*=5.5 Hz, 1 H) 8.03 (d, *J*=8.5 Hz, 1 H) 7.35 - 7.46 (m, 1 H) 7.16 - 7.33 (m, 2 H) 7.03 - 7.14 (m, 1 H) 3.38 - 3.49 (m, 1 H) 3.04 - 3.26 (m, 4 H) 2.90 - 3.01 (m, 1 H) 2.70 - 2.84 (m, 2 H) 2.07 - 2.24 (m, 1 H) 1.89 - 2.06 (m, 2 H) 1.73 - 1.87 (m, 1 H) 1.36 - 1.66 (m, 5 H) 1.04 - 1.34 (m, 7 H)
243	
244	^{1}H NMR (400 MHz, DMSO-*d*6) *δ* 11.40 (s, 1H), 8.15 (d, *J* = 5.6 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 1H), 7.42 (d, *J* = 5.6 Hz, 1H), 7.18 (d, *J* = 1.6 Hz, 1 H), 7.11-6.89 (m, 2H), 3.75 (s, 2H), 3.49-3.40 (m, 2H), 3.06-2.80 (m, 4H), 2.17-2.00 (m, 2H), 1.52 (s, 4H), 1.36-1.05 (m, 8H), 1.03-0.82 (m, 5H).
245	^{1}H NMR (400 MHz, DMSO-*d*6) *δ* 11.30 (s, 1H), 8.14 (s, 1H), 8.04-7.83 (m, 1H), 7.42 (s, 1H), 7.26-6.85 (m, 3H), 3.76 (s, 2H), 3.44 (s, 2H), 2.96 (s, 2H), 2.84 (s, 2H), 2.08 (s, 2H), 1.69-0.81 (m, 15H).
247	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 10.22 (s, 1H), 8.15 (d, *J* = 5.5 Hz, 1H), 7.84-.782 (d, *J* = 8.5 Hz, 1H), 7.40-7.35 (d, *J* = 5.5 Hz, 1H), 7.15-7.12 (m, 1H), 7.05-7.02 (m, 2H), 5.54-5.52 (m, 2H), 3.51 (s, 2H), 3.13-3.11 (m, 2H), 2.66-2.64 (m, 3H), 2.32 (s, 1H), 2.15 (s, 2H), 2.07-2.05 (m, 2H), 1.84-1.70 (m, 2H), 1.65-1.62 (m, 1H), 1.51-1.50 (m, 2H), 1.21-1.20 (m, 3H), 0.88-0.79 (m, 2H).

Cpd No.	^{1}H NMR (ppm)
248	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.16 (br s, 1 H) 10.28 (br s, 1 H) 8.18 (d, *J*=5.5 Hz, 1 H) 8.03 (d, *J*=8.8 Hz, 1 H) 7.42 (d, *J*=5.5 Hz, 1 H) 7.23 - 7.33 (m, 2 H) 7.12 (dd, *J*=8.6, 1.9 Hz, 1 H) 3.37 - 3.50 (m, 1 H) 3.04 - 3.22 (m, 2 H) 2.94 (br d, *J*=10.3 Hz, 1 H) 2.70 - 2.86 (m, 2 H) 2.38 - 2.46 (m, 1 H) 2.08 - 2.26 (m, 1 H) 1.90 - 2.07 (m, 2 H) 1.74 - 1.88 (m, 1 H) 1.43 - 1.70 (m, 5 H) 1.40 (s, 3 H) 1.07 - 1.34 (m, 5 H) 0.77 - 0.91 (m, 2 H)
249	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.98 (s, 1 H) 10.30 (s, 1 H) 8.19 (d, *J*=5.3 Hz, 1 H) 8.08 (d, *J*=8.8 Hz, 1 H) 7.28 - 7.36 (m, 2 H) 7.25 (d, *J*=5.3 Hz, 1 H) 7.18 (dd, *J*=8.8, 2.0 Hz, 1 H) 5.44 - 5.57 (m, 2 H) 3.22 - 3.30 (m, 2 H) 3.07 (br d, *J*=11.3 Hz, 2 H) 2.77 (br t, *J*=11.0 Hz, 2 H) 2.13 - 2.29 (m, 4 H) 1.85 - 1.99 (m, 2 H) 1.78 (br d, *J*=10.5 Hz, 3 H) 1.40 (s, 3 H) 1.17 - 1.23 (m, 2 H) 0.80 - 0.90 (m, 2 H)
250	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (s, 1H), 8.15 (d, *J* = 2.4 Hz, 1H), 8.03 (d, *J* = 8.6 Hz, 1H), 7.78 (d, *J* = 1.9 Hz, 1H), 7.76-7.48 (m, 2H), 7.24-7.09 (m, 2H), 7.06 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.54-6.50 (m, 2H), 3.76-3.72 (m, 2H), 3.60-3.58 (m, 1H), 3.35-3.52 (m, 3H), 3.16-3.14 (m, 2H), 3.00-2.97 (m, 1H), 2.55-2.53 (m, 3H), 2.22-2.20 (m, 1H), 2.00-1.98 (m, 2H), 1.83 (s, 1H), 1.54-1.50 (m, 4H), 1.24-1.20 (m, 4H).
251	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.74 (s, 1H), 10.21 (s, 1H), 8.16 (d, *J* = 2.5 Hz, 1H), 8.05 (d, *J* = 8.6 Hz, 1H), 7.79 (d, *J* = 1.6 Hz, 1H), 7.67 (q, *J* = 8.4 Hz, 2H), 7.18-7.15 (m, 2H), 7.08 (d, *J* = 8.5 Hz, 1H), 6.54-6.50 (m, 1H), 4.94-4.90 (m, 1H), 3.76-3.74 (m, 2H), 3.61-3.60 (m, 1H), 3.36-3.34 (m, 3H), 3.17-3.15 (m, 2H), 3.05-2.86 (m, 2H), 2.75 (s, 1H), 2.23-2.22 (m, 1H), 2.04-2.00 (m, 2H), 1.83 (s, 1H), 1.54-1.50 (m, 4H), 1.39- 1.12 (m, 4H).
252	^{1}H NMR (400 MHz, DMSO) δ 11.74 (s, 1H), 8.15 (d, *J* = 2.5 Hz, 1H), 8.05 (d, *J* = 8.6 Hz, 1H), 7.79 (d, *J* = 1.9 Hz, 1H), 7.66 (q, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 2.1 Hz, 1H), 7.16 (t, *J* = 5.9 Hz, 1H), 7.08 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.54 (t, *J* = 2.2 Hz, 1H), 3.77 (t, *J* = 6.5 Hz, 2H), 3.60 (s, 2H), 3.39–3.34 (m, 3H), 3.1 –3.11 (m, 2H), 3.04–2.89 (m, 2H), 2.78–2.66 (m, 1H), 2.35–2.16 (m, 2H), 2.13–1.93 (m, 2H), 1.82 (s, 1H), 1.65–1.42 (m, 5H), 1.35–1.15 (m, 3H).
253	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 10.22 (s, 1H), 7.86 (dd, *J* = 8.5, 2.4 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.13 – 6.97 (m, 3H), 5.60 – 5.43 (m, 2H), 3.62 (q, *J* = 5.9, 5.4 Hz, 2H), 3.27 – 3.09 (m, 5H), 2.74 – 2.59 (m, 2H), 2.29 – 2.15 (m, 2H), 2.04 (dd, *J* = 8.0, 3.1 Hz, 2H), 1.79 – 1.58 (m, 3H), 1.51 (d, *J* = 11.5 Hz, 2H), 1.20 (t, *J* = 7.3 Hz, 3H).
254	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 10.12 (s, 1H), 7.85 (t, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.19 – 6.94 (m, 3H), 5.52 (tdd, *J* = 22.2, 15.2, 7.1 Hz, 2H), 4.98 (s, 1H), 3.75 (s, 2H), 3.61 (d, *J* = 9.1 Hz, 2H), 3.14 (d, *J* = 11.2 Hz, 2H), 2.65 (t, *J* = 11.3 Hz, 2H), 2.21 (d, *J* = 5.1 Hz, 2H), 2.05 (dd, *J* = 7.6, 3.2 Hz, 2H), 1.69 (q, *J* = 15.5, 13.5 Hz, 3H), 1.52 (d, *J* = 11.6 Hz, 2H), 1.14 (q, *J* = 4.6, 4.0 Hz, 2H), 0.98 (q, *J* = 4.8 Hz, 2H).
255	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (s, 1 H) 10.17 (br s, 1 H) 8.15 (d, *J*=5.3 Hz, 1 H) 7.83 (d, *J*=8.5 Hz, 1 H) 7.39 (d, *J*=5.5 Hz, 1 H) 7.05 - 7.19 (m, 2 H) 7.01 (dd, *J*=8.5, 1.8 Hz, 1 H) 5.43 - 5.74 (m, 2 H) 4.96 (br s, 1 H) 3.76 (t, *J*=6.5 Hz, 2 H) 3.47 - 3.60 (m, 2 H) 3.35 - 3.39 (m, 2 H) 2.93 - 3.03 (m, 2 H) 2.80 - 2.93 (m, 2 H) 2.16 (br d, *J*=3.8 Hz, 2 H) 1.83 - 2.02 (m, 4 H) 1.17 (br d, *J*=12.5 Hz, 2 H) 0.99 (s, 3 H)

Cpd No.	^{1}H NMR (ppm)
256	^{1}H NMR (400 MHz, DMSO-*d*6) δ 10.94 (s, 1H), 10.22 (s, 1H), 8.16 (d, *J* = 5.6 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 5.2 Hz, 1H), 7.20-6.93 (m, 3H), 5.72-5.48 (m, 2H), 3.58-3.49 (m, 2H), 3.27-3.14 (m, 2H), 3.08-2.82 (m, 4H), 2.17 (s, 2H), 2.05-1.86 (m, 4H), 1.31-1.15 (m, 5H), 1.08-0.98 (m, 3H).
257	^{1}H NMR (400 MHz, DMSO-*d*6) δ 10.98 (s, 1H), 8.15 (d, *J* = 4.8 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 4.8 Hz, 1H), 7.30-6.95 (m, 3H), 5.93-5.36 (m, 2H), 3.75 (s, 2H), 3.53 (s, 2H), 3.70-2.72 (m, 4H), 2.16 (s, 2H), 2.05-1.84 (m, 4H), 1.40-0.73 (m, 10H).
258	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (s, 1H), 7.84 (dd, *J* = 14.3, 8.5 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.11 (d, *J* = 9.2 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 1H), 5.67 - 5.44 (m, 2H), 3.75 (t, *J* = 6.5 Hz, 2H), 3.65 (q, *J* = 6.0 Hz, 3H), 2.98 (d, *J* = 11.4 Hz, 2H), 2.86 (t, *J* = 12.1 Hz, 2H), 2.23 (q, *J* = 5.8 Hz, 2H), 1.94 - 1.86 (m, 4H), 1.23 (s, 1H), 1.16 (d, *J* = 12.9 Hz, 2H), 0.98 (s, 3H).
259	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.27 (d, *J* = 2.9 Hz, 1H), 8.18 – 8.16 (m, 1H), 8.09 – 8.04 (m, 1H), 7.47 – 7.33 (m, 2H), 7.28 – 7.04 (m, 2H), 5.54 – 5.50 (m, 1H), 5.15 – 5.05 (m, 1H), 3.97 (s, 2H), 3.75 (td, *J* = 6.5, 1.7 Hz, 2H), 3.03 (t, *J* = 5.1 Hz, 2H), 2.96 (d, *J* = 10.7 Hz, 2H), 2.82 (t, *J* = 10.9 Hz, 2H), 2.69 (d, *J* = 10.8 Hz, 2H), 2.38 – 2.20 (m, 2H), 1.48 – 1.17 (m, 9H), 0.86 (t, *J* = 6.7 Hz, 1H).
260	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.63 (s, 1H), 8.50 (s, 1H), 8.08 (d, *J* = 5.5 Hz, 1H), 7.74 (s, 1H), 7.44 (s, 1H), 6.99 (d, J = 7.1 Hz, 1H), 6.86- 6.74 (m, 3H), 6.65 (d, *J* = 8.8 Hz, 1H), 5.45 (s, 3H), 3.77-3.49 (m, 6H), 2.97-2.75 (m, 3H), 2.46-2.12 (m, 2H), 2.14-1.79 (m, 2H), 1.71-1.44 (m, 1H), 0.95-0.73 (m, 2H), 0.58- 0.25 (m, 4H).
261	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.27 (d, *J* = 2.9 Hz, 1H), 8.18 – 8.16 (m, 1H), 8.09 – 8.04 (m, 1H), 7.47 – 7.33 (m, 2H), 7.28 – 7.04 (m, 2H), 5.54 – 5.50 (m, 1H), 5.15 – 5.05 (m, 1H), 3.97 (s, 2H), 3.75 (td, *J* = 6.5, 1.7 Hz, 2H), 3.03 (t, *J* = 5.1 Hz, 2H), 2.96 (d, *J* = 10.7 Hz, 2H), 2.82 (t, *J* = 10.9 Hz, 2H), 2.69 (d, *J* = 10.8 Hz, 2H), 2.38 – 2.20 (m, 2H), 1.48 – 1.17 (m, 9H), 0.86 (t, *J* = 6.7 Hz, 1H).
262	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 1H), 8.38 (s, 1H), 8.13 (d, *J* = 5.4 Hz, 1H), 7.74 (s, 1H), 7.41 (d, *J* = 5.5 Hz, 1H), 7.07 (s, 1H), 6.87 (s, 2H), 3.74 (t, *J* = 6.4 Hz, 2H), 3.50 (s, 2H), 3.20 (d, *J* = 13.1 Hz, 3H), 2.85 (t, *J* = 12.3 Hz, 2H), 2.47 (d, *J* = 6.8 Hz, 1H), 2.31 (s, 3H), 2.18 (s, 3H), 1.98 (d, *J* = 12.3 Hz, 2H), 1.83 (d, *J* = 13.2 Hz, 2H).
263	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1 H) 8.17 (d, *J*=5.5 Hz, 1 H) 7.87 (d, *J*=8.5 Hz, 1 H) 7.40 (d, *J*=5.5 Hz, 1 H) 7.33 (d, *J*=2.0 Hz, 1 H) 7.24 (dd, *J*=8.5, 2.0 Hz, 1 H) 7.07 - 7.16 (m, 1 H) 5.41 - 5.76 (m, 2 H) 5.06 (t, *J*=5.4 Hz, 1 H) 3.75 (q, *J*=6.0 Hz, 2 H) 3.47 - 3.60 (m, 3 H) 3.32 - 3.32 (m, 4 H) 2.90 - 3.04 (m, 4 H) 2.12 - 2.22 (m, 2 H) 1.87 - 2.01 (m, 4 H) 1.11 - 1.22 (m, 2 H) 1.00 (s, 3 H)
264	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (s, 1H), 10.28 (s, 1H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.34 (s, 1H), 7.24 – 7.14 (m, 2H), 7.09 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.71 (s, 6H), 3.42 (s, 1H), 3.24 (d, *J* = 7.3 Hz, 1H), 3.24 – 3.06 (m, 3H), 2.95 (q, *J* = 7.4 Hz, 4H), 2.75 (s, 2H), 2.23 (s, 2H), 2.18 (d, *J* = 13.2 Hz, 1H), 1.99 (s, 2H), 1.81 (s, 1H), 1.54 (s, 2H), 1.47 (d, *J* = 10.5 Hz, 2H).
265	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.02 (s, 1H), 10.28 (s, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.33 (s, 1H), 7.23 – 7.15 (m, 2H), 3.33 (s, 3H), 3.25 – 3.05 (m, 2H), 2.97 (d, *J* = 10.9 Hz, 1H), 2.74 (s, 2H), 2.51 (s, 1H), 2.22 (s, 2H), 1.97 (s, 2H), 1.81 (s, 1H), 1.54 (s, 2H), 1.46 (s, 3H), 1.23 (s, 3H), 1.21 (q, *J* = 8.4 Hz, 4H), 1.12 (s, 2H).

Cpd No.	^{1}H NMR (ppm)
266	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.02 (s, 1H), 10.27 (s, 1H), 8.02 (d, J = 8.6 Hz, 1H), 7.33 (s, 1H), 7.24 – 7.15 (m, 2H), 7.08 (dd, J = 8.6, 2.1 Hz, 1H), 3.27 – 3.12 (m, 2H), 3.09 (d, J = 13.5 Hz, 1H), 2.95 (q, J = 7.4 Hz, 1H), 2.74 (s, 2H), 2.22 (s, 2H), 2.17 (s, 1H), 1.98 (s, 2H), 1.56 (d, J = 16.9 Hz, 2H), 1.46 (d, J = 10.8 Hz, 3H), 1.22 (t, J = 7.4 Hz, 8H), 1.12 (s, 2H).
267	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (s, 1 H) 8.08 (d, J=8.8 Hz, 1 H) 7.89 (d, J=8.5 Hz, 1 H) 7.41 (d, J=8.5 Hz, 1 H) 7.33 (br t, J=6.1 Hz, 1 H) 7.23 (d, J=1.5 Hz, 1 H) 7.13 (dd, J=8.8, 1.5 Hz, 1 H) 5.41 - 5.60 (m, 2 H) 3.76 (t, J=6.5 Hz, 2 H) 3.36 - 3.47 (m, 4 H) 3.08 (br d, J=11.3 Hz, 2 H) 2.77 (br t, J=10.8 Hz, 2 H) 2.10 - 2.36 (m, 4 H) 1.65 - 1.91 (m, 5 H)
268	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.67 (br s, 1 H) 10.11 (br s, 1 H) 8.71 (br s, 1 H) 7.97 (br s, 1 H) 7.84 (br d, J=7.5 Hz, 1 H) 7.67 - 7.79 (m, 1 H) 7.48 (br d, J=1.0 Hz, 1 H) 6.94 - 7.15 (m, 2 H) 5.44 - 5.72 (m, 2 H) 4.96 (br s, 1 H) 3.58 - 3.92 (m, 5 H) 3.18 (br d, J=2.5 Hz, 2 H) 2.59 - 2.76 (m, 3 H) 2.19 - 2.39 (m, 2 H) 1.97 - 2.15 (m, 2 H) 1.74 - 1.93 (m, 2 H) 1.43 - 1.73 (m, 3 H)
269	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.41 (s, 1H), 10.19 (s, 1H), 8.41 (s, 1 H), 8.21-7.80 (m, 3H), 7.48 (s, 1H), 7.25-7.02 (m, 2H), 5.53 (s, 2H), 4.94 (s, 1H), 3.85-3.70 (m, 2H), 3.2-3.40 (m, 2H), 3.20-3.05 (m, 3H), 2.88-2.72 (m, 2H), 2.38-2.20 (m, 2H), 2.08-1.90 (m, 2H), 1.89-1.54 (m, 5H).
270	^{1}H NMR (400 MHz, DMSO-*d*6) δ 10.90 (s, 1H), 10.28 (s, 1H), 8.19 (d, J = 5.2 Hz, 1H), 8.10 (d, J = 8.8 Hz, 1H), 7.38-7.12 (m, 4H), 5.70-5.44 (m, 2H), 3.28-3.20 (m, 4H), 2.98-2.82 (m, 4H), 2.35-2.20 (m, 2H), 2.19-2.02 (m, 4H), 1.58-1.50 (m, 2H), 1.30-1.17 (m, 3H), 1.13 (s, 3H).
271	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.90 (s, 1H), 10.27 (s, 1H), 8.15 – 8.05 (m, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.46 – 7.27 (m, 3H), 7.16 (dd, J = 8.8, 2.1 Hz, 1H), 5.64 – 5.52 (m, 2H), 3.40 (s, 2H), 3.23 (q, J = 7.3 Hz, 2H), 2.92 (d, J = 8.5 Hz, 4H), 2.39 – 1.92 (m, 6H), 1.49 (d, J = 13.1 Hz, 2H), 1.27 – 1.16 (m, 4H), 1.13 (s, 3H).
272	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (s, 1 H) 10.23 (br s, 1 H) 8.19 (d, J=5.3 Hz, 1 H) 8.11 (d, J=8.8 Hz, 1 H) 7.34 (d, J=1.8 Hz, 1 H) 7.30 (t, J=6.5 Hz, 1 H) 7.23 (d, J=5.3 Hz, 1 H) 7.16 (dd, J=8.8, 2.0 Hz, 1 H) 5.48 - 5.68 (m, 2 H) 4.96 (br s, 1 H) 3.77 (t, J=6.4 Hz, 2 H) 3.37 (br t, J=6.4 Hz, 2 H) 3.20 - 3.30 (m, 2 H) 2.88 - 2.96 (m, 4 H) 2.26 (br s, 2 H) 2.04 - 2.19 (m, 4 H) 1.49 (br d, J=13.0 Hz, 2 H) 1.13 (s, 3 H)
273	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (s, 1H), 10.28 (s, 1H), 8.07 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.32 (t, J = 6.2 Hz, 1H), 7.22 (d, J = 2.2 Hz, 1H), 7.13 (dd, J = 8.7, 2.2 Hz, 1H), 5.50 (t, J = 5.8 Hz, 2H), 3.21 (q, J = 7.3 Hz, 3H), 3.08 (d, J = 11.2 Hz, 2H), 2.76 (t, J = 10.4 Hz, 2H), 2.25 (dd, J = 10.4, 5.5 Hz, 2H), 2.17 (t, J = 6.8 Hz, 2H), 1.85 – 1.76 (m, 5H), 1.20 (t, J = 7.3 Hz, 3H).
274	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.97 (s, 1H), 8.05 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.37 – 7.26 (m, 2H), 7.14 (dd, J = 8.7, 2.1 Hz, 1H), 5.50 (t, J = 5.7 Hz, 2H), 3.74 (s, 2H), 3.17 (d, J = 5.1 Hz, 1H), 3.06 (d, J = 11.1 Hz, 2H), 2.76 (t, J = 10.2 Hz, 2H), 2.27 – 2.15 (m, 4H), 1.89 – 1.70 (m, 5H), 1.24 – 0.93 (m, 5H).
275	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.93 (s, 1H), 8.09 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.35 – 7.28 (m, 2H), 7.14 (dd, J = 8.7, 2.1 Hz, 1H), 5.57 (qd, J = 10.7, 5.3 Hz, 2H), 3.76 (t, J = 6.5 Hz, 2H), 2.93 – 2.91 (m, 5H), 2.27 (s, 2H), 2.20 – 1.95 (m, 5H), 1.49 (d, J = 13.2 Hz, 2H), 1.24 (s, 2H), 1.13 (s, 3H).

Cpd No.	^{1}H NMR (ppm)
276	^{1}H NMR (400 MHz, DMSO-d6) δ 11.41 (s, 1H), 10.21 (s, 1H), 8.16 (s, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.79 (s, 1H), 7.62 (s, 2H), 7.14 (s, 1H), 7.06 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 6.95 (t, *J* = 6.4 Hz, 1H), 6.54 (s, 1H), 3.57-3.53 (m, 2H), 3.24-3.18 (m, 4H), 2.70 (t, *J* = 11.6 Hz, 2H), 2.09-1.95 (m, 2H), 1.77-1.65 (m, 1H), 1.63-1.58 (m, 2H), 1.56-1.38 (m, 8H), 1.27-1.19 (m, 3H).
278	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.21 (d, *J* = 5.5 Hz, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.47 (d, *J* = 5.4 Hz, 1H), 7.40 (s, 1H), 7.19 (s, 1H), 7.08 (d, *J* = 8.6 Hz, 1H), 5.61 – 5.59 (m, 1H), 5.49 – 5.46 (m, 1H), 3.76 (t, *J* = 6.4 Hz, 2H), 3.66 – 3.49 (m, 1H), 3.36 (d, *J* = 6.9 Hz, 3H), 3.20 – 3.00 (m, 5H), 2.47 – 1.90 (m, 6H), 1.62 (d, *J* = 12.0 Hz, 1H), 1.47 (d, *J* = 13.0 Hz, 2H), 1.24 (s, 2H).
279	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 8.21 (d, *J* = 5.5 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 7.60 – 7.00 (m, 4H), 5.60 – 5.47 (m, 2H), 3.76 (t, *J* = 6.5 Hz, 2H), 3.59 – 3.52 (m, 1H), 3.18 – 3.00 (m, 6H), 2.44 – 1.89 (m, 7H), 1.70 – 1.36 (m, 3H), 1.24 (s, 2H).
280	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 10.28 (s, 1H), 8.21 (d, *J* = 5.5 Hz, 1H), 8.00 (d, *J* = 8.7 Hz, 1H), 7.46 (d, *J* = 5.5 Hz, 1H), 7.41 (s, 1H), 7.32 (s, 1H), 7.20 (s, 1H), 7.08 (d, *J* = 8.6 Hz, 1H), 5.60 (d, *J* = 8.7 Hz, 1H), 5.47 (d, *J* = 10.9 Hz, 1H), 3.57 (d, *J* = 13.3 Hz, 1H), 3.20 (dd, *J* = 16.5, 9.2 Hz, 3H), 3.10 (d, *J* = 11.3 Hz, 2H), 3.00 (s, 2H), 2.43 (d, *J* = 12.1 Hz, 1H), 2.24 (s, 2H), 1.97 (d, *J* = 14.2 Hz, 1H), 1.72 (s, 1H), 1.61 (d, *J* = 12.7 Hz, 1H), 1.45 (s, 2H), 1.21 (q, *J* = 6.8 Hz, 2H).
282	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (br s, 1 H) 10.31 (s, 1 H) 8.22 (d, *J*=5.5 Hz, 1 H) 7.95 - 8.11 (m, 1 H) 7.38 - 7.58 (m, 2 H) 7.22 (br s, 1 H) 7.04 - 7.15 (m, 1 H) 5.35 - 5.73 (m, 2 H) 3.50 - 3.64 (m, 1 H) 2.92 - 3.28 (m, 8 H) 2.38 - 2.46 (m, 1 H) 2.14 - 2.29 (m, 2 H) 1.91 - 2.11 (m, 2 H) 1.56 - 1.68 (m, 1 H) 1.36 - 1.52 (m, 2 H) 1.13 - 1.26 (m, 3 H)
283	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.84 (s, 1H), 10.26 (s, 1H), 8.00 (d, *J* = 8.7 Hz, 1H), 7.48 – 7.02 (m, 4H), 5.53 (dd, *J* = 50.2, 9.8 Hz, 2H), 4.94 (s, 1H), 3.76 (t, *J* = 6.5 Hz, 2H), 3.59 – 3.53 (m, 1H), 3.36 – 3.35 (m, 3H), 3.24 – 2.93 (m, 6H), 2.45 – 2.42 (m, 1H), 2.34 – 2.26 (m, 5H), 2.12 – 1.90 (m, 2H), 1.61 (d, *J* = 13.0 Hz, 1H), 1.46 (d, *J* = 12.5 Hz, 2H).
284	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.50 – 7.00 (m, 4H), 5.59 – 5.45 (m, 2H), 3.76 (td, *J* = 6.5, 2.5 Hz, 2H), 3.60 – 3.54 (m, 2H), 3.25 – 2.90 (m, 6H), 2.47 – 1.90 (m, 8H), 1.61 (d, *J* = 12.7 Hz, 1H), 1.44 (s, 2H), 1.24 (s, 1H).
285	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.79 (s, 1H), 10.24 (s, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.50 – 6.93 (m, 4H), 5.52 (d, *J* = 54.1 Hz, 2H), 4.95 (s, 1H), 3.76 (t, *J* = 6.3 Hz, 2H), 3.63 – 3.51 (m, 1H), 3.25 – 2.92 (m, 6H), 2.25 – 1.87 (m, 9H), 1.69 – 1.35 (m, 4H), 1.24 (s, 1H), 0.86 (s, 1H).
286	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.78 (br s, 1 H) 10.30 (br s, 1 H) 7.99 (br d, *J*=8.5 Hz, 1 H) 7.38 (s, 1 H) 7.32 (br s, 1 H) 7.14 - 7.25 (m, 1 H) 7.08 (br d, *J*=8.3 Hz, 1 H) 5.29 - 5.72 (m, 2 H) 3.50 - 3.68 (m, 1 H) 2.89 - 3.27 (m, 7 H) 2.38 - 2.48 (m, 1 H) 2.24 (s, 5 H) 1.90 - 2.10 (m, 2 H) 1.60 (br d, *J*=12.8 Hz, 1 H) 1.33 - 1.52 (m, 2 H) 1.15 - 1.30 (m, 4 H)
287	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.78 (br s, 1 H) 10.30 (s, 1 H) 8.00 (br d, *J*=8.3 Hz, 1 H) 7.07 - 7.42 (m, 4 H) 5.35 - 5.69 (m, 2 H) 3.51 - 3.66 (m, 1 H) 2.92 - 3.28 (m, 8 H) 2.38 - 2.46 (m, 1 H) 2.15 - 2.29 (m, 5 H) 1.89 - 2.11 (m, 2 H) 1.60 (br d, *J*=2.0 Hz, 1 H) 1.34 - 1.50 (m, 2 H) 1.21 (t, *J*=7.3 Hz, 3 H)

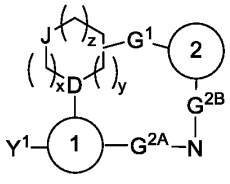
Cpd No.	^{1}H NMR (ppm)
288	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.82 (br s, 1 H) 10.30 (s, 1 H) 8.00 (br d, *J*=8.5 Hz, 1 H) 7.29 - 7.48 (m, 2 H) 7.21 (br s, 1 H) 7.04 - 7.15 (m, 1 H) 5.38 - 5.71 (m, 2 H) 3.50 - 3.66 (m, 1 H) 2.92 - 3.28 (m, 8 H) 2.40 - 2.47 (m, 1 H) 2.14 - 2.30 (m, 5 H) 1.91 - 2.12 (m, 2 H) 1.54 - 1.67 (m, 1 H) 1.34 - 1.51 (m, 2 H) 1.21 (t, *J*=7.3 Hz, 3 H)
289	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.98 (s, 1H), 11.10 (s, 1H), 8.12 (d, *J* = 8.7 Hz, 1H), 7.58 – 7.09 (m, 5H), 6.60 (d, *J* = 7.8 Hz, 1H), 5.61 – 5.46 (m, 3H), 5.06 (s, 1H), 3.73 (t, *J* = 6.2 Hz, 2H), 3.12 – 3.04 (m, 4H), 2.97 – 2.80 (m, 2H), 2.65 (t, *J* = 11.3 Hz, 1H), 2.30 – 2.01 (m, 4H), 2.00 – 1.84 (m, 2H), 1.77 (d, *J* = 12.3 Hz, 4H), 1.68 – 1.57 (m, 1H), 1.56 – 1.41 (m, 1H), 1.24 (s, 1H).
290	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.48 (s, 1H), 8.82 (s, 1H), 7.88 (d, *J* = 8.6 Hz, 1H), 7.57 (t, *J* = 6.4 Hz, 1H), 7.07 (d, *J* = 2.1 Hz, 1H), 7.01 (dd, *J* = 8.6, 2.0 Hz, 1H), 5.53 (tdd, *J* = 22.3, 15.4, 7.2 Hz, 2H), 3.75 (t, *J* = 6.5 Hz, 2H), 3.59 (q, *J* = 6.0 Hz, 2H), 3.33 (t, *J* = 6.5 Hz, 2H), 3.20 – 3.11 (m, 2H), 2.73 – 2.63 (m, 2H), 2.23 (q, *J* = 6.1 Hz, 2H), 2.10 – 2.02 (m, 2H), 1.66 (s, 3H), 1.52 (d, *J* = 9.2 Hz, 2H), 1.24 (s, 1H).
291	^{1}H NMR (400 MHz, DMSO-d6) δ 13.46 (s, 1H), 10.32 (s, 1H), 8.62 (s, 1H), 8.17 – 8.08 (m, 1H), 7.81 (t, *J* = 6.2 Hz, 1H), 7.26 (d, *J* = 2.0 Hz, 1H), 7.21 – 7.09 (m, 1H), 5.51 (q, *J* = 5.6 Hz, 2H), 4.96 (s, 1H), 3.76 (t, *J* = 6.4 Hz, 2H), 3.37 (t, *J* = 6.5 Hz, 4H), 3.31 (s, 1H), 3.08 (d, *J* = 11.2 Hz, 2H), 2.79 (t, *J* = 10.5 Hz, 2H), 2.28 (s, 2H), 2.16 (s, 2H), 1.79 (s, 2H), 1.24 (s, 1H).
292	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1 H) 10.17 (br s, 1 H) 8.63 (s, 1 H) 7.88 (d, *J*=8.5 Hz, 1 H) 7.64 (s, 1 H) 7.18 (br t, *J*=6.6 Hz, 1 H) 7.09 (d, *J*=1.8 Hz, 1 H) 7.03 (dd, *J*=8.5, 2.0 Hz, 1 H) 5.44 - 5.67 (m, 2 H) 4.94 (br t, *J*=5.5 Hz, 1 H) 3.70 - 3.82 (m, 2 H) 3.54 (br d, *J*=3.3 Hz, 2 H) 3.34 - 3.39 (m, 2 H) 3.16 (br d, *J*=11.5 Hz, 2 H) 2.61 - 2.73 (m, 2 H) 2.17 (br d, *J*=3.8 Hz, 2 H) 2.07 (dt, *J*=6.4, 3.2 Hz, 2 H) 1.58 - 1.83 (m, 3 H) 1.52 (br d, *J*=11.8 Hz, 2 H)
293	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.67 (s, 1H), 10.22 (s, 1H), 8.34 (s, 1H), 8.11 (d, *J* = 8.6 Hz, 1H), 7.67 (s, 1H), 7.40 (t, *J* = 6.4 Hz, 1H), 7.24 (d, *J* = 2.2 Hz, 1H), 7.14 (dd, *J* = 8.7, 2.2 Hz, 1H), 5.51 (t, *J* = 5.6 Hz, 2H), 3.76 (t, *J* = 6.4 Hz, 2H), 3.36 (t, *J* = 6.6 Hz, 3H), 3.09 (d, *J* = 11.1 Hz, 2H), 2.78-2.75 (m, 2H), 2.26 (s, 2H), 2.17 (d, *J* = 7.3 Hz, 2H), 1.92 (t, *J* = 12.1 Hz, 2H), 1.84 – 1.64 (m, 3H), 1.53-1.51 (m, 1H).
294	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 10.20 (s, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.60 (s, 1H), 7.18 (s, 2H), 7.07 (s, 1H), 7.05 – 6.96 (m, 2H), 5.63 – 5.41 (m, 2H), 4.94 (s, 1H), 3.94 (s, 2H), 3.75 (t, *J* = 6.5 Hz, 1H), 3.62 (s, 2H), 3.21 – 3.12 (m, 2H), 2.66 (t, *J* = 11.4 Hz, 1H), 2.35 (s, 2H), 2.21 (s, 2H), 2.04 (dd, J = 7.8, 3.1 Hz, 2H), 1.73 (d, *J* = 11.9 Hz, 1H), 1.66 (d, *J* = 16.9 Hz, 2H), 1.51 (d, *J* = 11.8 Hz, 2H), 1.25 (d, *J* = 6.4 Hz, 1H).
295	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.84 (s, 1H), 8.07 (d, *J* = 8.6 Hz, 1H), 7.38 (s, 1H), 7.33 (s, 2H), 7.22 (s, 2H), 7.14 (d, *J* = 8.8 Hz, 1H), 5.50 (d, *J* = 6.5 Hz, 2H), 3.76 (t, *J* = 6.4 Hz, 2H), 3.35 (s, 2H), 3.08 (d, *J* = 11.2 Hz, 1H), 2.77 (t, *J* = 11.2 Hz, 1H), 2.35 (s, 2H), 2.31 (d, *J* = 2.1 Hz, 1H), 2.26 (s, 2H), 2.17 (s, 2H), 1.88 – 1.74 (m, 6H), 1.24 (s, 1H).
296	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.53 (s, 1 H) 8.01 (d, *J*=8.8 Hz, 1 H) 7.36 (s, 1 H) 7.14 - 7.24 (m, 2 H) 7.07 (br d, *J*=9.0 Hz, 1 H) 5.25 - 5.55 (m, 2 H) 4.22 (br d, *J*=3.8 Hz, 2 H) 4.10 (br t, *J*=5.6 Hz, 2 H) 3.75 (t, *J*=6.4 Hz, 2 H) 3.27 - 3.32 (m, 3 H) 3.08 (br dd, *J*=11.6, 1.1 Hz, 2 H) 2.86 (br t, *J*=11.8 Hz, 2 H) 2.48 (br s, 1 H) 2.23 (s, 3 H) 1.58 (br d, *J*=12.0 Hz, 2 H) 1.30 (s, 3 H)

Cpd No.	^{1}H NMR (ppm)
297	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (br s, 1 H) 7.72 (d, *J*=8.5 Hz, 1 H) 7.35 (s, 1 H) 7.25 (t, *J*=5.0 Hz, 1 H) 6.73 - 6.89 (m, 3 H) 5.48 - 5.99 (m, 2 H) 4.89 (t, *J*=5.5 Hz, 1 H) 4.11 (br s, 2 H) 3.69 - 3.80 (m, 4 H) 2.96 - 3.12 (m, 4 H) 2.74 - 2.87 (m, 2 H) 2.21 - 2.32 (m, 5 H) 1.64 (br d, *J*=12.0 Hz, 2 H) 1.23 (s, 3 H)
298	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.26 (s, 1 H) 8.05 (d, *J*=8.5 Hz, 1 H) 7.24 (s, 1 H) 7.20 (s, 1 H) 7.10 (dd, *J*=8.6, 1.6 Hz, 1 H) 6.93 (t, *J*=6.6 Hz, 1 H) 3.75 (t, *J*=6.4 Hz, 2 H) 3.41 - 3.58 (m, 4 H) 3.28 - 3.32 (m, 2 H) 3.07 (br d, *J*=11.8 Hz, 2 H) 2.83 (br t, *J*=12.4 Hz, 2 H) 2.32 - 2.45 (m, 2 H) 2.21 (s, 3 H) 1.87 (br d, *J*=12.5 Hz, 2 H) 1.42 - 1.57 (m, 4 H) 1.28 (s, 3 H)
299	^{1}H NMR (400 MHz, DMSO-d6) δ 11.38 (s, 1H), 10.16 (s, 1H), 8.17 (s, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.81 (s, 1H), 7.65-7.58 (m, 2H), 7.16 (s, 1H), 7.05 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 6.87 (t, *J* = 6.8 Hz, 1H), 6.55 (s, 1H), 4.95 (s, 1H), 3.77 (t, *J* = 6.8 Hz, 2H), 3.64-3.59 (m, 2H), 3.37-3.34 (m, 2H), 3.08-3.02 (m, 2H), 2.87 (t, *J* = 11.2 Hz, 2H), 2.19-2.13 (m, 2H), 1.59-1.49 (m, 4H), 1.39-1.27 (m, 6H), 1.00 (s, 3H).
300	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.34 (s, 1H), 10.20 (s, 1H), 8.17 (d, *J* = 2.5 Hz, 1H), 7.96 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.81 (d, *J* = 2.1 Hz, 1H), 7.61 (qd, *J* = 8.4, 2.3 Hz, 2H), 7.17 (d, *J* = 2.4 Hz, 1H), 7.06 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.87 (s, 1H), 6.55 (q, *J* = 2.3 Hz, 1H), 3.65 – 3.58 (m, 2H), 3.27 – 3.17 (m, 2H), 3.03 (d, *J* = 11.4 Hz, 2H), 2.86 (t, *J* = 12.0 Hz, 2H), 2.49 (s, 1H), 2.15 (t, *J* = 12.4 Hz, 2H), 1.54 (s, 4H), 1.35 (s, 2H), 1.32 – 1.13 (m, 4H), 1.00 (d, *J* = 2.5 Hz, 3H), 0.97 (s, 1H).
301	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.51 (s, 1H), 7.96 – 7.83 (m, 2H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.14 (d, *J* = 2.0 Hz, 1H), 7.04 (dt, *J* = 8.8, 1.9 Hz, 1H), 6.93 (t, *J* = 6.3 Hz, 1H), 4.94 (s, 1H), 3.80 – 3.72 (m, 2H), 3.57 (d, *J* = 6.7 Hz, 2H), 3.39 – 3.28 (m, 2H), 3.00 (d, *J* = 11.2 Hz, 2H), 2.85 (t, *J* = 11.9 Hz, 2H), 2.08 (s, 2H), 1.60 (s, 2H), 1.48 (d, *J* = 7.5 Hz, 2H), 1.34 – 1.22 (m, 6H), 0.99 (s, 3H).
302	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.48 (s, 1H), 10.23 (s, 1H), 7.89 (dd, *J* = 23.1, 8.5 Hz, 1H), 7.89 (s, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.15 (d, *J* = 2.2 Hz, 1H), 7.04 (dd, *J* = 8.6, 2.1 Hz, 2H), 6.93 (t, *J* = 6.2 Hz, 1H), 3.57 (d, *J* = 6.9 Hz, 2H), 3.22 (q, *J* = 7.3 Hz, 1H), 3.00 (d, *J* = 11.7 Hz, 2H), 2.85 (t, *J* = 11.9 Hz, 2H), 2.05 (s, 2H), 1.59 (s, 2H), 1.48 (d, *J* = 8.0 Hz, 3H), 1.34 – 1.17 (m, 4H), 1.20 (s, 4H), 0.98 (s, 2H).
303	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.52 (s, 1H), 8.35 (s, 2H), 8.18 (d, *J* = 5.4 Hz, 1H), 7.97 (d, *J* = 9.0 Hz, 1H), 7.29 (s, 1H), 7.23 (d, *J* = 5.4 Hz, 1H), 7.08 (s, 1H), 6.99 (d, *J* = 8.7 Hz, 1H), 5.72 (q, *J* = 8.4 Hz, 1H), 5.57 (q, *J* = 8.7 Hz, 1H), 3.74 (t, *J* = 6.5 Hz, 2H), 3.24 (t, *J* = 7.9 Hz, 2H), 2.93 (t, *J* = 12.1 Hz, 2H), 2.58 (d, *J* = 8.4 Hz, 2H), 2.28 (s, 2H), 2.07 (d, *J* = 13.7 Hz, 2H), 1.39 (s, 3H), 1.24 (s, 1H).
304	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (s, 1H), 8.36 (s, 1H), 8.21-8.06 (m, 1H), 8.01 (d, *J* = 8.7 Hz, 1H), 7.79 (d, *J* = 1.9 Hz, 1H), 7.65-7.39 (m, 2H), 7.18-6.86 (m, 3H), 6.53 (d, *J* = 2.2 Hz, 1H), 3.74-3.70 (m, 2H), 3.59-3.57 (m, 4H), 3.17-3.15(m, 5H), 2.82-2.83 (m, 3H), 2.26-2.24 (m, 2H), 1.53 (d, *J* = 16.6 Hz, 4H), 1.24 (s, 1H).
305	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.20 (s, 1H), 8.12 (d, *J* = 2.5 Hz, 1H), 7.87 (d, *J* = 8.6 Hz, 1H), 7.78 (d, *J* = 1.9 Hz, 1H), 7.57 (d, *J* = 2.3 Hz, 2H), 6.84 (d, *J* = 11.3 Hz, 2H), 6.52 (t, *J* = 2.2 Hz, 1H), 3.71 (t, *J* = 6.7 Hz, 2H), 3.02 (s, 2H), 2.84 (t, *J* = 12.3 Hz, 2H), 2.55 (s, 3H), 2.55 (d, *J* = 3.4 Hz, 1H), 2.50 (s, 1H), 2.39 (s, 2H), 1.89 (d, *J* = 12.4 Hz, 2H), 1.51 (s, 3H), 1.29 (s, 3H), 1.24 (s, 3H), 0.85 (d, *J* = 8.0 Hz, 1H).

Cpd No.	^{1}H NMR (ppm)
306	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 7.89-7.80 (m, 2H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.38-7.18 (m, 2H), 7.11-7.01 (m, 1H), 5.51-5.46 (m, 2H), 5.05-5.00 (m, 1H), 3.74-3.70 (m, 2H), 3.63 (s, 2H), 3.18-3.15 (m, 2H), 2.82-2.66 (m, 3H), 2.22 (s, 4H), 2.10-1.97 (m, 2H), 1.85-1.57 (m, 3H), 1.52 (d, *J* = 11.9 Hz, 2H), 1.24 (s, 2H).
308	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.68 (s, 1 H) 8.16 (d, *J*=1.8 Hz, 1 H) 7.99 (dd, *J*=8.6, 1.9 Hz, 1 H) 7.77 (d, *J*=2.0 Hz, 1 H) 7.49 - 7.70 (m, 2 H) 7.00 - 7.20 (m, 3 H) 6.53 (t, *J*=2.1 Hz, 1 H) 3.82 (br s, 2 H) 3.76 (br t, *J*=6.3 Hz, 5 H) 3.59 - 3.66 (m, 4 H) 2.95 - 3.20 (m, 4 H) 1.95 - 2.43 (m, 3 H) 1.62 - 1.77 (m, 1 H) 1.38 - 1.59 (m, 4 H)
309	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.68 (s, 1 H) 8.17 (d, *J*=2.3 Hz, 1 H) 8.00 (br dd, *J*=8.5, 1.3 Hz, 1 H) 7.78 (s, 1 H) 7.52 - 7.68 (m, 2 H) 7.01 - 7.18 (m, 3 H) 6.54 (br d, *J*=1.8 Hz, 1 H) 3.58 - 3.86 (m, 9 H) 3.43 - 3.48 (m, 2 H) 2.97 - 3.21 (m, 5 H) 1.94 - 2.28 (m, 1 H) 1.59 - 1.79 (m, 1 H) 1.34 - 1.58 (m, 5 H)
310	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.68 (s, 1H), 8.17 (d, *J* = 2.0 Hz, 1H), 8.00 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.78 (s, 1H), 7.64 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.56 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.18 – 7.07 (m, 2H), 7.06 (dt, *J* = 8.7, 2.2 Hz, 1H), 6.54 (q, *J* = 2.1 Hz, 1H), 4.93 (s, 1H), 3.82 (s, 1H), 3.80 – 3.72 (m, 3H), 3.63 (t, *J* = 9.1 Hz, 1H), 3.48 – 3.41 (m, 1H), 3.36 (dq, *J* = 9.2, 3.2 Hz, 2H), 3.28 (s, 1H), 3.15 (d, *J* = 11.5 Hz, 1H), 3.11 – 3.01 (m, 2H), 2.22 (s, 1H), 2.09 (d, *J* = 13.3 Hz, 1H), 1.69 (s, 1H), 1.47 (d, *J* = 13.9 Hz, 3H), 1.24 (s, 1H), 1.18 (s, 1H).
317	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.95 (s, 1 H) 8.84 (s, 1 H) 7.95 (d, *J*=8.8 Hz, 1 H) 7.50 (br t, *J*=6.3 Hz, 1 H) 7.13 (s, 1 H) 7.06 (dd, *J*=8.8, 1.5 Hz, 1 H) 3.76 (t, *J*=6.5 Hz, 2 H) 3.43 - 3.56 (m, 2 H) 3.16 (br d, *J*=10.5 Hz, 2 H) 2.65 - 2.77 (m, 2 H) 1.77 - 1.98 (m, 2 H) 1.33 - 1.72 (m, 10 H) 1.24 (s, 3 H)
318	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.73 (s, 1H), 8.07 – 7.99 (m, 2H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.21 (t, *J* = 5.9 Hz, 1H), 7.16 (d, *J* = 2.1 Hz, 1H), 7.05 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.45 (d, *J* = 2.4 Hz, 1H), 5.14 (s, 1H), 4.51 (s, 2H), 3.75 (t, *J* = 6.5 Hz, 2H), 3.60 (s, 1H), 3.20 – 3.12 (m, 1H), 3.15 (s, 2H), 2.99 (d, *J* = 11.1 Hz, 1H), 2.74 (s, 1H), 2.53 (s, 2H), 2.21 (d, *J* = 13.0 Hz, 1H), 2.07 (s, 2H), 2.00 (s, 1H), 1.82 (s, 1H), 1.57 (d, *J* = 12.7 Hz, 1H), 1.50 (s, 3H), 1.29 (s, 3H), 1.26 – 1.13 (m, 1H).
319	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.73 (s, 1H), 8.07 – 7.99 (m, 2H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.24 – 7.14 (m, 2H), 7.05 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.45 (d, *J* = 2.4 Hz, 1H), 5.16 (s, 1H), 4.51 (s, 2H), 3.76 (t, *J* = 6.5 Hz, 2H), 3.36 (s, 5H), 3.15 (s, 1H), 3.01 (s, 1H), 2.92 (s, 1H), 2.21 (d, *J* = 13.1 Hz, 1H), 2.06 (s, 2H), 2.00 (s, 1H), 1.82 (s, 1H), 1.56 (s, 2H), 1.53 – 1.43 (m, 3H), 1.30 (d, *J* = 10.7 Hz, 1H), 1.29 (s, 2H), 1.19 (q, *J* = 12.9, 10.8 Hz, 1H).
320	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.72 (br s, 1 H) 7.97 - 8.08 (m, 2 H) 7.56 - 7.72 (m, 2 H) 7.13 - 7.28 (m, 2 H) 7.06 (dd, *J*=8.5, 2.0 Hz, 1 H) 6.45 (d, *J*=2.3 Hz, 1 H) 5.16 (br t, *J*=5.4 Hz, 1 H) 4.51 (br d, *J*=4.8 Hz, 2 H) 3.71 - 3.82 (m, 5 H) 2.82 - 3.22 (m, 6 H) 2.14 - 2.28 (m, 1 H) 1.92 - 2.13 (m, 2 H) 1.73 - 1.88 (m, 1 H) 1.40 - 1.67 (m, 5 H) 1.09 - 1.38 (m, 3 H)
321	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.46 (s, 1H), 8.17 (d, *J* = 2.5 Hz, 1H), 8.02 (d, *J* = 8.3 Hz, 1H), 7.80 (d, *J* = 1.9 Hz, 1H), 7.64 (s, 2H), 7.26 – 7.19 (m, 2H), 6.98 (t, *J* = 6.5 Hz, 1H), 6.59 – 6.51 (m, 1H), 5.02 (s, 2H), 4.09 (dd, *J* = 5.7, 3.4 Hz, 2H), 3.96 (t, *J* = 4.5 Hz, 2H), 3.56 (q, *J* = 6.3 Hz, 2H), 3.21 (d, *J* = 11.4 Hz, 3H), 2.79 (t, *J* = 11.6 Hz, 2H), 2.07 – 1.93 (m, 2H), 1.77 – 1.56 (m, 2H), 1.54 – 1.47 (m, 8H).

Cpd No.	^{1}H NMR (ppm)
322	^{1}H NMR (400 MHz, DMSO) δ 11.49 (s, 1H), 8.18 (d, *J* = 2.4 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 2.0 Hz, 1H), 7.63 (q, *J* = 8.4 Hz, 2H), 7.29 – 7.20 (m, 2H), 6.90 (t, *J* = 6.8 Hz, 1H), 6.55 (t, *J* = 2.2 Hz, 1H), 5.03 (s, 2H), 4.83 (s, 1H), 4.69 (d, *J* = 12.6 Hz, 2H), 4.09 (t, *J* = 4.6 Hz, 2H), 4.01 – 3.94 (m, 2H), 3.71 – 3.56 (m, 3H), 3.38 (d, *J* = 5.0 Hz, 2H), 3.04 – 2.94 (m, 3H), 2.21 – 2.10 (m, 2H), 1.55 (s, 3H), 1.35 (d, *J* = 7.6 Hz, 2H), 1.32 – 1.23 (m, 2H), 1.01 (s, 3H).
324	^{1}H NMR (400 MHz, DMSO) δ 11.40 (s, 1H), 8.21-8.14 (m, 1H), 7.96 (d, *J* = 8.5 Hz, 1H), 7.77-7.75 (m, 1H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.12 (d, *J* = 2.2 Hz, 2H), 7.05-7.00 (m, 1H), 6.56-6.50 (m, 1H), 3.76 (t, *J* = 6.5 Hz, 2H), 3.49 (s, 2H), 3.35 (s, 1H), 3.21 (m, 2H), 3.01 (d, *J* = 8.8 Hz, 1H), 2.90 (s,1H), 2.83-2.73 (m, 1H), 2.68 (d, *J* = 2.0 Hz, 1H), 2.59-2.55 (m, 1H), 2.46-2.35 (m, 1H), 2.34-2.21 (m, 1H), 1.97-1.92 (m, 2H), 1.64-1.62 (m, 2H), 1.45-1.42 (m, 2H), 1.33-1.30 (m, 1H), 1.24 (s, 3H).
325	^{1}H NMR (400 MHz, DMSO) δ 11.41 (s, 1H), 8.21-8.14 (m, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.77-7.75 (m, 1H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.12 (d, *J* = 2.2 Hz, 2H), 7.05-7.00 (m, 1H), 6.56-6.50 (m, 1H), 3.76 (t, *J* = 6.5 Hz, 2H), 3.49 (s, 2H), 3.35 (s, 1H), 3.21 (m, 2H), 3.01 (d, *J* = 8.8 Hz, 1H), 2.90 (s,1H), 2.83-2.73 (m, 1H), 2.68 (d, *J* = 2.0 Hz, 1H), 2.59-2.55 (m, 1H), 2.46-2.35 (m, 1H), 2.34-2.21 (m, 1H), 1.97-1.95 (m, 2H), 1.64-1.62 (m, 2H), 1.45-1.42 (m, 2H), 1.33-1.30 (m, 1H), 1.24 (s, 3H).
326	^{1}H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 8.21-8.14 (m, 1H), 7.96 (d, *J* = 8.5 Hz, 1H), 7.77-7.75 (m, 1H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.12 (d, *J* = 2.2 Hz, 2H), 7.05-7.00 (m, 1H), 6.56-6.50 (m, 1H), 3.76 (t, *J* = 6.5 Hz, 2H), 3.49 (s, 2H), 3.35 (s, 1H), 3.21 (m, 2H), 3.01 (d, *J* = 8.8 Hz, 1H), 2.90 (s,1H), 2.80-2.75 (m, 1H), 2.68 (d, *J* = 2.0 Hz, 1H), 2.59-2.55 (m, 1H), 2.46-2.35 (m, 1H), 2.34-2.21 (m, 1H), 1.97-1.95 (m, 2H), 1.64-1.62 (m, 2H), 1.45-1.42 (m, 2H), 1.33-1.30 (m, 1H), 1.24 (s, 3H).
327	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (s, 1H), 8.36 (s, 1H), 8.21-8.06 (m, 1H), 8.01-7.99 (m, 1H), 7.79-7.72 (m, 1H), 7.65-7.39 (m, 2H), 7.18-6.86 (m, 3H), 6.53 (d, *J* = 2.2 Hz, 1H), 3.74-3.70 (m, 2H), 3.59-3.57 (m, 4H), 3.17-3.15(m, 5H), 2.82-2.83 (m, 3H), 2.26-2.24 (m, 2H), 1.53-1.50 (m, 1H), 1.24 (s, 1H).
332	^{1}H NMR (400 MHz, DMSO-*d*6) *δ* 10.98 (s, 1H), 8.15 (d, *J* = 4.8 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 4.8 Hz, 1H), 7.30-6.95 (m, 3H), 5.93-5.36 (m, 2H), 3.75 (s, 2H), 3.53 (s, 2H), 3.70-2.72 (m, 4H), 2.16 (s, 2H), 2.05-1.84 (m, 4H), 1.40-0.73 (m, 10H). LCMS (ESI-MS) m/z = 527.0 $[M+H]^+$.

[000128] In some embodiments, a compound provided herein has the structure of Formula (IV-A), or a pharmaceutically acceptable salt or solvate, thereof:



(IV-A)

wherein

Y^1 is a halogen, cyanide, alcohol, amide, sulfonamide, sulfoxide, ether, cyclic amine, alkyl amine, heteroaryl, saturated heterocycle, organoboranes, or organophosphophorus;

Ring 1 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl;

Ring 2 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl;

G^{2A} is a bond or -(C=O);

G^{2B} is a bond or -(C=O);

N is NH;

J is $CR^{J1}R^{J2}$, where R^{J1} and R^{J2} are independently selected from H, F, Cl, alkyl, or wherein R^{J1} and R^{J2} can be taken together to form a ring;

D is nitrogen or carbon;

x is 0, 1, or 2;

y is 0, 1, or 2;

z is 0 or 1; and

G^1 is a group configured to extend into a pocket of KIF18 located between an α6-helix and a β-sheet of KIF18a and to interact with at least one hydrophobic side chain of Ala352 in the α6-helix, Met328 in the β-sheet, or Tyr112 in the β-sheet.

[000129] In some embodiments of a compound of Formula (IV-A), G^1 is further configured to hydrogen bond with Asn293 in an α4-helix of KIF18A.

[000130] In some embodiments of a compound of Formula (IV-A), G^1 is further configured to interact with at least one hydrophobic side chain of Leu110, Leu259, and Met328 in the β-sheet of KIF18A.

[000131] In some embodiments of a compound of Formula (IV-A),

G^1 is -K-(r)-M-(p)-Q-;

K is -O- or $CR^{K1}R^{K2}$;

R^{K1} and R^{K2} are independently hydrogen, halogen, F, Cl, or C_1-C_6 alkyl; or R^{K1} and R^{K2} are combined to form a C_3-C_5 cycloalkyl or 3- to 5- membered heterocycle ring;

r is 0, 1, or 2;

M is $CR^{M3}R^{M4}$;

R^{M3} and R^{M4} are independently hydrogen or C_1-C_6 alkylene optionally substituted with halogen or oxo;

p is 0, 1, or 2

Q is -O-, -NR^5-, -SO_2-, -SO_2NR^5- or -NR^5SO_2-;

R^5 is hydrogen, -SO_2R^6, or C_1-C_6 alkylene optionally substituted with halogen or oxo; and

R^6 is hydrogen or C_1-C_6 alkyl.

[000132] In some embodiments of a compound of Formula (IV-A), G^1 is further configured to hydrogen bond with Asn293 in an α4-helix of KIF18A;

wherein G^1 is represented by the formula -K-(r)-M-(p)-Q-;

K is -O- or $CR^{K1}R^{K2}$;

R^{K1} and R^{K2} are independently hydrogen, halogen (F), or C_1-C_6 alkyl; or R^{K1} and R^{K2} are combined to form a ring;

r is 0, 1, or 2;

M is $CR^{M3}R^{M4}$;

R^3 and R^4 are independently hydrogen or C_1-C_6 alkylene optionally substituted with halogen or oxo;

p is 0, 1, or 2; and

Q is -O-, -NH-, -$NHSO_2$-, or -SO_2NH-.

[000133] In some embodiments of a compound of Formula (IV-A), G^1 is further configured to interact with at least one hydrophobic side chain of Leu110, Leu259, and Met328 in the β-sheet of KIF18A;

wherein G^1 is -K-(r)-M-(p)-Q-;

K is $CR^{K1}R^{K2}$;

R^{K1} and R^{K2} are independently halogen, or C_1-C_6 alkylene; or R^{K1} and R^{K2} are combined to form a ring;

r is 0, 1, or 2;

M is $CR^{M3}R^{M4}$;

R^{M3} and R^{M4} are independently hydrogen or C_1-C_6 alkylene optionally substituted with halogen or oxo;

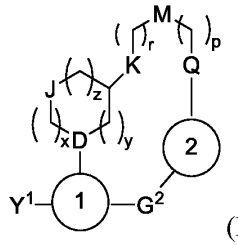
p is 0, 1, or 2

Q is -O-, -NR^5-, -SO_2-, -SO_2NR^5- or -NR^5SO_2-;

R^5 is hydrogen or C_1-C_6 alkyl optionally substituted with halogen or oxo.

[000134] In some embodiments of a compound of Formula (IV-A), G^{2A} is not equal to G^{2B}.

[000135] In some embodiments, a compound provided herein has the structure of Formula (IV-B), or a pharmaceutically acceptable salt or solvate thereof:



(IV-B)

wherein:

Y^1 is a halogen, cyanide, alcohol, amide, sulfonamide, sulfoxide, ether, cyclic amine, alkyl amine, heteroaryl, saturated heterocycle, organoboranes, or organophosphophorus;

Ring 1 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl;

Ring 2 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl;

D is nitrogen or carbon;

J is $CR^{J1}R^{J2}$, where R^{J1} and R^{J2} are independently selected from H, F, Cl, alkyl, or wherein R^{J1} and R^{J2} can be taken together to form a ring;

K is O or $CR^{K1}R^{K2}$;

R^{K1} and R^{K2} are independently hydrogen, halogen (F), or C_1-C_6 alkyl; or R^{K1} and R^{K2} are combined to form a C_3-C_5 cycloalkyl or 3- to 5- membered heterocycle ring;

x is 0, 1, or 2;

y is 0, 1, or 2;

z is 0 or 1;

M is $CR^{M3}R^{M4}$;

R^{M3} and R^{M4} are independently hydrogen or C_1-C_6 alkyl optionally substituted with halogen (fluorine);

Q is -O-, $-NR^5$-, $-SO_2$-, $-SO_2NR^5$- or $-NR^5SO_2$-;

R^5 is hydrogen, $-SO_2R^6$, or C_1-C_6 alkylene optionally substituted with halogen or oxo; and

R^6 is hydrogen or C_1-C_6 alkyl;

r is 0, 1, or 2;

p is 0, 1, or 2; and

G^2 is a group configured to provide a linkage with Ar/HetAr ring 1 and Ar/HetAr ring 2.

[000136] In some embodiments of a compound of Formula (IV-B), G^2 is further configured to provide a rigid and quasi-planar linkage with Ar/HetAr ring 1 and Ar/HetAr ring 2 to position the Ar/HetAr ring 1 and Ar/HetAr ring 2 in approximately the same plane and allow delocalization of electrons across the entire conjugated system.

[000137] In some embodiments of a compound of Formula (IV-B), G^2 is represented by the formula $-G^{2A}-N-G^{2B}$;

N is NH;

G^{2A} and G^{2B} are independently a bond or -(C=O)-, provided that G^{2A} and G^{2B} are not both -(C=O);

Optionally, N may be taken together with D to form a 5 or 6 membered ring.

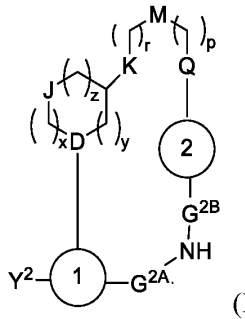
[000138] In some embodiments of a compound of Formula (IV-B), G^2 is further configured to provide a rigid and quasi-planar linkage with Ar/HetAr ring 1 and Ar/HetAr ring 2 to position the Ar/HetAr ring 1 and Ar/HetAr ring 2 in approximately the same plane and allow delocalization of electrons across the entire conjugated system;

wherein G^2 is represented by the formula -A-N-B-;

N is NH or N may be taken together with D to form a 5 or 6 membered ring;

A and B are independently a bond or -(C=O), provided that A and B are not both -(C=O).

[000139] In some embodiments, a compound provided herein has the structure of Formula (IV-C), or a pharmaceutically acceptable salt or solvate thereof:



(IV-C)

wherein:

Ring 1 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl;

Ring 2 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl;

D is nitrogen or carbon;

J is $CR^{J1}R^{J2}$, where R^{J1} and R^{J2} are independently selected from H, F, alkyl, or wherein R^{J1} and R^{J2} can be taken together to form a ring;

K is O or $CR^{K1}R^{K2}$;

R^{K1} and R^{K2} are independently hydrogen, halogen (F), or C_1-C_6 alkyl; or R^1 and R^2 are combined to form a ring;

x is 0, 1, or 2;

y is 0, 1, or 2;

z is 0 or 1;

M is $CR^{M3}R^{M4}$;

R^{M3} and R^{M4} are independently hydrogen or C_1-C_6 alkyl optionally substituted with halogen (fluorine);

Q is -O-, $-NR^5$-, $-SO_2$-, $-SO_2NR^5$- or $-NR^5SO_2$-;

R^5 is hydrogen, $-SO_2R^6$, or C_1-C_6 alkylene optionally substituted with halogen or oxo; and

R^6 is hydrogen or C_1-C_6 alkyl;

r is 0, 1, or 2;

p is 0, 1, or 2;

G^{2A} is a bond or -(C=O)-;

G^{2B} is a bond or -(C=O)-; and

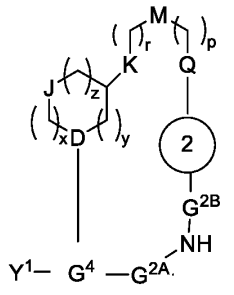
Y^2 is a group configured to form one or more hydrogen bonds with one or more of: a back bone of KIF18A, a side chain of Ser262 of KIF18a, or a residue of α-tubulin.

[000140] In some embodiments of a compound of Formula (IV-C), G^{2A} is not equal to G^{2B}.

[000141] In some embodiments of a compound of Formula (IV-C),

Y^2 is an amide, sulfonamide, ether, cyclic amine, alkyl amine, aromatic heterocycle, or saturated heterocycle.

[000142] In some embodiments, a compound provided herein has the structure of Formula (IV-D), or a pharmaceutically acceptable salt or solvate thereof:



(IV-D)

wherein:

Y^1 is a halogen, cyanide, alcohol, amide, sulfonamide, sulfoxide, ether, cyclic amine, alkyl amine, heteroaryl, saturated heterocycle, organoboranes, or organophosphophorus;

Ring 2 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl;

D is nitrogen or carbon;

J is $CR^{J1}R^{J2}$, where R^{J1} and R^{J2} are independently selected from H, F, alkyl, or wherein R^{J1} and R^{J2} can be taken together to form a ring;

K is O or $CR^{K1}R^{K2}$;

R^{K1} and R^{K2} are independently hydrogen, halogen (F), or C_1-C_6 alkyl; or

R^{K1} and R^{K2} are combined to form a ring;

x is 0, 1, or 2;

y is 0, 1, or 2;

z is 0 or 1; and

M is $CR^{M3}R^{M4}$;

R^{M3} and R^{M4} are independently hydrogen or C_1-C_6 alkyl optionally substituted with halogen (fluorine);

Q is -O-, $-NR^5$-, $-SO_2$-, $-SO_2NR^5$- or $-NR^5SO_2$-;

R^5 is hydrogen, $-SO_2R^6$, or C_1-C_6 alkylene optionally substituted with halogen or oxo; and

R^6 is hydrogen or C_1-C_6 alkyl;

r is 0, 1, or 2;

p is 0, 1, or 2;

G^{2A} is a bond or -(C=O)-;

G^{2B} is a bond or -(C=O)-; and

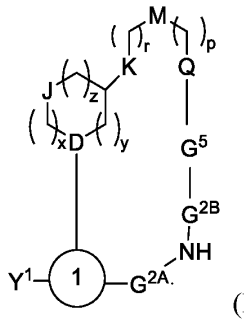
G^4 is a group configured to extend between side chains of Leu285 of KIF18A α4-helix and Tyr348 of a KIF18A α6-helix.

[000143] In some embodiments of a compound of Formula (IV-D), G^{2A} is not equal to G^{2B}.

[000144] In some embodiments of a compound of Formula (IV-D), G^4 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl and forms a cyclic conjugated π system.

[000145] In some embodiments of a compound of Formula (IV-D), G4 is further configured to hydrogen bond with KIF18A or to engage in water-mediated interactions with KIF18A or α-tubulin; and more particularly, may be an optionally substituted optionally substituted 5 to 12 membered heteroaryl and form a cyclic conjugated π system.

[000146] In some embodiments, a compound provided herein has the structure of Formula (IV-E), or a pharmaceutically acceptable salt or solvate thereof:



(IV-E)

wherein:

Y^1 is an halogen, cyanide, alcohol, amide, sulfonamide, sulfoxide, ether, cyclic amine, alkyl amine, heteroaryl, saturated heterocycle, organoboranes, or organophosphophorus;

Ring 1 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl;

D is nitrogen or carbon;

J is $CR^{J1}R^{J2}$, where R^{J1} and R^{J2} are independently selected from H, F, alkyl, or wherein R^{J1} and R^{J2} can be taken together to form a ring;

K is O or $CR^{K1}R^{K2}$;

R^{K1} and R^{K2} are independently hydrogen, halogen (F), or C_1-C_6 alkyl; or R^{K1} and R^{K2} are combined to form a ring;

x is 0, 1, or 2;

y is 0, 1, or 2;

z is 0 or 1;

M is $CR^{M3}R^{M4}$;

R^{M3} and R^{M4} are independently hydrogen or C_1-C_6 alkyl optionally substituted with halogen or oxo;

Q is -O-, $-NR^5$-, $-SO_2$-, $-SO_2NR^5$- or $-NR^5SO_2$-;

R^5 is hydrogen, $-SO_2R^6$, or C_1-C_6 alkylene optionally substituted with halogen or oxo; and

R^6 is hydrogen or C_1-C_6 alkyl;

r is 0, 1, or 2;

p is 0, 1, or 2;

G^{2A} is a bond or -(C=O)-;

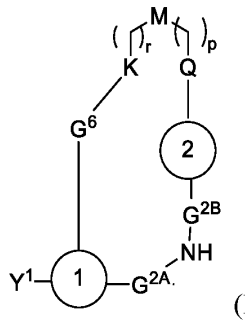
G^{2B} is a bond or -(C=O)-; and

G^5 is a group configured to pack against a flat surface on a KIF18A α4-helix formed by Gly289 and to interact with a side chain of Asn293 in the KIF18A α4-helix, and optionally, to hydrogen bond with the side chain of Asn293.

[000147] In some embodiments of a compound of Formula (IV-E), G^{2A} is not equal to G^{2B}.

[000148] In some embodiments of a compound of Formula (IV-E), G^5 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl.

[000149] In some embodiments, a compound provided herein has the structure of Formula (IV-F), or a pharmaceutically acceptable salt or solvate thereof:



(IV-F)

wherein:

Y^1 is a halogen, cyanide, alcohol, amide, sulfonamide, sulfoxide, ether, cyclic amine, alkyl amine, heteroaryl, saturated heterocycle, organoboranes, or organophosphophorus;

Ring 1 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl;

Ring 2 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl;

M is $CR^{M3}R^{M4}$;

R^3 and R^4 are independently hydrogen or C_1-C_6 alkyl optionally substituted with halogen (fluorine);

Q is -O-, $-NR^5$-, $-SO_2$-, $-SO_2NR^5$- or $-NR^5SO_2$-;

R^5 is hydrogen, $-SO_2R^6$, or C_1-C_6 alkylene optionally substituted with halogen or oxo; and

R^6 is hydrogen or C_1-C_6 alkyl;

r is 0, 1, or 2;

p is 0, 1, or 2;

G^{2A} is a bond or -(C=O)-;

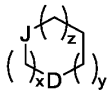
G^{2B} is a bond or -(C=O); and

G^6 is a group configured to interact with hydrophobic side chains of Tyr112, Leu285, and Leu 288 in a KIF18A α4-helix and a hydrophobic side chain of Tyr348 in a KIF18a α6-helix.

[000150] In some embodiments of a compound of Formula (IV-F), G^{2A} is not equal to G^{2B}.

[000151] In some embodiments of a compound of Formula (IV-F), G^6 is further configured to interact with hydrophobic side chains of Leu110, Leu259, and Met328 in a KIF18A β-sheet.

[000152] In some embodiments of a compound of Formula (IV-F), G^6 is represented by the formula:



wherein

D is nitrogen or carbon;

J is $CR^{J1}R^{J2}$, where R^{J1} and R^{J2} are independently selected from H, F, alkyl, or

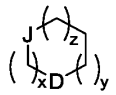
wherein R^{J1} and R^{J2} can be taken together to form a ring;

x is 0, 1, or 2;

y is 0, 1, or 2; and

z is 0 or 1.

[000153] In some embodiments of a compound of Formula (IV-F), G^6 is further configured to interact with hydrophobic side chains of Leu110, Leu259, and Met328 in a KIF18A β-sheet; wherein G^6 is represented by the formula:



wherein

D is nitrogen or carbon;

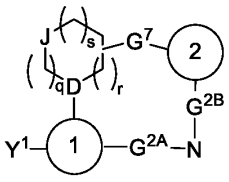
J is $CR^{J1}R^{J2}$, where R^{J1} and R^{J2} are independently selected from hydrogen, F, or alkyl, or R^{J1} and R^{J2} with the carbon atom it is attached form a C_3-C_5 cycloalkyl, or a 3- to -5-membered heterocycle.

x is 0, 1, or 2;

y is 0, 1, or 2; and

z is 0 or 1.

[000154] In some embodiments, a compound provided herein has the structure of Formula (IV-G) or a pharmaceutically acceptable salt or solvate, thereof:



(IV-G),

wherein

Y^1 is an halogen, cyanide, alcohol, amide, sulfonamide, sulfoxide, ether, cyclic amine, alkyl amine, heteroaryl, saturated heterocycle, organoboranes, or organophosphophorus;

Ring 1 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl;

Ring 2 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl;

A is a bond or -(C=O);

B is a bond or -(C=O);

N is NH;

J is $CR^{J1}R^{J2}$, where R^{J1} and R^{J2} are independently selected from H, F, Cl, alkyl, or wherein R^{J1} and R^{J2} can be taken together to form a ring;

D is nitrogen or carbon;

x is 0, 1, or 2;

y is 0, 1, or 2;

z is 0 or 1; and

G^7 represents a means, between ring 2 and ring 3, for extending into a pocket between an α6-helix and a β-sheet of KIF18a and interacting with at least one hydrophobic side chain of Ala352 in the α6-helix, Met328 in the β-sheet, and Tyr112 in the β-sheet.

[000155] In some embodiments of a compound of Formula (IV-G), the means comprises a group having the formula -K-(r)-M-(p)-Q-;

K is O or $CR^{K1}R^{K2}$;

R^{K1} and R^{K2} are independently hydrogen, halogen (F), or C_1-C_6 alkyl; or R^{K1} and R^{K2} are combined to form a ring;

r is 0, 1, or 2;

M is $CR^{M3}R^{M4}$;

R^{M3} and R^{M4} are independently hydrogen or C_1-C_6 alkyl optionally substituted with halogen (fluorine);

p is 0, 1, or 2; and

Q is -O-, $-NR^5$-, $-SO_2$-, $-SO_2NR^5$- or $-NR^5SO_2$-; ;

R^5 is hydrogen or C_1-C_6 alkyl optionally substituted with halogen (fluorine);

R^6 is hydrogen or optionally substituted alkyl.

Optionally, Q is -O-, or -NH2-; R^5 is hydrogen; R^6 is hydrogen.

Optionally, K is $CR^{K1}R^{K2}$; R^{K1} and R^{K2} are independently halogen (F) or C_1-C_6 alkyl; or R^{K1} and R^{K2} are combined to form a ring.

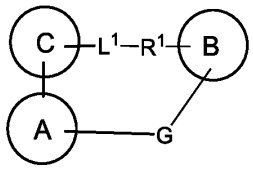
Adducts

[000156] The compounds described herein, for example, the compounds described in the "Compound" section above can be useful for forming an adduct with a KIF18A enzyme. The formation of an adduct between the compounds described herein and KIF18A can be useful for treating cancer. In some embodiments, the formation of the adduct inhibits the KIF18A protein, thereby treating cancer.

[000157] An adduct can comprise a KIFA18A protein and a compound of any Formula described herein.

[000158] Provided in some embodiments herein is an adduct comprising a KIF18A and a compound of Formula (B) as described herein. The compounds of Formula (B) can be any suitable compound described herein, for example the compounds described in the "Compound" section above.

[000159] Provided in some embodiments herein is an adduct comprising a KIF18A and a compound of Formula (B), wherein the structure of Formula (B) is:



(B)

wherein:

ring A is optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12- membered heteroaryl;

ring B is optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12- membered heteroaryl;

ring C is optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 5- to 12 membered heterocyclyl, optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12- membered heteroaryl;

G is -(C=O)-NH- or -NH-(C=O)-;

L^1 is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond, -O-, -NL^{1a1}-, -S-, or -SO_2-;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene;

R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-Q-, -NR^{1a}-CO-, -CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a};

R^{1a} is hydrogen, -C(=O)H, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl; and

Q is optionally substituted C_1-C_6alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene.

[000160] The compounds described herein have structures which are useful for interacting with KIF18A to bind with it and form an adduct. For example, in non-limiting Formula (B), ring A can be sandwiched between the side chains of the KIF18A in the α4-helix and α6-helix location of the KIF18A. Aromatic rings which have a planar structure are useful for sandwiching between the α4-helix and α6-helix. Ring A can also be substituted with a diverse range of polar groups that can form hydrogen bonds that an interact with KIF18A. The linker G between ring A and ring B may be useful for keeping rings A and B in the same plane due

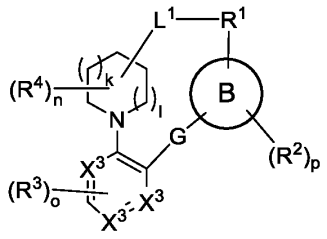
to the carbonyl group allowing for delocalization of the aromatic rings. Ring B can interact against the flat surface of KIF18A α4-helix, and can also be useful for forming hydrogen bonds. Ring C can interact with hydrophobic KIF18 residues as a saturated cycloalkyl ring or a heterocycloalkyl ring. For example, ring C can interact with the hydrophobic residues within the α4-helix and α6-helix region of KIF18A. Additionally, if ring C is substituted with halogens, alkyls, or cycloalkyls, it can contact with a deeper layer of the hydrophobic side chains of the KIF18A β-sheet. The L^1-R^1 tether can be useful for interacting with the hydrophobic side chains of the KIF18A β-sheet region. Additionally, the L^1-R^1 tether can interact with KIF18A via hydrogen bonding in the α4-helix region. The L^1-R^1 tether region can weave through the α6-helix and β-sheet region of KIF18A and interact with the sidechains.

[000161] Ring A can be any suitable functional group described herein. In some embodiments, ring A is optionally substituted C_6-C_{12} aryl. In some embodiments, ring A is optionally substituted phenyl.

[000162] Ring B can be any suitable functional group described herein. In some embodiments, ring B is a 5- to 12- membered heteroaryl or C_6-C_{12} aryl. In some embodiments, ring B is a 5- to 12- membered heteroaryl or phenyl. In some embodiments, ring B is a 5- to 8-membered heteroaryl or phenyl. In some embodiments, ring B is a 5- or 6- membered heteroaryl or phenyl. In some embodiments, ring B is a phenyl. In some embodiments, ring B is a 5-membered heteroaryl. In some embodiments, ring B is a 6- membered heteroaryl. In some embodiments, ring B is triazine, pyridine, pyrimidine, pyridazine, pyrazinone, or pyrazine. In some embodiments, ring B is pyridine, pyrimidine, pyridazine, or pyrazine. In some embodiments, ring B is pyridine or pyrimidine. In some embodiments, ring B is pyridine. In some embodiments, ring B is pyrimidine.

[000163] Ring C can be any suitable functional group described herein. In some embodiments, ring C is optionally substituted C_3-C_{10} cycloalkyl or optionally substituted 5- to 12 membered heterocyclyl. In some embodiments, ring C is optionally substituted 5- to 12 membered heterocyclyl. In some embodiments, ring C is optionally substituted 5- to 8-membered heterocyclyl. In some embodiments, ring C is optionally substituted 5- to 6-membered heterocyclyl. In some embodiments, ring C is optionally substituted piperidinyl.

[000164] In some embodiments, the adduct comprises the compound of Formula (B) which has the structure of Formula (I-0):



(I-0)

wherein:

each X^3 is independently CH or N;

ring B is a 5- or 6- membered heteroaryl or phenyl;

L^1 is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond, -O-, -NL^{1a1}-, -S-, or -SO_2-;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene;

G is -(C=O)-NH- or -NH-(C=O)-;

R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-Q-, -NR^{1a}-CO-, -CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a};

R^{1a} is hydrogen, -C(=O)H, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

R^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

Q is optionally substituted C_1-C_6alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene;

each R^2 is independently halogen, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl, or two R^2 are taken together to form an oxo, an optionally substituted C_3-C_8 cycloalkyl, an optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl;

each R^{2a} is independently hydrogen or optionally substituted C_1-C_6 alkyl;

each R^3 is independently halogen, -CN, -$(CH_2)_m$-$N(R^{3a})_2$-, -OR^{3a}, -$N(R^{3a})_2$, -$N(SO_2R^{3b})R^{3a}$, -SR^{3a}, -SO_2R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-R^{3a}, -NH-S(O)(NH)-R^{3a}, -NH-S(O)(NH)-$(CH_2)_m$-R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-OR^{3b}, -NH-S(O)R^{3a}-$(CH_2)_m$-OR^{3b}, -NH-$S(O)_2$-R^{3c}, -$B(R^{3a})_3$, -$P(R^{3a})_3$, optionally substituted C_3-C_8

cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl;

each R^{3a} is independently hydrogen, -C(O)OR^{3b}, optionally substituted C_1-C_6 alkyl, or -N(R^{3b})$_2$;

R^{3b} is hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_2-C_6 alkenyl;

R^{3c} is C_3-C_8 cycloalkyl or 3- to 8- membered heterocycle;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, two or more R^4 combine to form a C_3-C_8 cycloalkyl, or two R^4 combine to form a C_1-C_3 alkylene bridge;

k is 0 to 2;

l is 0 to 2 ;

m is 1 to 6;

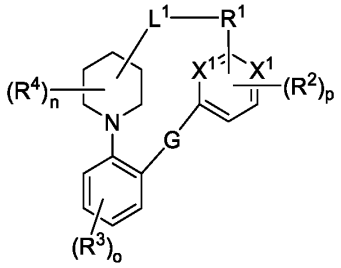
n is 0 to 9;

o is 1 to 4;

p is 0 to 4; and

wherein when any one of variable G, L^1, R^1, R^2, R^3, or R^4 are present, the bond to variable G, L^1, R^1, R^2, R^3 or R^4 replaces a hydrogen on a carbon or nitrogen atom.

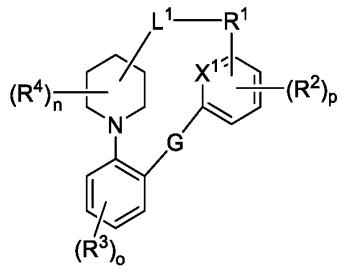
[000165] In some embodiments, the adduct comprises the compound of Formula (B) which has the structure of Formula (I-0a):



(I-0a)

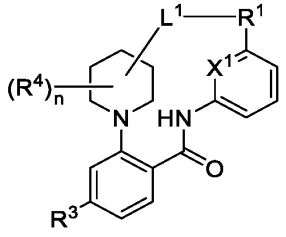
wherein: each X^1 is independently CH or N.

[000166] In some embodiments, the adduct comprises the compound of Formula (B) which has the structure of Formula (I):



(I).

[000167] In some embodiments, the adduct comprises the compound of Formula (B) which has the structure of Formula (II):



(II)

wherein:

X^1 is CH or N;

$L^1$is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond, -O-, or -NL^{1a1}-;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

L^{1b} is optionally substituted C_1-C_8 alkylene;

R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-C_1-C_6alkylene-, -NR^{1a}-CO-,-CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a};

R^{1a} is hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

R^3 is halogen, -CN, -OR^{3a}, -$N(R^{3a})_2$, -SO_2R^{3a}, or -NH-$S(O)_2$-$(CH_2)_m$-OR^{3b},

each R^{3a} is independently hydrogen or C_1-C_6 alkyl;

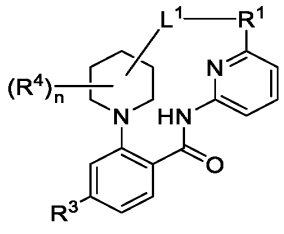
R^{3b} is hydrogen or C_1-C_6 alkyl;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, two or more R^4 combine to form a C_3-C_8 cycloalkyl, or two R^4 combine to form a C_1-C_3 alkylene bridge;

m is 1 to 3; and

n is 1 or 2.

[000168] In some embodiments, the adduct comprises the compound of Formula (B) which has the structure of Formula (III-A):



(III-A)

wherein:

$L^1$is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond or -O-;

L^{1b} is optionally substituted C_1-C_8 alkylene;

R^1 is a bond, -O-, -NR^{1a}-, or -NR^{1a}-C_1-C_3 alkylene-;

R^{1a} is hydrogen, -C(=O)H, optionally substituted C_1-C_6 alkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl;

R^3 is halogen, -NH-$S(O)_2$-$(CH_2)_m$-R^{3a}, or -NH-$S(O)_2$-$(CH_2)_m$-OR^{3b},

R^{3a} is C_1-C_6 alkyl;

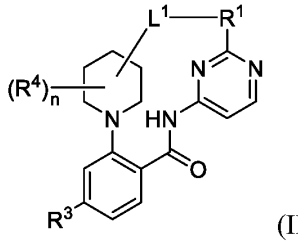
R^{3b} is hydrogen or C_1-C_6 alkyl;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, or two or more R^4 combine to form a C_3-C_8 cycloalkyl;

m is 1 to 3; and

n is 0 to 2.

[000169] In some embodiments, the adduct comprises the compound of Formula (B) which has the structure of Formula (III-B):



(III-B)

wherein:

$L^1$is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond or -O-;

L^{1b} is optionally substituted C_1-C_8 alkylene;

R^1 is a bond, -O-, -NR^{1a}-, or -NR^{1a}-C_1-C_3 alkylene-

R^{1a} is hydrogen, -C(=O)H, optionally substituted C_1-C_6 alkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl;

R^3 is halogen, -NH-$S(O)_2$-$(CH_2)_m$-R^{3a}, or -NH-$S(O)_2$-$(CH_2)_m$-OR^{3b},

R^{3a} is C_1-C_6 alkyl;

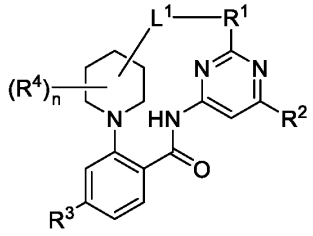
R^{3b} is hydrogen or C_1-C_6 alkyl;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, or two or more R^4 combine to form a C_3-C_8 cycloalkyl;

m is 1 to 3; and

n is 0 to 2.

[000170] In some embodiments, the adduct comprises the compound of Formula (B) which has the structure of Formula (III-C):



(III-C)

wherein:

L^1 is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond, -O-, or -NL^{1a1}-;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

L^{1b} is optionally substituted C_1-C_8 alkylene;

R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-C_1-C_6alkylene-, -NR^{1a}-CO-,-CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a};

R^{1a} is hydrogen, -C(=O)H, C_1-C_6 alkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl;

R^2 is halogen, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl;

each R^{2a} is independently hydrogen or C_1-C_6 alkyl;

R^3 is halogen, -CN, -OR^{3a}, -$N(R^{3a})_2$, -SO_2R^{3a}, or -NH-$S(O)_2$-$(CH_2)_m$-OR^{3b},

R^{3a} is hydrogen or C_1-C_6 alkyl;

R^{3b} is hydrogen or C_1-C_6 alkyl;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, or two or more R^4 combine to form a C_3-C_8 cycloalkyl;

m is 1 to 3; and

n is 0, 1, or 2.

[000171] In some embodiments, R^2 is any suitable functional group described herein.

[000172] In some embodiments, each R^2 is independently halogen, -CN, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl, or two R^2 are taken together to form an oxo, an optionally substituted C_3-C_8 cycloalkyl, an optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl. In some embodiments, R^2 is halogen, -CN, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl. In some embodiments, R^2 is halogen, -CN, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl. In some embodiments, R^2 is halogen, -CN, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl. In some embodiments, R^2 is halogen, -CN, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl. In some embodiments, R^2 is halogen, -CN, -OR^{2a}, -$N(R^{2a})_2$, or -$S(O)_2N(R^{2a})_2$. In some embodiments, R^2 is -$S(O)_2N(R^{2a})_2$ or -SO_2-C_1-C_6 alkyl. In some embodiments, R^2 is -$S(O)_2N(R^{2a})_2$.

[000173] In some embodiments, R^2 is halogen, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl. In some embodiments, R^2 is halogen, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl. In some embodiments, R^2 is halogen, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl. In some embodiments, R^2 is halogen, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl. In some embodiments, R^2 is halogen, -OR^{2a}, -$N(R^{2a})_2$, or -$S(O)_2N(R^{2a})_2$. In some embodiments, R^2 is -$S(O)_2N(R^{2a})_2$ or -SO_2-C_1-C_6 alkyl. In some embodiments, R^2 is -$S(O)_2N(R^{2a})_2$.

[000174] In some embodiments, each R^{2a} is any suitable functional group described herein. In some embodiments, each R^{2a} is independently hydrogen or optionally substituted C_1-C_6 alkyl. In some embodiments, each R^{2a} is independently optionally substituted C_1-C_4 alkyl. In some embodiments, each R^{2a} is independently methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, or tert-butyl. In some embodiments, each R^{2a} is methyl. In some embodiments, one R^{2a} is hydrogen and the other R^{2a} is optionally substituted C_1-C_6 alkyl. In some

embodiments, R^2 is $-S(O)_2N(R^{2a})_2$ and each R^{2a} is hydrogen. In some embodiments, R^2 is $-S(O)_2N(R^{2a})_2$ and each R^{2a} is independently optionally substituted C_1-C_6 alkyl. In some embodiments, R^2 is $-S(O)_2N(R^{2a})_2$ and each R^{2a} is methyl. In some embodiments, R^2 is $S(O)_2NHC(CH_3)_3$.

[000175] In some embodiments, R^2 is a 5- to 8- membered heteroaryl. In some embodiments, R^2 is a 5- to 6- membered heteroaryl. In some embodiments, R^2 is a 5- membered heteroaryl. In some embodiments, R^2 is a 6- membered heteroaryl. In some embodiments, R^2 is a furanyl, furanonyl, isothiazolyl, imidazolyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl. In some embodiments, R^2 is a pyrazolyl.

[000176] In some embodiments, L^1 can be any suitable linker structure in any combination of variables L^{1a} and L^{1b} described herein. In some embodiments, L^1 is a linker comprising the structure $-L^{1a}-L^{1b}-$.

[000177] In some embodiments, L^{1a} can be any suitable functional group described herein. In some embodiments, L^{1a} is a bond, -O-, $-NL^{1a1}-$, -S-, or $-SO_2-$. In some embodiments, L^{1a} is a bond, -O-, or $-NL^{1a1}-$. In some embodiments, L^{1a} is a bond or -O-. In some embodiments, L^{1a} is a bond. In some embodiments, L^{1a} is -O-. In some embodiments, L^{1a} is $-NL^{1a1}-$. In some embodiments, L^{1a} is -S-. In some embodiments, L^{1a} is $-SO_2-$.

[000178] In some embodiments, L^{1a1} is any suitable functional group described herein. In some embodiments, L^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or $-SO_2-C_1$-C_6 alkyl. In some embodiments, L^{1a1} is hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or $-SO_2-C_1$-C_6 alkyl. In some embodiments, L^{1a1} is hydrogen, C_1-C_6 alkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl. In some embodiments, L^{1a1} is hydrogen or C_1-C_6 alkyl. In some embodiments, L^{1a1} is hydrogen. In some embodiments, L^{1a1} is C_1-C_6 alkyl. In some embodiments, L^{1a1} is methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, or tert-butyl. In some embodiments, L^{1a1} is methyl.

[000179] In some embodiments, L^{1a} is $-NL^{1a1}-$ and L^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or $-SO_2-C_1$-C_6 alkyl. In some embodiments, L^{1a} is $-NL^{1a1}-$ and L^{1a1} is hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or $-SO_2-C_1$-C_6 alkyl. In some embodiments, L^{1a} is $-NL^{1a1}-$ and L^{1a1} is hydrogen or C_1-C_6 alkyl. In some embodiments, L^{1a} is $-NL^{1a1}-$ and L^{1a1} is hydrogen. In some embodiments, L^{1a} is $-NL^{1a1}-$ and L^{1a1} is C_1-C_6 alkyl. In some embodiments, L^{1a} is $-NL^{1a1}-$ and L^{1a1} is methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, or tert-butyl. In some embodiments, L^{1a} is $-NL^{1a1}-$ and L^{1a1} is methyl.

[000180] In some embodiments, L^{1b} is any suitable functional group described herein. In some embodiments, L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene. In some embodiments, L^{1b} is optionally substituted C_1-C_6 alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene. In some embodiments, L^{1b} is optionally substituted C_1-C_6 alkylene. In some embodiments, L^{1b} is optionally substituted C_1-C_4 alkylene. L^{1b} can be substituted with any suitable substituent described herein. In some embodiments, L^{1b} is C_1-C_4 alkylene substituted with oxo, C_3-C_6 cycloalkyl, or 3- to 6- membered heterocyclyl. In some embodiments, L^{1b} is C_1-C_4 alkylene substituted with oxo or C_3-C_6 cycloalkyl. In some embodiments, L^{1b} is C_1-C_4 alkylene substituted with oxo, cyclopropyl, or cyclobutyl. In some embodiments, L^{1b} is C_1-C_4 alkylene substituted with oxo. In some embodiments, L^{1b} is C_1-C_4 alkylene substituted with cyclopropyl. In some embodiments, L^{1b} is methylene, ethylene, propylene, butylene, or pentylene. In some embodiments, L^{1b} is methylene. In some embodiments, L^{1b} is ethylene. In some embodiments, L^{1b} is propylene. In some embodiments, L^{1b} is butylene. In some embodiments, L^{1b} is pentylene.

[000181] In some embodiments, L^{1a} is a bond, -O-, or -NL^{1a1}- and L^{1b} is optionally substituted C_1-C_6 alkylene. In some embodiments, L^{1a} is a bond and L^{1b} is optionally substituted C_1-C_6 alkylene. In some embodiments, L^{1a} is -O- and L^{1b} is optionally substituted C_1-C_6 alkylene. In some embodiments, L^{1a} is -NL^{1a1}-, L^{1a1} is hydrogen or C_1-C_6 alkyl, and L^{1b} is optionally substituted C_1-C_6 alkylene.

[000182] In some embodiments, L^1 is -O(optionally substituted alkylene)-, -(optionally substituted alkylene)O-, or optionally substituted alkylene. In some embodiments, L^1 is -O(unsubstituted alkylene)-, -(unsubstituted alkylene)O-, unsubstituted alkylene, or substituted alkylene. In some embodiments, L^1 is -O(unsubstituted alkylene)-. In some embodiments, L^1 is -(unsubstituted alkylene)O-. In some embodiments, L^1 is unsubstituted alkylene. In some embodiments, L^1 is substituted alkylene.

[000183] In some embodiments, L^1 is $–(CH_2)_4–$, $–(CH_2)_3–$, $–(CH_2)_2–$, $–CH_2–$ –cyclopropyl-$(CH_2)_3–$, –cyclopropyl-$(CH_2)_2–$, $–O(CH_2)_3–$, $–O(CH_2)_2–$, or $–O(CH_2)–$. In some embodiments, L^1 is $–(CH_2)_4–$, –cyclopropyl-$(CH_2)_3–$, $–(CH_2)_3–$, $–(CH_2)_2CO–$, $–(CH_2)_2–$, $–O(CH_2)_2–$, or $–CH_2–$.

[000184] In some embodiments, R^1 is any suitable functional group described herein. In some embodiments, R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-Q-, -NR^{1a}-CO-, -CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a}. In some embodiments, R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-C_1-C_6alkylene-, -NR^{1a}-CO-,-CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a}. In some embodiments, R^1 is a

bond, -O-, -NR^{1a}-, -NR^{1a}-Q-, -NR^{1a}-CO-, -CO-NR^{1a}-, -NR^{1a}-SO_2-, or -SO_2-NR^{1a}. In some embodiments, R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-C_1-C_6alkylene-, -NR^{1a}-CO-, -CO-NR^{1a}-, -NR^{1a}-SO_2-, or -SO_2-NR^{1a}. In some embodiments, R^1 is a bond. In some embodiments, R^1 is -O-. In some embodiments, R^1 is -NR^{1a}-Q-. In some embodiments, R^1 is -O-. In some embodiments, R^1 is -NR^{1a}-. In some embodiments, R^1 is -NR^{1a}-CO-. In some embodiments, R^1 is -CO-NR^{1a}-. In some embodiments, R^1 is -NR^{1a}-SO_2-. In some embodiments, R^1 is -SO_2-NR^{1a}.

[000185] In some embodiments, R^{1a} is hydrogen, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, R^{1a} is hydrogen, C_1-C_6 alkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl. In some embodiments, R^{1a} is hydrogen, C_1-C_3 alkyl, C_1-C_3 alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, $R^{1a}$is hydrogen. In some embodiments, $R^{1a}$is optionally substituted C_1-C_6 alkyl. In some embodiments, R^{1a} is methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, or tert-butyl. In some embodiments, R^{1a} is methyl. In some embodiments, R^{1a} is substituted C_1-C_6 alkyl. In some embodiments, R^{1a} is C_1-C_6alkylene-C_3-C_6 cycloalkyl. In some embodiments, R^{1a} is methylene-C_3-C_6 cycloalkyl. In some embodiments, R^{1a} is methylene-cyclopropyl. In some embodiments, R^{1a} is -SO_2-C_1-C_6 alkyl. In some embodiments, R^{1a} is -SO_2-Me.

[000186] In some embodiments, R^1 is -NR^{1a}-Q- and R^{1a} is hydrogen, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, R^1 is a -NR^{1a}-Q- and R^{1a} is hydrogen. In some embodiments, R^1 is -NR^{1a}-Q- and R^{1a} is optionally substituted C_1-C_6 alkyl. In some embodiments, R^1 is -NR^{1a}-Q- and R^{1a} is C_1-C_6alkylene-C_3-C_6 cycloalkyl. In some embodiments, R^1 is -NR^{1a}-Q- and R^{1a} is -SO_2-C_1-C_6 alkyl.

[000187] In some embodiments, Q is optionally substituted C_1-C_6alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene. In some embodiments, Q is optionally substituted C_1-C_6alkylene. In some embodiments, Q is methylene, ethylene, propylene, or butylene. In some embodiments, Q is methylene.

[000188] In some embodiments, R^1 is -NR^{1a}-Q-, Q is optionally substituted C_1-C_6alkylene, and R^{1a} is hydrogen, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, R^1 is -NR^{1a}-Q-, Q is optionally substituted C_1-C_6alkylene, and R^{1a} is hydrogen. In some embodiments, R^1 is -NR^{1a}-Q-, Q is optionally substituted C_1-C_6alkylene, and $R^{1a}$is optionally substituted C_1-C_6 alkyl. In some embodiments, R^1 is -NR^{1a}-Q-, Q is optionally substituted C_1-C_6alkylene, and R^{1a} is C_1-C_6alkylene-C_3-C_6 cycloalkyl. In some embodiments, R^1 is -NR^{1a}-Q-, Q is optionally substituted C_1-C_6alkylene, and R^{1a} is -SO_2-C_1-C_6 alkyl.

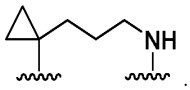
[000189] In some embodiments, R^1 is -NR^{1a}- and R^{1a} is hydrogen, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, R^1 is -NR^{1a}- and R^{1a} is hydrogen. In some embodiments, R^1 is -NR^{1a}- and R^{1a} is optionally substituted C_1-C_6 alkyl (e.g., methyl). In some embodiments, R^1 is -NR^{1a}- and R^{1a} is C_1-C_6alkylene-C_3-C_6 cycloalkyl (e.g., methylene-cyclopropyl). In some embodiments, R^1 is -NR^{1a}- and R^{1a} is -SO_2-C_1-C_6 alkyl (e.g., methyl).

[000190] In some embodiments, R^1 is -NR^{1a}-CO- or -CO-NR^{1a}- and R^{1a} is hydrogen, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, R^1 is -NR^{1a}-CO- or -CO-NR^{1a}- and R^{1a} is hydrogen. In some embodiments, R^1 is -NR^{1a}-CO- or -CO-NR^{1a}- and R^{1a} is optionally substituted C_1-C_6 alkyl (e.g., methyl). In some embodiments, R^1 is -NR^{1a}-CO- or -CO-NR^{1a}- and R^{1a} is C_1-C_6alkylene-C_3-C_6 cycloalkyl (e.g., methylene-cyclopropyl). In some embodiments, R^1 is -NR^{1a}-CO- or -CO-NR^{1a}- and R^{1a} is -SO_2-C_1-C_6 alkyl (e.g., methyl).

[000191] In some embodiments, R^1 is -NR^{1a}-SO_2- or -SO_2-NR^{1a} and R^{1a} is hydrogen, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, R^1 is -NR^{1a}-SO_2- or -SO_2-NR^{1a} and R^{1a} is hydrogen. In some embodiments, R^1 is -NR^{1a}-SO_2- or -SO_2-NR^{1a} and R^{1a} is optionally substituted C_1-C_6 alkyl (e.g., methyl). In some embodiments, R^1 is -NR^{1a}-SO_2- or -SO_2-NR^{1a} and R^{1a} is C_1-C_6alkylene-C_3-C_6 cycloalkyl (e.g., methylene-cyclopropyl). In some embodiments, R^1 is -NR^{1a}-SO_2- or -SO_2-NR^{1a} and R^{1a} is -SO_2-C_1-C_6 alkyl (e.g., methyl).

[000192] In some embodiments, an L^1 described herein is attached to R^1 to form -L^1-R^1-, such as tethering two parts of a compound described herein. In some embodiments, L^1R^1 can be any suitable combination of the L^1 and R^1 functional groups described herein. In some embodiments, L^1-R^1 is –$(CH_2)_4NH$–, –cyclopropyl-$(CH_2)_3NH$–, –$(CH_2)_3NH$–, –$(CH_2)_3NCH_3$–, –$(CH_2)_3N$-(CH_2-cyclopropyl)–, –$(CH_2)_2NH$–, –$(CH_2)_3$–, –$(CH_2)_3$–, –$(CH_2)_2$–, –CH_2–, –$O(CH_2)_3$–, –$O(CH_2)_2$–, –$O(CH_2)_2O$–, –$O(CH_2)_2NH$–, –$(CH_2)_3NSO_2$–, –$(CH_2)_2N(SO_2Me)CH_2$–, -–$(CH_2)_2N(Me)CH_2$–, –$(CH_2)_2N(CH_2$-cyclopropyl)CH_2–, –$(CH_2)_2NHCH_2$–, –$(CH_2)_2CONH$–, –$(CH_2)_2CONMe$–, –$(CH_2)_2CON(CH_2$-cyclopropyl)–, –$(CH_2)_2SO_2NH$–, –$(CH_2)_2NHCO$–, –$(CH_2)_2N(Me)CO$–, –$(CH_2)_2N(CH_2$-cyclopropyl)CO–, or –$(CH_2)_2NHSO_2$–. In some embodiments, L^1-R^1 is –$(CH_2)_4NH$–, –cyclopropyl-$(CH_2)_3NH$–, –$(CH_2)_3NH$–, –$(CH_2)_3NCH_3$–, –$(CH_2)_3N$-(CH_2-cyclopropyl)–, –$(CH_2)_2NH$–, –$O(CH_2)_2NH$–, –$(CH_2)_3NSO_2$–, –$(CH_2)_2N(SO_2Me)CH_2$–, -–$(CH_2)_2N(Me)CH_2$–, –$(CH_2)_2N(CH_2$-cyclopropyl)CH_2–, –$(CH_2)_2NHCH_2$–, –$(CH_2)_2CONH$–, –$(CH_2)_2CONMe$–, –$(CH_2)_2CON(CH_2$-cyclopropyl)–, –$(CH_2)_2NHCO$–, –$(CH_2)_2N(Me)CO$–, or –$(CH_2)_2N(CH_2$-cyclopropyl)CO–. In some

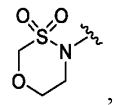
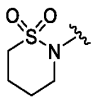
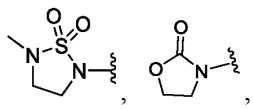
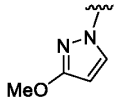
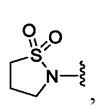
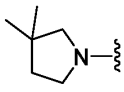
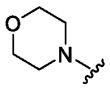
embodiments, L^1-R^1 is $–(CH_2)_4NH–$, $–$cyclopropyl-$(CH_2)_3NH–$, $–(CH_2)_3NH–$, $–(CH_2)_3NCH_3–$, $–(CH_2)_3N$-(CH_2-cyclopropyl)$–$, $–(CH_2)_2NH–$, $–O(CH_2)_2NH–$, $–(CH_2)_2N(Me)CH_2–$, $–(CH_2)_2N(CH_2$-cyclopropyl$)CH_2–$, or $–(CH_2)_2NHCH_2–$. In some embodiments, L^1-R^1 is $–(CH_2)_4NH–$ or $–(CH_2)_3NH–$. In some embodiments, L^1-R^1 is:



[000193] In some embodiments, each R^3 is any suitable functional group described herein. In some embodiments each R^3 is independently halogen, -CN, -$(CH_2)_m$-$N(R^{3a})_2$-, -OR^{3a}, -$N(R^{3a})_2$, -$N(SO_2R^{3b})R^{3a}$, -SR^{3a}, -SO_2R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-R^{3a}, -NH-S(O)(NH)-$(CH_2)_m$-R^{3a}, -NH-S(O)(NH)-R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-OR^{3b}, -NH-S(O)R^{3a}-$(CH_2)_m$-OR^{3b}, -NH-$S(O)_2$-R^{3c}, -$B(R^{3a})_3$, -$P(R^{3a})_3$, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8-membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl. In some embodiments, each R^3 is independently -$(CH_2)_m$-$N(R^{3a})_2$-, -OR^{3a}, -$N(R^{3a})_2$, -$N(SO_2R^{3b})R^{3a}$, -SR^{3a}, -SO_2R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-R^{3a}, -NH-S(O)(NH)-$(CH_2)_m$-R^{3a}, -NH-S(O)(NH)-R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-OR^{3b}, -NH-S(O)R^{3a}-$(CH_2)_m$-OR^{3b}, -NH-$S(O)_2$-R^{3c}, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8-membered heterocycle. In some embodiments, In some embodiments, each R^3 is independently -$NR^{3a}S(O)_2$-$(CH_2)_m$-OR^{3b} or -NR^{3a}-$S(O)_2$-$(CH_2)_m$-R^{3a}.

[000194] In some embodiments, each R^3 is independently halogen, -CN, -OR^{3a}, -$N(R^{3a})_2$, -SR^{3a}, -SO_2R^{3a}, -NH-S(O)(NH)-R^{3a}, -NH-$S(O)_2$-$(CH_2)_m$-R^{3a}, -NH-$S(O)_2$-$(CH_2)_m$-OR^{3b}, -$B(R^{3a})_3$, or -$P(R^{3a})_3$. In some embodiments, each R^3 is independently halogen, -CN, -OR^{3a}, -$N(R^{3a})_2$, -SO_2R^{3a}, or -NH-$S(O)_2$-$(CH_2)_m$-OR^{3b}. In some embodiments, each R^3 is -SO_2R^{3a} or -NH-$S(O)_2$-$(CH_2)_m$-OR^{3b}. In some embodiments, each R^3 is -SO_2R^{3a}. In some embodiments, each R^3 is independently -NH-$S(O)_2$-$(CH_2)_m$-OR^{3b}. In some embodiments, an R^3 is a point of attachment to G.

[000195] In some embodiments, wherein R^3 is optionally substituted 5- to 8- membered heterocycle, which is optionally substituted with one or more substituents selected from oxo, methyl, ethyl, propyl, methoxy, or ethoxy. In some embodiments, wherein R^3 is optionally substituted 5- to 8- membered heterocycle, which is optionally substituted with one or more substituents selected from oxo, methyl, and methoxy. In some embodiments, the 5- to 8-

membered heterocycle is  ,  ,  , ,  ,  ,  , or  .

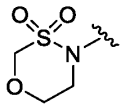
[000196] In some embodiments, each R^{3a} is independently hydrogen, -C(O)OR^{3b}, optionally substituted C_1-C_6 alkyl, or -N(R^{3b})$_2$. In some embodiments, each R^{3a} is independently hydrogen or C_1-C_6 alkyl. In some embodiments, each R^{3a} is independently hydrogen methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, or tert-butyl. In some embodiments, each R^{3a} is independently hydrogen, methyl, or ethyl, wherein the ethyl is optionally substituted with one or more substituents selected from methyl and -OH. In some embodiments, each R^{3a} is hydrogen. In some embodiments, each R^{3a} is independently C_1-C_6 alkyl. In some embodiments, R^{3a} is methyl.

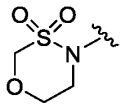
[000197] In some embodiments, R^{3b} is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, or optionally substituted C_3-C_6 cycloalkyl. In some embodiments, R^{3b} is hydrogen or C_1-C_6 alkyl. In some embodiments, R^{3b} is hydrogen. In some embodiments, R^{3b} is C_1-C_6 alkyl. In some embodiments, R^{3b} is hydrogen, methyl, ethyl, or propyl. In some embodiments, R^{3b} is methyl. In some embodiments, R^{3b} is ethyl. In some embodiments, R^{3b} is n-propyl or isopropyl. In some embodiments, R^{3b} is optionally substituted C_3-C_6 cycloalkyl. In some embodiments, R^{3b} is optionally substituted cyclopropyl. In some embodiments, R^{3b} is cyclopropyl optionally substituted with C_1-C_6 alkyl or C_1-C_6 hydroxyalkyl.

[000198] In some embodiments, R^{3b} is hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_2-C_6 alkenyl. In some embodiments, R^{3b} is hydrogen or C_1-C_6 alkyl. In some embodiments, R^{3b} is hydrogen. In some embodiments, R^{3b} is C_1-C_6 alkyl. In some embodiments, R^{3b} is hydrogen, methyl, ethyl, or propyl. In some embodiments, R^{3b} is methyl. In some embodiments, R^{3b} is ethyl. In some embodiments, R^{3b} is n-propyl or isopropyl.

[000199] IN some embodiments, R^{3c} is C_3-C_8 cycloalkyl or 3- to 8- membered heterocycle. In some embodiments, R^{3c} is C_3-C_8 cycloalkyl. In some embodiments, R^{3c} is 3- to 8- membered heterocycle. In some embodiments, 4- to 6- membered heterocycle. In some embodiments, R^{3c} is oxetanyl, azetidinyl, or thietanyl. In some embodiments, R^{3c} is oxetanyl or azetidinyl. In some embodiments, R^{3c} is oxetanyl.

[000200] In some embodiments, each R^3 is independently -NHSO$_2$(CH$_2$)$_2$OH, -NHSO$_2$C(CH$_3$)$_2$CH$_2$OH, -NHSO$_2$C(cyclopropyl)CH$_2$OH, -NHSO$_2$CH(CH$_3$)CH$_2$OH, -

$NMeSO_2(CH_2)_2OH$, $-NHSO_2CH_2CH_3$, $-NHSO_2CHCH_2$, $-NHSO_2$-oxetanyl, $-NMeSO_2CH_3$, $-N(SO_2Me)(CH_2)_2OH$, or  .

[000201] In some embodiments, each R^3 is independently $-NHSO_2(CH_2)_2OH$, $-NMeSO_2(CH_2)_2OH$, $-NHSO_2CH_2CH_3$, $-NHSO_2$-oxetanyl, $-NMeSO_2CH_3$, $-N(SO_2Me)(CH_2)_2OH$, or  .

[000202] In some embodiments, R^3 is $-SO_2R^{3a}$ and R^{3b} is methyl. In some embodiments, R^3 is $-NH\text{-}S(O)_2\text{-}(CH_2)_m\text{-}OR^{3b}$ and R^{3b} is hydrogen. In some embodiments, each R^3 is independently $-NHS(O)_2\text{-}(CH_2)_2\text{-}OH$.

[000203] In some embodiments, m is 1 to 6. In some embodiments, m is 1 to 4. In some embodiments, m is 1 to 3. In some embodiments, m is 1 to 2. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3. In some embodiments, m is 4.

[000204] In some embodiments, o is any suitable integer described herein. In some embodiments, o is 1 to 4. In some embodiments, o is 1 to 3. In some embodiments, o is 1 to 2. In some embodiments, o is 1. In some embodiments, o is 2. In some embodiments, o is 3. In some embodiments, o is 4.

[000205] In some embodiments, o is 1 and R^3 is $-SO_2R^{3a}$ or $-NH\text{-}S(O)_2\text{-}(CH_2)_m\text{-}OR^{3b}$.

[000206] In some embodiments, n is any suitable integer described herein. In some embodiments, n is 0 to 9. In some embodiments, n is 1 to 5. In some embodiments, n is 1 to 3. In some embodiments, n is 1 to 2. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4. In some embodiments, n is 5.

[000207] In some embodiments, R^4 is any suitable functional group described herein.

[000208] In some embodiments, each R^4 is independently halogen, -OH, -CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, two or more R^4 combine to form a C_3-C_8 cycloalkyl, or two R^4 combine to form a C_1-C_3 alkylene bridge, or two R^4 combine to form an oxo. In some embodiments, two R^4 combine to form a C_3-C_8 cycloalkyl. In some embodiments, two R^4 are on the same carbon atom. In some embodiments, the two R^4 groups combine to form a cyclopropyl. In some embodiments, the two R^4 groups combine to form a butyl. In some embodiments, two R^4 are on different carbon atoms. In some embodiments, two R^4 groups combine to form a (1R,5S)-8-azabicyclo[3.2.1]octane. In some embodiments, two R^4 combine to form a C_1-C_3 alkylene bridge. In some embodiments, n is 2 and two R^4 combine to form a C_3-C_8 cycloalkyl.

[000209] In some embodiments, each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, two or more R^4 combine to form a C_3-C_8 cycloalkyl, or two R^4 combine to form a C_1-C_3 alkylene bridge. In some embodiments, two R^4 combine to form a C_3-C_8 cycloalkyl. In some embodiments, two R^4 are on the same carbon atom. In some embodiments, the two R^4 groups combine to form a cyclopropyl. In some embodiments, the two R^4 groups combine to form a butyl. In some embodiments, two R^4 are on different carbon atoms. In some embodiments, two R^4 groups combine to form a (1R,5S)-8-azabicyclo[3.2.1]octane. In some embodiments, two R^4 combine to form a C_1-C_3 alkylene bridge. In some embodiments, n is 2 and two R^4 combine to form a C_3-C_8 cycloalkyl.

[000210] The compounds described herein can interact or contact with the protein described herein when there is suitable adjacent distance between the compound and the protein to form an adduct. In some embodiments, the compounds described herein are adjacent to KIF18A. In some embodiments, adjacent can refer to the distance of about 1 to 10 angstroms between the compound and KIF18A. In some embodiments, it can be about 1 to 8 angstroms between the compound and KIF18A. In some embodiments, it can be about 1 to 5 angstroms between the compound and KIF18A. In some embodiments, it can be about 3 to 5 angstroms between the compound and KIF18A.

[000211] The compounds described herein have structures which are useful for interacting with KIF18A to bind with it and form an adduct. For example, ring A can be sandwiched between the side chains of the KIF18A in the α4-helix and α6-helix location of the KIF18A. Aromatic rings which have a planar structure are useful for sandwiching between the α4-helix and α6-helix. Ring A can also be substituted with a diverse range of polar groups that can form hydrogen bonds that an interact with KIF18A. The linker G between ring A and ring B may be useful for keeping rings A and B in the same plane due to the carbonyl group allowing for delocalization of the aromatic rings. Ring B can interact against the flat surface of KIF18A α4-helix, and can also be useful for forming hydrogen bonds. Ring C can interact with hydrophobic KIF18 residues as a saturated cycloalkyl ring or a heterocycloalkyl ring. For example, ring C can interact with the hydrophobic residues within the α4-helix and α6-helix region of KIF18A. Additionally, if ring C is substituted with halogens, alkyls, or cycloalkyls, it can contact with a deeper layer of the hydrophobic side chains of the KIF18A β-sheet. The L^1-R^1 tether can be useful for interacting with the hydrophobic side chains of the KIF18A β-sheet region. Additionally, the L^1-R^1 tether can interact with KIF18A via hydrogen bonding in the α4-helix

region. The L^1-R^1 tether region can weave through the α6-helix and β-sheet region of KIF18A and interact with the sidechains.

[000212] In some embodiments, ring A is adjacent to the KIF18A between the KIF18 α4-helix and α6-helix. In some embodiments, ring A is adjacent to the KIF18A between Leu285 residue and Tyr348 residue.

[000213] In some embodiments, ring B is adjacent to a flat surface of the KIF18A α4-helix. In some embodiments, ring B is adjacent to the KIF18A Gly289 residue or Asn293 residue. In some embodiments, ring B interacts with the KIF18A Asn293 residue via a hydrogen bond.

[000214] In some embodiments, ring C is adjacent to hydrophobic residues of the KIF18A. In some embodiments, the hydrophobic residues of the KIF18A are in α4-helix or α6-helix, or a combination thereof. In some embodiments, ring C is adjacent to the KIF18A Tyr112 residue, Leu284 residue, Leu288 residue, and Tyr348 residue. In some embodiments, ring C is adjacent to the KIF18A Leu110 residue, Leu259 residue, Met328 residue, or a combination thereof.

[000215] In some embodiments, L^1-R^1 is adjacent to the hydrophobic side chain of the KIF18A α6-helix and β-sheet. L^1-R^1 is adjacent to the Ala352 residue, Met328 residue, and Tyr112 residue of KIF18A. In some embodiments, L^1-R^1 is adjacent to the hydrophobic side chain of the KIF18A β-sheet. In some embodiments, L^1-R^1 is adjacent to the KIF18A Leu110 residue, Leu259 residue, and Met328 residue.

[000216] In some embodiments, R^1 interacts with the KIF18A α4-helix via a hydrogen bond. In some embodiments, R^1 interacts with the KIF18A Asn293 residue via the hydrogen bond.

[000217] In some embodiments, R^3 interacts with KIF18A via a hydrogen bond. In some embodiments, R^3 interacts with the KIF18A Ser262 residue via a hydrogen bond.

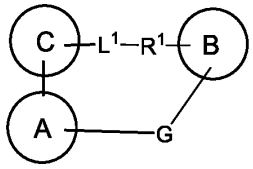
[000218] Provided in some embodiments is an adduct comprising a KIF18A and a compound of Formula (B), wherein the structure of formula (B) is a compound provided in Table 1.

Compositions

[000219] The compounds described herein, for example, the compounds described in the "Compound" section above can be useful for forming a composition with a protein. In some embodiments, the composition comprising a protein and a compound described herein form an adduct. In some embodiments, the protein is KIF18A. In some embodiments, the compound can be any suitable compound described herein.

[000220] The composition can be useful for treating cancer. In some embodiments, the formation of the adduct inhibits the KIF18A protein, thereby treating cancer.

[000221] Provided in some embodiments herein is a composition comprising a protein and a compound, wherein the protein is KIF18A, the compound is a compound of Formula (B), and the protein and the compound form an adduct, wherein structure of Formula (B) is:



(B)

wherein:

ring A is optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12- membered heteroaryl;

ring B is optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12- membered heteroaryl;

ring C is optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 5- to 12 membered heterocyclyl, optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12- membered heteroaryl;

G is -(C=O)-NH- or -NH-(C=O)-;

L^1 is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond, -O-, -NL^{1a1}-, -S-, or -SO_2-;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

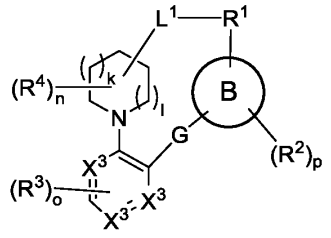
L^{1b} is optionally substituted C_1-C_6 alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene;

R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-Q-, -NR^{1a}-CO-, -CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a};

R^{1a} is hydrogen, -C(=O)H, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl; and

Q is optionally substituted C_1-C_6alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene.

[000222] In some embodiments, the composition comprises the compound of Formula (B) which has the structure of Formula (I-0):



(I-0)

wherein:

each X^3 is independently CH or N;

ring B is a 5- or 6- membered heteroaryl or phenyl;

L^1 is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond, -O-, -NL^{1a1}-, -S-, or -SO_2-;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene;

G is -(C=O)-NH- or -NH-(C=O)-;

R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-Q-, -NR^{1a}-CO-, -CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a};

R^{1a} is hydrogen, -C(=O)R^{1a1}, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

R^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

Q is optionally substituted C_1-C_6alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene;

each R^2 is independently halogen, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl, or two R^2 are taken together to form an oxo, an optionally substituted C_3-C_8 cycloalkyl, an optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl;

each R^{2a} is independently hydrogen or optionally substituted C_1-C_6 alkyl;

each R^3 is independently halogen, -CN, -$(CH_2)_m$-$N(R^{3a})_2$-, -OR^{3a}, -$N(R^{3a})_2$, -$N(SO_2R^{3b})R^{3a}$, -SR^{3a}, -SO_2R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-R^{3a}, -NH-S(O)(NH)-$(CH_2)_m$-R^{3a}, -NH-S(O)(NH)-R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-OR^{3b}, -NH-S(O)R^{3a}-

$(CH_2)_m$-OR^{3b}, -NH-$S(O)_2$-R^{3c}, -$B(R^{3a})_3$, -$P(R^{3a})_3$, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl ;

each R^{3a} is independently hydrogen, -$C(O)OR^{3b}$, optionally substituted C_1-C_6 alkyl, or -$N(R^{3b})_2$;

R^{3b} is hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_2-C_6 alkenyl;

R^{3c} is C_3-C_8 cycloalkyl or 3- to 8- membered heterocycle;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, two or more R^4 combine to form a C_3-C_8 cycloalkyl, or two R^4 combine to form a C_1-C_3 alkylene bridge;

k is 0 to 2;

l is 0 to 2 ;

m is 1 to 6;

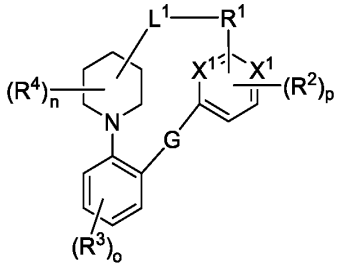
n is 0 to 9;

o is 1 to 4;

p is 0 to 4; and

wherein when any one of variable G, L^1, R^1, R^2, R^3, or R^4 are present, the bond to variable G, L^1, R^1, R^2, R^3 or R^4 replaces a hydrogen on a carbon or nitrogen atom.

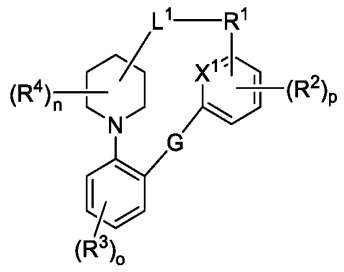
[000223] In some embodiments, the composition comprises the compound of Formula (B) which has a structure of Formula (I-0a):



(I-0a)

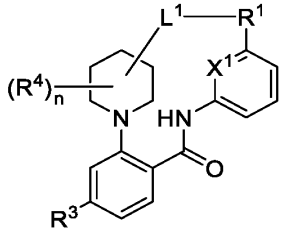
wherein: each X^1 is independently CH or N.

[000224] In some embodiments, the composition comprises the compound of Formula (B) which has a structure of Formula (I):



(I).

[000225] In some embodiments, the composition comprises the compound of Formula (B) which has a structure of Formula (II):



(II)

wherein:

X^1 is CH or N;

$L^1$is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond, -O-, or -NL^{1a1}-;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

L^{1b} is optionally substituted C_1-C_8 alkylene;

R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-C_1-C_6alkylene-, -NR^{1a}-CO-,-CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a};

R^{1a} is hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

R^3 is halogen, -CN, -OR^{3a}, -$N(R^{3a})_2$, -SO_2R^{3a}, or -NH-$S(O)_2$-$(CH_2)_m$-OR^{3b},

each R^{3a} is independently hydrogen or C_1-C_6 alkyl;

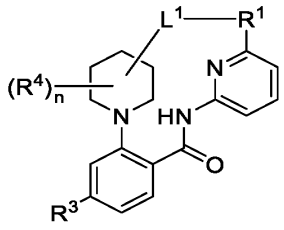
R^{3b} is hydrogen or C_1-C_6 alkyl;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, two or more R^4 combine to form a C_3-C_8 cycloalkyl, or two R^4 combine to form a C_1-C_3 alkylene bridge;

m is 1 to 3; and

n is 1 or 2.

[000226] In some embodiments, the composition comprises the compound of Formula (B) which has a structure of Formula (III-A):



(III-A)

wherein:

$L^1$is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond or -O-;

L^{1b} is optionally substituted C_1-C_8 alkylene;

R^1 is a bond, -O-, -NR^{1a}-, or -NR^{1a}-C_1-C_3 alkylene-;

R^{1a} is hydrogen, -C(=O)H, optionally substituted C_1-C_6 alkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl;

R^3 is halogen, -NH-$S(O)_2$-$(CH_2)_m$-R^{3a}, or -NH-$S(O)_2$-$(CH_2)_m$-OR^{3b},

R^{3a} is C_1-C_6 alkyl;

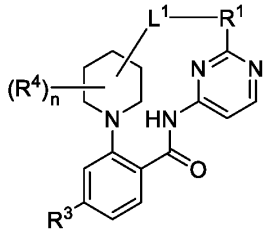
R^{3b} is hydrogen or C_1-C_6 alkyl;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, or two or more R^4 combine to form a C_3-C_8 cycloalkyl;

m is 1 to 3; and

n is 0 to 2.

[000227] In some embodiments, the composition comprises the compound of Formula (B) which has a structure of Formula (III-B):



(III-B)

wherein:

$L^1$is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond or -O-;

L^{1b} is optionally substituted C_1-C_8 alkylene;

R^1 is a bond, -O-, -NR^{1a}-, or -NR^{1a}-C_1-C_3 alkylene-

R^{1a} is hydrogen, -C(=O)H, optionally substituted C_1-C_6 alkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl;

R^3 is halogen, -NH-$S(O)_2$-$(CH_2)_m$-R^{3a}, or -NH-$S(O)_2$-$(CH_2)_m$-OR^{3b},

R^{3a} is C_1-C_6 alkyl;

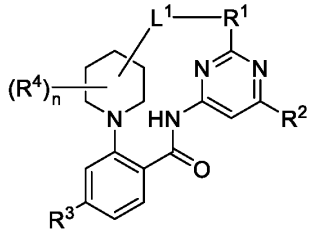
R^{3b} is hydrogen or C_1-C_6 alkyl;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, or two or more R^4 combine to form a C_3-C_8 cycloalkyl;

m is 1 to 3; and

n is 0 to 2.

[000228] In some embodiments, the composition comprises the compound of Formula (B) which has a structure of Formula (III-C):



(III-C)

wherein:

L^1 is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond, -O-, or -NL^{1a1}-;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

L^{1b} is optionally substituted C_1-C_8 alkylene;

R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-C_1-C_6alkylene-, -NR^{1a}-CO-,-CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a};

R^{1a} is hydrogen, C_1-C_6 alkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl;

R^2 is halogen, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl;

each R^{2a} is independently hydrogen or C_1-C_6 alkyl;

R^3 is halogen, -CN, -OR^{3a}, -$N(R^{3a})_2$, -SO_2R^{3a}, or -NH-$S(O)_2$-$(CH_2)_m$-OR^{3b},

R^{3a} is hydrogen or C_1-C_6 alkyl;

R^{3b} is hydrogen or C_1-C_6 alkyl;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, or two or more R^4 combine to form a C_3-C_8 cycloalkyl;

m is 1 to 3; and

n is 0, 1, or 2.

[000229] In some embodiments, R^2 is any suitable functional group described herein.

[000230] In some embodiments, each R^2 is independently halogen, -CN, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl, or two R^2 are taken together to form an oxo, an optionally substituted C_3-C_8 cycloalkyl, an optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl. In some embodiments, R^2 is halogen, -CN, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl. In some embodiments, R^2 is halogen, -CN, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl. In some embodiments, R^2 is halogen, -CN, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl. In some embodiments, R^2 is halogen, -CN, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl. In some embodiments, R^2 is halogen, -OR^{2a}, -$N(R^{2a})_2$, or -$S(O)_2N(R^{2a})_2$. In some embodiments, R^2 is -$S(O)_2N(R^{2a})_2$ or -SO_2-C_1-C_6 alkyl. In some embodiments, R^2 is -$S(O)_2N(R^{2a})_2$.

[000231] In some embodiments, R^2 is halogen, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl. In some embodiments, R^2 is halogen, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl. In some embodiments, R^2 is halogen, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl. In some embodiments, R^2 is halogen, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl. In some embodiments, R^2 is halogen, -OR^{2a}, -$N(R^{2a})_2$, or -$S(O)_2N(R^{2a})_2$. In some embodiments, R^2 is -$S(O)_2N(R^{2a})_2$ or -SO_2-C_1-C_6 alkyl. In some embodiments, R^2 is -$S(O)_2N(R^{2a})_2$.

[000232] In some embodiments, each R^{2a} is any suitable functional group described herein. In some embodiments, each R^{2a} is independently hydrogen or optionally substituted C_1-C_6 alkyl. In some embodiments, each R^{2a} is independently optionally substituted C_1-C_4 alkyl. In some embodiments, each R^{2a} is independently methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, or tert-butyl. In some embodiments, each R^{2a} is methyl. In some embodiments, one R^{2a} is hydrogen and the other R^{2a} is optionally substituted C_1-C_6 alkyl. In some

embodiments, R^2 is $-S(O)_2N(R^{2a})_2$ and each R^{2a} is hydrogen. In some embodiments, R^2 is $-S(O)_2N(R^{2a})_2$ and each R^{2a} is independently optionally substituted C_1-C_6 alkyl. In some embodiments, R^2 is $-S(O)_2N(R^{2a})_2$ and each R^{2a} is methyl. In some embodiments, R^2 is $S(O)_2NHC(CH_3)_3$.

[000233] In some embodiments, R^2 is a 5- to 8- membered heteroaryl. In some embodiments, R^2 is a 5- to 6- membered heteroaryl. In some embodiments, R^2 is a 5- membered heteroaryl. In some embodiments, R^2 is a 6- membered heteroaryl. In some embodiments, R^2 is a furanyl, furanonyl, isothiazolyl, imidazolyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl. In some embodiments, R^2 is a pyrazolyl.

[000234] In some embodiments, L^1 can be any suitable linker structure in any combination of variables L^{1a} and L^{1b} described herein. In some embodiments, L^1 is a linker comprising the structure $-L^{1a}-L^{1b}-$.

[000235] In some embodiments, L^{1a} can be any suitable functional group described herein. In some embodiments, L^{1a} is a bond, -O-, $-NL^{1a1}-$, -S-, or $-SO_2-$. In some embodiments, L^{1a} is a bond, -O-, or $-NL^{1a1}-$. In some embodiments, L^{1a} is a bond or -O-. In some embodiments, L^{1a} is a bond. In some embodiments, L^{1a} is -O-. In some embodiments, L^{1a} is $-NL^{1a1}-$. In some embodiments, L^{1a} is -S-. In some embodiments, L^{1a} is $-SO_2-$.

[000236] In some embodiments, L^{1a1} is any suitable functional group described herein. In some embodiments, L^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or $-SO_2-C_1$-C_6 alkyl. In some embodiments, L^{1a1} is hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or $-SO_2-C_1$-C_6 alkyl. In some embodiments, L^{1a1} is hydrogen, C_1-C_6 alkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl. In some embodiments, L^{1a1} is hydrogen or C_1-C_6 alkyl. In some embodiments, L^{1a1} is hydrogen. In some embodiments, L^{1a1} is C_1-C_6 alkyl. In some embodiments, L^{1a1} is methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, or tert-butyl. In some embodiments, L^{1a1} is methyl.

[000237] In some embodiments, L^{1a} is $-NL^{1a1}-$ and L^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or $-SO_2-C_1$-C_6 alkyl. In some embodiments, L^{1a} is $-NL^{1a1}-$ and L^{1a1} is hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or $-SO_2-C_1$-C_6 alkyl. In some embodiments, L^{1a} is $-NL^{1a1}-$ and L^{1a1} is hydrogen or C_1-C_6 alkyl. In some embodiments, L^{1a} is $-NL^{1a1}-$ and L^{1a1} is hydrogen. In some embodiments, L^{1a} is $-NL^{1a1}-$ and L^{1a1} is C_1-C_6 alkyl. In some embodiments, L^{1a} is $-NL^{1a1}-$ and L^{1a1} is methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, or tert-butyl. In some embodiments, L^{1a} is $-NL^{1a1}-$ and L^{1a1} is methyl.

[000238] In some embodiments, L^{1b} is any suitable functional group described herein. In some embodiments, L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene. In some embodiments, L^{1b} is optionally substituted C_1-C_6 alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene. In some embodiments, L^{1b} is optionally substituted C_1-C_6 alkylene. In some embodiments, L^{1b} is optionally substituted C_1-C_4 alkylene. L^{1b} can be substituted with any suitable substituent described herein. In some embodiments, L^{1b} is C_1-C_4 alkylene substituted with oxo, C_3-C_6 cycloalkyl, or 3- to 6- membered heterocyclyl. In some embodiments, L^{1b} is C_1-C_4 alkylene substituted with oxo or C_3-C_6 cycloalkyl. In some embodiments, L^{1b} is C_1-C_4 alkylene substituted with oxo, cyclopropyl, or cyclobutyl. In some embodiments, L^{1b} is C_1-C_4 alkylene substituted with oxo. In some embodiments, L^{1b} is C_1-C_4 alkylene substituted with cyclopropyl. In some embodiments, L^{1b} is methylene, ethylene, propylene, butylene, or pentylene. In some embodiments, L^{1b} is methylene. In some embodiments, L^{1b} is ethylene. In some embodiments, L^{1b} is propylene. In some embodiments, L^{1b} is butylene. In some embodiments, L^{1b} is pentylene.

[000239] In some embodiments, L^{1a} is a bond, -O-, or -NL^{1a1}- and L^{1b} is optionally substituted C_1-C_6 alkylene. In some embodiments, L^{1a} is a bond and L^{1b} is optionally substituted C_1-C_6 alkylene. In some embodiments, L^{1a} is -O- and L^{1b} is optionally substituted C_1-C_6 alkylene. In some embodiments, L^{1a} is -NL^{1a1}-, L^{1a1} is hydrogen or C_1-C_6 alkyl, and L^{1b} is optionally substituted C_1-C_6 alkylene.

[000240] In some embodiments, L^1 is -O(optionally substituted alkylene)-, -(optionally substituted alkylene)O-, or optionally substituted alkylene. In some embodiments, L^1 is -O(unsubstituted alkylene)-, -(unsubstituted alkylene)O-, unsubstituted alkylene, or substituted alkylene. In some embodiments, L^1 is -O(unsubstituted alkylene)-. In some embodiments, L^1 is -(unsubstituted alkylene)O-. In some embodiments, L^1 is unsubstituted alkylene. In some embodiments, L^1 is substituted alkylene.

[000241] In some embodiments, L^1 is $–(CH_2)_4–$, $–(CH_2)_3–$, $–(CH_2)_2–$, $–CH_2–$ –cyclopropyl-$(CH_2)_3–$, –cyclopropyl-$(CH_2)_2–$, $–O(CH_2)_3–$, $–O(CH_2)_2–$, or $–O(CH_2)–$. In some embodiments, L^1 is $–(CH_2)_4–$, –cyclopropyl-$(CH_2)_3–$, $–(CH_2)_3–$, $–(CH_2)_2CO–$, $–(CH_2)_2–$, $–O(CH_2)_2–$, or $–CH_2–$.

[000242] In some embodiments, R^1 is any suitable functional group described herein. In some embodiments, R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-Q-, -NR^{1a}-CO-, -CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a}. In some embodiments, R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-C_1-C_6alkylene-, -NR^{1a}-CO-,-CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a}. In some embodiments, R^1 is a

bond, -O-, -NR^{1a}-, -NR^{1a}-Q-, -NR^{1a}-CO-, -CO-NR^{1a}-, -NR^{1a}-SO_2-, or -SO_2-NR^{1a}. In some embodiments, R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-C_1-C_6alkylene-, -NR^{1a}-CO-, -CO-NR^{1a}-, -NR^{1a}-SO_2-, or -SO_2-NR^{1a}. In some embodiments, R^1 is a bond. In some embodiments, R^1 is -O-. In some embodiments, R^1 is -NR^{1a}-Q-. In some embodiments, R^1 is -O-. In some embodiments, R^1 is -NR^{1a}-. In some embodiments, R^1 is -NR^{1a}-CO-. In some embodiments, R^1 is -CO-NR^{1a}-. In some embodiments, R^1 is -NR^{1a}-SO_2-. In some embodiments, R^1 is -SO_2-NR^{1a}.

[000243] In some embodiments, R^{1a} is hydrogen, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, R^{1a} is hydrogen, C_1-C_6 alkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl. In some embodiments, R^{1a} is hydrogen, C_1-C_3 alkyl, C_1-C_3 alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, $R^{1a}$is hydrogen. In some embodiments, $R^{1a}$is optionally substituted C_1-C_6 alkyl. In some embodiments, R^{1a} is methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, or tert-butyl. In some embodiments, R^{1a} is methyl. In some embodiments, R^{1a} is substituted C_1-C_6 alkyl. In some embodiments, R^{1a} is C_1-C_6alkylene-C_3-C_6 cycloalkyl. In some embodiments, R^{1a} is methylene-C_3-C_6 cycloalkyl. In some embodiments, R^{1a} is methylene-cyclopropyl. In some embodiments, R^{1a} is -SO_2-C_1-C_6 alkyl. In some embodiments, R^{1a} is -SO_2-Me.

[000244] In some embodiments, R^1 is -NR^{1a}-Q- and R^{1a} is hydrogen, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, R^1 is a -NR^{1a}-Q- and R^{1a} is hydrogen. In some embodiments, R^1 is -NR^{1a}-Q- and R^{1a} is optionally substituted C_1-C_6 alkyl. In some embodiments, R^1 is -NR^{1a}-Q- and R^{1a} is C_1-C_6alkylene-C_3-C_6 cycloalkyl. In some embodiments, R^1 is -NR^{1a}-Q- and R^{1a} is -SO_2-C_1-C_6 alkyl.

[000245] In some embodiments, Q is optionally substituted C_1-C_6alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene. In some embodiments, Q is optionally substituted C_1-C_6alkylene. In some embodiments, Q is methylene, ethylene, propylene, or butylene. In some embodiments, Q is methylene.

[000246] In some embodiments, R^1 is -NR^{1a}-Q-, Q is optionally substituted C_1-C_6alkylene, and R^{1a} is hydrogen, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, R^1 is -NR^{1a}-Q-, Q is optionally substituted C_1-C_6alkylene, and R^{1a} is hydrogen. In some embodiments, R^1 is -NR^{1a}-Q-, Q is optionally substituted C_1-C_6alkylene, and $R^{1a}$is optionally substituted C_1-C_6 alkyl. In some embodiments, R^1 is -NR^{1a}-Q-, Q is optionally substituted C_1-C_6alkylene, and R^{1a} is C_1-C_6alkylene-C_3-C_6 cycloalkyl. In some embodiments, R^1 is -NR^{1a}-Q-, Q is optionally substituted C_1-C_6alkylene, and R^{1a} is -SO_2-C_1-C_6 alkyl.

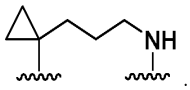
[000247] In some embodiments, R^1 is -NR^{1a}- and R^{1a} is hydrogen, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, R^1 is -NR^{1a}- and R^{1a} is hydrogen. In some embodiments, R^1 is -NR^{1a}- and R^{1a} is optionally substituted C_1-C_6 alkyl (e.g., methyl). In some embodiments, R^1 is -NR^{1a}- and R^{1a} is C_1-C_6alkylene-C_3-C_6 cycloalkyl (e.g., methylene-cyclopropyl). In some embodiments, R^1 is -NR^{1a}- and R^{1a} is -SO_2-C_1-C_6 alkyl (e.g., methyl).

[000248] In some embodiments, R^1 is -NR^{1a}-CO- or -CO-NR^{1a}- and R^{1a} is hydrogen, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, R^1 is -NR^{1a}-CO- or -CO-NR^{1a}- and R^{1a} is hydrogen. In some embodiments, R^1 is -NR^{1a}-CO- or -CO-NR^{1a}- and R^{1a} is optionally substituted C_1-C_6 alkyl (e.g., methyl). In some embodiments, R^1 is -NR^{1a}-CO- or -CO-NR^{1a}- and R^{1a} is C_1-C_6alkylene-C_3-C_6 cycloalkyl (e.g., methylene-cyclopropyl). In some embodiments, R^1 is -NR^{1a}-CO- or -CO-NR^{1a}- and R^{1a} is -SO_2-C_1-C_6 alkyl (e.g., methyl).

[000249] In some embodiments, R^1 is -NR^{1a}-SO_2- or -SO_2-NR^{1a} and R^{1a} is hydrogen, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl. In some embodiments, R^1 is -NR^{1a}-SO_2- or -SO_2-NR^{1a} and R^{1a} is hydrogen. In some embodiments, R^1 is -NR^{1a}-SO_2- or -SO_2-NR^{1a} and R^{1a} is optionally substituted C_1-C_6 alkyl (e.g., methyl). In some embodiments, R^1 is -NR^{1a}-SO_2- or -SO_2-NR^{1a} and R^{1a} is C_1-C_6alkylene-C_3-C_6 cycloalkyl (e.g., methylene-cyclopropyl). In some embodiments, R^1 is -NR^{1a}-SO_2- or -SO_2-NR^{1a} and R^{1a} is -SO_2-C_1-C_6 alkyl (e.g., methyl).

[000250] In some embodiments, an L^1 described herein is attached to R^1 to form -L^1-R^1-, such as tethering two parts of a compound described herein. In some embodiments, L^1R^1 can be any suitable combination of the L^1 and R^1 functional groups described herein. In some embodiments, L^1-R^1 is –$(CH_2)_4NH$–, –cyclopropyl-$(CH_2)_3NH$–, –$(CH_2)_3NH$–, –$(CH_2)_3NCH_3$–, –$(CH_2)_3N$-(CH_2-cyclopropyl)–, –$(CH_2)_2NH$–, –$(CH_2)_3$–, –$(CH_2)_3$–, –$(CH_2)_2$–, –CH_2–, –$O(CH_2)_3$–, –$O(CH_2)_2$–, –$O(CH_2)_2O$–, –$O(CH_2)_2NH$–, –$(CH_2)_3NSO_2$–, –$(CH_2)_2N(SO_2Me)CH_2$–, -–$(CH_2)_2N(Me)CH_2$–, –$(CH_2)_2N(CH_2$-cyclopropyl)CH_2–, –$(CH_2)_2NHCH_2$–, –$(CH_2)_2CONH$–, –$(CH_2)_2CONMe$–, –$(CH_2)_2CON(CH_2$-cyclopropyl)–, –$(CH_2)_2SO_2NH$–, –$(CH_2)_2NHCO$–, –$(CH_2)_2N(Me)CO$–, –$(CH_2)_2N(CH_2$-cyclopropyl)CO–, or –$(CH_2)_2NHSO_2$–. In some embodiments, L^1-R^1 is –$(CH_2)_4NH$–, –cyclopropyl-$(CH_2)_3NH$–, –$(CH_2)_3NH$–, –$(CH_2)_3NCH_3$–, –$(CH_2)_3N$-(CH_2-cyclopropyl)–, –$(CH_2)_2NH$–, –$O(CH_2)_2NH$–, –$(CH_2)_3NSO_2$–, –$(CH_2)_2N(SO_2Me)CH_2$–, -–$(CH_2)_2N(Me)CH_2$–, –$(CH_2)_2N(CH_2$-cyclopropyl)CH_2–, –$(CH_2)_2NHCH_2$–, –$(CH_2)_2CONH$–, –$(CH_2)_2CONMe$–, –$(CH_2)_2CON(CH_2$-cyclopropyl)–, –$(CH_2)_2NHCO$–, –$(CH_2)_2N(Me)CO$–, or –$(CH_2)_2N(CH_2$-cyclopropyl)CO–. In some

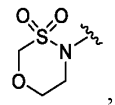
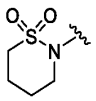
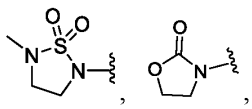
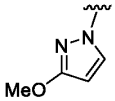
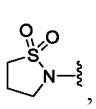
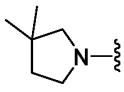
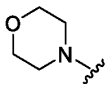
embodiments, L^1-R^1 is $–(CH_2)_4NH–$, $–$cyclopropyl-$(CH_2)_3NH–$, $–(CH_2)_3NH–$, $–(CH_2)_3NCH_3–$, $–(CH_2)_3N$-(CH_2-cyclopropyl)$–$, $–(CH_2)_2NH–$, $–O(CH_2)_2NH–$, $–(CH_2)_2N(Me)CH_2–$, $–(CH_2)_2N(CH_2$-cyclopropyl$)CH_2–$, or $–(CH_2)_2NHCH_2–$. In some embodiments, L^1-R^1 is $–(CH_2)_4NH–$ or $–(CH_2)_3NH–$. In some embodiments, L^1-R^1 is:



[000251] In some embodiments, each R^3 is any suitable functional group described herein. In some embodiments each R^3 is independently halogen, -CN, $-(CH_2)_m$-$N(R^{3a})_2$-, $-OR^{3a}$, $-N(R^{3a})_2$, $-N(SO_2R^{3b})R^{3a}$, $-SR^{3a}$, $-SO_2R^{3a}$, $-NR^{3a}$-$S(O)_2$-$(CH_2)_m$-R^{3a}, -NH-S(O)(NH)-R^{3a}, -NH-S(O)(NH)-$(CH_2)_m$-R^{3a}, $-NR^{3a}$-$S(O)_2$-$(CH_2)_m$-OR^{3b}, -NH-S(O)R^{3a}-$(CH_2)_m$-OR^{3b}, -NH-$S(O)_2$-R^{3c}, $-B(R^{3a})_3$, $-P(R^{3a})_3$, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8-membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl. In some embodiments, each R^3 is independently $-(CH_2)_m$-$N(R^{3a})_2$-, $-OR^{3a}$, $-N(R^{3a})_2$, $-N(SO_2R^{3b})R^{3a}$, $-SR^{3a}$, $-SO_2R^{3a}$, $-NR^{3a}$-$S(O)_2$-$(CH_2)_m$-R^{3a}, -NH-S(O)(NH)-R^{3a}, -NH-S(O)(NH)-$(CH_2)_m$-R^{3a}, $-NR^{3a}$-$S(O)_2$-$(CH_2)_m$-OR^{3b}, -NH-S(O)R^{3a}-$(CH_2)_m$-OR^{3b}, -NH-$S(O)_2$-R^{3c}, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8-membered heterocycle. In some embodiments, In some embodiments, each R^3 is independently $-NR^{3a}S(O)_2$-$(CH_2)_m$-OR^{3b} or $-NR^{3a}$-$S(O)_2$-$(CH_2)_m$-R^{3a}.

[000252] In some embodiments, each R^3 is independently halogen, -CN, $-OR^{3a}$, $-N(R^{3a})_2$, $-SR^{3a}$, $-SO_2R^{3a}$, -NH-S(O)(NH)-R^{3a}, -NH-$S(O)_2$-$(CH_2)_m$-R^{3a}, -NH-$S(O)_2$-$(CH_2)_m$-OR^{3b}, $-B(R^{3a})_3$, or $-P(R^{3a})_3$. In some embodiments, each R^3 is independently halogen, -CN, $-OR^{3a}$, $-N(R^{3a})_2$, $-SO_2R^{3a}$, or -NH-$S(O)_2$-$(CH_2)_m$-OR^{3b}. In some embodiments, each R^3 is $-SO_2R^{3a}$ or -NH-$S(O)_2$-$(CH_2)_m$-OR^{3b}. In some embodiments, each R^3 is $-SO_2R^{3a}$. In some embodiments, each R^3 is independently -NH-$S(O)_2$-$(CH_2)_m$-OR^{3b}. In some embodiments, an R^3 is a point of attachment to G.

[000253] In some embodiments, wherein R^3 is optionally substituted 5- to 8- membered heterocycle, which is optionally substituted with one or more substituents selected from oxo, methyl, ethyl, propyl, methoxy, or ethoxy. In some embodiments, wherein R^3 is optionally substituted 5- to 8- membered heterocycle, which is optionally substituted with one or more substituents selected from oxo, methyl, and methoxy. In some embodiments, the 5- to 8-

membered heterocycle is  ,  ,  , ,  ,  ,  , or  .

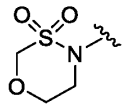
[000254] In some embodiments, each R^{3a} is independently hydrogen, -C(O)OR^{3b}, optionally substituted C_1-C_6 alkyl, or -N(R^{3b})$_2$. In some embodiments, each R^{3a} is independently hydrogen or C_1-C_6 alkyl. In some embodiments, each R^{3a} is independently hydrogen methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, or tert-butyl. In some embodiments, each R^{3a} is independently hydrogen, methyl, or ethyl, wherein the ethyl is optionally substituted with one or more substituents selected from methyl and -OH. In some embodiments, each R^{3a} is hydrogen. In some embodiments, each R^{3a} is independently C_1-C_6 alkyl. In some embodiments, R^{3a} is methyl.

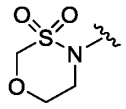
[000255] In some embodiments, R^{3b} is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, or optionally substituted C_3-C_6 cycloalkyl. In some embodiments, R^{3b} is hydrogen or C_1-C_6 alkyl. In some embodiments, R^{3b} is hydrogen. In some embodiments, R^{3b} is C_1-C_6 alkyl. In some embodiments, R^{3b} is hydrogen, methyl, ethyl, or propyl. In some embodiments, R^{3b} is methyl. In some embodiments, R^{3b} is ethyl. In some embodiments, R^{3b} is n-propyl or isopropyl. In some embodiments, R^{3b} is optionally substituted C_3-C_6 cycloalkyl. In some embodiments, R^{3b} is optionally substituted cyclopropyl. In some embodiments, R^{3b} is cyclopropyl optionally substituted with C_1-C_6 alkyl or C_1-C_6 hydroxyalkyl.

[000256] In some embodiments, R^{3b} is hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_2-C_6 alkenyl. In some embodiments, R^{3b} is hydrogen or C_1-C_6 alkyl. In some embodiments, R^{3b} is hydrogen. In some embodiments, R^{3b} is C_1-C_6 alkyl. In some embodiments, R^{3b} is hydrogen, methyl, ethyl, or propyl. In some embodiments, R^{3b} is methyl. In some embodiments, R^{3b} is ethyl. In some embodiments, R^{3b} is n-propyl or isopropyl.

[000257] IN some embodiments, R^{3c} is C_3-C_8 cycloalkyl or 3- to 8- membered heterocycle. In some embodiments, R^{3c} is C_3-C_8 cycloalkyl. In some embodiments, R^{3c} is 3- to 8- membered heterocycle. In some embodiments, 4- to 6- membered heterocycle. In some embodiments, R^{3c} is oxetanyl, azetidinyl, or thietanyl. In some embodiments, R^{3c} is oxetanyl or azetidinyl. In some embodiments, R^{3c} is oxetanyl.

[000258] In some embodiments, each R^3 is independently -NHSO$_2$(CH$_2$)$_2$OH, -NHSO$_2$C(CH$_3$)$_2$CH$_2$OH, -NHSO$_2$C(cyclopropyl)CH$_2$OH, -NHSO$_2$CH(CH$_3$)CH$_2$OH, -

$NMeSO_2(CH_2)_2OH$, $-NHSO_2CH_2CH_3$, $-NHSO_2CHCH_2$, $-NHSO_2$-oxetanyl, $-NMeSO_2CH_3$, $-N(SO_2Me)(CH_2)_2OH$, or  .

[000259] In some embodiments, each R^3 is independently $-NHSO_2(CH_2)_2OH$, $-NMeSO_2(CH_2)_2OH$, $-NHSO_2CH_2CH_3$, $-NHSO_2$-oxetanyl, $-NMeSO_2CH_3$, $-N(SO_2Me)(CH_2)_2OH$, or  .

[000260] In some embodiments, R^3 is $-SO_2R^{3a}$ and R^{3b} is methyl. In some embodiments, R^3 is $-NH\text{-}S(O)_2\text{-}(CH_2)_m\text{-}OR^{3b}$ and R^{3b} is hydrogen. In some embodiments, each R^3 is independently $-NHS(O)_2\text{-}(CH_2)_2\text{-}OH$.

[000261] In some embodiments, m is 1 to 6. In some embodiments, m is 1 to 4. In some embodiments, m is 1 to 3. In some embodiments, m is 1 to 2. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3. In some embodiments, m is 4.

[000262] In some embodiments, o is any suitable integer described herein. In some embodiments, o is 1 to 4. In some embodiments, o is 1 to 3. In some embodiments, o is 1 to 2. In some embodiments, o is 1. In some embodiments, o is 2. In some embodiments, o is 3. In some embodiments, o is 4.

[000263] In some embodiments, o is 1 and R^3 is $-SO_2R^{3a}$ or $-NH\text{-}S(O)_2\text{-}(CH_2)_m\text{-}OR^{3b}$.

[000264] In some embodiments, n is any suitable integer described herein. In some embodiments, n is 0 to 9. In some embodiments, n is 1 to 5. In some embodiments, n is 1 to 3. In some embodiments, n is 1 to 2. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4. In some embodiments, n is 5.

[000265] In some embodiments, R^4 is any suitable functional group described herein.

[000266] In some embodiments, each R^4 is independently halogen, -OH, -CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, two or more R^4 combine to form a C_3-C_8 cycloalkyl, or two R^4 combine to form a C_1-C_3 alkylene bridge, or two R^4 combine to form an oxo. In some embodiments, two R^4 combine to form a C_3-C_8 cycloalkyl. In some embodiments, two R^4 are on the same carbon atom. In some embodiments, the two R^4 groups combine to form a cyclopropyl. In some embodiments, the two R^4 groups combine to form a butyl. In some embodiments, two R^4 are on different carbon atoms. In some embodiments, two R^4 groups combine to form a (1R,5S)-8-azabicyclo[3.2.1]octane. In some embodiments, two R^4 combine to form a C_1-C_3 alkylene bridge. In some embodiments, n is 2 and two R^4 combine to form a C_3-C_8 cycloalkyl.

[000267] In some embodiments, each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, two or more R^4 combine to form a C_3-C_8 cycloalkyl, or two R^4 combine to form a C_1-C_3 alkylene bridge. In some embodiments, two R^4 combine to form a C_3-C_8 cycloalkyl. In some embodiments, two R^4 are on the same carbon atom. In some embodiments, the two R^4 groups combine to form a cyclopropyl. In some embodiments, the two R^4 groups combine to form a butyl. In some embodiments, two R^4 are on different carbon atoms. In some embodiments, two R^4 groups combine to form a (1R,5S)-8-azabicyclo[3.2.1]octane. In some embodiments, two R^4 combine to form a C_1-C_3 alkylene bridge. In some embodiments, n is 2 and two R^4 combine to form a C_3-C_8 cycloalkyl.

[000268] The composition described herein comprises compounds described herein which can interact or contact with the protein described herein when there is suitable adjacent distance between the compound and the protein to form an adduct. In some embodiments, the compounds described herein are adjacent to KIF18A.

[000269] The compounds described herein have structures which are useful for interacting with KIF18A to bind with it and form an adduct in the composition. For example, ring A can be sandwiched between the side chains of the KIF18A in the α4-helix and α6-helix location of the KIF18A. Aromatic rings which have a planar structure are useful for sandwiching between the α4-helix and α6-helix. Ring A can also be substituted with a diverse range of polar groups that can form hydrogen bonds that an interact with KIF18A. The linker G between ring A and ring B may be useful for keeping rings A and B in the same plane due to the carbonyl group allowing for delocalization of the aromatic rings. Ring B can interact against the flat surface of KIF18A α4-helix, and can also be useful for forming hydrogen bonds. Ring C can interact with hydrophobic KIF18 residues as a saturated cycloalkyl ring or a heterocycloalkyl ring. For example, ring C can interact with the hydrophobic residues within the α4-helix and α6-helix region of KIF18A. Additionally, if ring C is substituted with halogens, alkyls, or cycloalkyls, it can contact with a deeper layer of the hydrophobic side chains of the KIF18A β-sheet. The L^1-R^1 tether can be useful for interacting with the hydrophobic side chains of the KIF18A β-sheet region. Additionally, the L^1-R^1 tether can interact with KIF18A via hydrogen bonding in the α4-helix region. The L^1-R^1 tether region can weave through the α6-helix and β-sheet region of KIF18A and interact with the sidechains.

[000270] In some embodiments, ring A is adjacent to the KIF18A between the KIF18 α4-helix and α6-helix. In some embodiments, ring A is adjacent to the KIF18A between Leu285 residue and Tyr348 residue.

[000271] In some embodiments, ring B is adjacent to a flat surface of the KIF18A α4-helix. In some embodiments, ring B is adjacent to the KIF18A Gly289 residue or Asn293 residue. In some embodiments, ring B interacts with the KIF18A Asn293 residue via a hydrogen bond.

[000272] In some embodiments, ring C is adjacent to hydrophobic residues of the KIF18A. In some embodiments, the hydrophobic residues of the KIF18A are in α4-helix or α6-helix, or a combination thereof. In some embodiments, ring C is adjacent to the KIF18A Tyr112 residue, Leu284 residue, Leu288 residue, and Tyr348 residue. In some embodiments, ring C is adjacent to the KIF18A Leu110 residue, Leu259 residue, Met328 residue, or a combination thereof.

[000273] In some embodiments, L^1-R^1 is adjacent to the hydrophobic side chain of the KIF18A α6-helix and β-sheet. L^1-R^1 is adjacent to the Ala352 residue, Met328 residue, and Tyr112 residue of KIF18A. In some embodiments, L^1-R^1 is adjacent to the hydrophobic side chain of the KIF18A β-sheet. In some embodiments, L^1-R^1 is adjacent to the KIF18A Leu110 residue, Leu259 residue, and Met328 residue.

[000274] In some embodiments, R^1 interacts with the KIF18A α4-helix via a hydrogen bond. In some embodiments, R^1 interacts with the KIF18A Asn293 residue via the hydrogen bond.

[000275] In some embodiments, R^3 interacts with KIF18A via a hydrogen bond. In some embodiments, R^3 interacts with the KIF18A Ser262 residue via a hydrogen bond.

[000276] Provided in some embodiments herein is composition comprising a protein and a compound, wherein the protein is KIF18A, the compound is a compound of Formula (B), and the protein and the compound form an adduct, wherein structure of Formula (B) is a compound provided in Table 1.

Pharmaceutical Compositions

[000277] Provided in some embodiments herein is a pharmaceutical composition comprising a compound provided herein, or pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable excipient.

[000278] Provided in some embodiments herein is a method for preparing a pharmaceutical composition described herein. In some embodiments, the method comprises mixing a pharmaceutically acceptable carrier and a compound provided herein, or pharmaceutically acceptable salt or solvate thereof.

[000279] In some embodiments, the compounds described herein are formulated in oral dosage forms that include, by way of example only, tablets, powders, pills, dragees, capsules, liquids, gels, syrups, elixirs, slurries, suspensions and the like.

[000280] In some embodiments, pharmaceutical preparations for oral use are obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as: for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. In specific embodiments, disintegrating agents are optionally added. Disintegrating agents include, by way of example only, cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[000281] In one embodiment, dosage forms, such as dragee cores and tablets, are provided with one or more suitable coating. In specific embodiments, concentrated sugar solutions are used for coating the dosage form. The sugar solutions, optionally contain additional components, such as by way of example only, gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs and/or pigments are also optionally added to the coatings for identification purposes. Additionally, the dyestuffs and/or pigments are optionally utilized to characterize different combinations of active compound doses.

[000282] In some embodiments, therapeutically effective amounts of at least one of the compounds described herein are formulated into other oral dosage forms. Oral dosage forms include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In specific embodiments, push-fit capsules contain the active ingredients in admixture with one or more filler. Fillers include, by way of example only, lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In other embodiments, soft capsules, contain one or more active compound that is dissolved or suspended in a suitable liquid. Suitable liquids include, by way of example only, one or more fatty oil, liquid paraffin, or liquid polyethylene glycol. In addition, stabilizers are optionally added.

[000283] The pharmaceutically acceptable excipients in the pharmaceutical composition described herein can be any suitable pharmaceutically acceptable excipient. In some embodiments, the pharmaceutically acceptable excipient is sodium lauryl sulfate, partially pre-gelatinized maize starch, microcrystalline cellulose, sodium starch glycolate,

hydroxypropylcellulose LF, colloidal silicon dioxide, and magnesium stearate. In some embodiments, the sodium lauryl sulfate is Kolliphore SLS fine, the partially pre-gelatinized maize starch is Starch 1500, the microcrystalline cellulose is Avicel PH 101, the sodium starch glycolate is type A, the hydroxypropyl cellulose LF is Klucel HPC LF, and the colloidal silicon dioxide is Aerosil Pharma 200.

Methods of Treatment

[000284] In some embodiments, a compound provided herein, or pharmaceutically acceptable salt or solvate thereof is used in a method for treating cancer.

[000285] Provided in some embodiments herein is a method for treating cancer in an individual, the method comprising administering to the individual a compound provided herein or pharmaceutically acceptable salt or solvate thereof.

[000286] Provided in some embodiments is a method of inhibiting KIF18A, comprising forming an adduct by contacting KIF18A with any compound of Formula (B). The adduct can comprise any adduct described herein. In some embodiments, the adduct comprising a KIF18A and a compound as provided in Table 1.

[000287] Provided in some embodiments in a method of treating cancer in a patient by forming an adduct as described herein.

[000288] Cancer is often characterized by unregulated cell proliferation. Damage to one or more genes, responsible for the cellular pathways, which control progress of proliferation through the cell cycle and centrosome cycle, can cause the loss of normal regulation of cell proliferation. These deregulated genes can code for various tumor suppressor or oncogene proteins, which participate in a cascade of events, leading to unchecked cell-cycling progression and cell proliferation. Various kinase and kinesin proteins have been identified, which play key roles in cell cycle and mitotic regulation and progression of normal dividing cells and cancer cells.

[000289] In some embodiments, the cancer is mediated by KIF18A. In some embodiments, the cancer is mediated by a misregulation of KIF18A. In some embodiments, the cancer is treated by modulating KIF18A. In some embodiments, the cancer is treated by inhibiting KIF18A.

[000290] Provided in some embodiments herein is a method of inhibiting KIF18A with a compound provided herein, or pharmaceutically acceptable salt or solvate thereof. In some embodiments, the method comprises contacting KIF18A with the compound.

[000291] KIF18A belongs to the Kinesin-8 subfamily and is a plus-end directed motor protein. KIF18A is believed to influence dynamics at the plus end of kinetochore microtubules

to control correct chromosome positioning and spindle tension. Depletion of human KIF18A leads to longer spindles, increased chromosome oscillation at metaphase, and activation of the mitotic spindle assembly checkpoint in HeLa cervical cancer cells. KIF18A is overexpressed in various types of cancers, including but not limited to colon, breast, lung, pancreas, prostate, bladder, head, neck, cervix, and ovarian cancers. Further, genetic deletion or knockdown, or inhibition of KIF18A affects the mitotic spindle apparatus in cancer cell lines. Particularly, inhibition of KIF18A has been found to induce mitotic cell arrest, a known vulnerability that can promote cell death in mitosis via apoptosis, mitotic catastrophe, or multipolarity driven lethality or death after mitotic slippage in interphase.

[000292] In some embodiments, the cancer is (a) a solid or hematologically derived tumor selected from cancer of the bladder, endometrial, lung squamous cell, breast, colon, kidney, liver, lung, small cell lung cancer, esophagus, gall-bladder, brain, head and neck, ovary, pancreas, stomach, cervix, thyroid, prostate and skin, (b) a hematopoietic tumor of lymphoid lineage selected from leukemia, acute lymphocitic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma, (c) a hematopoietic tumor of myeloid lineage selected from acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia (d) a tumor of mesenchymal origin selected from fibrosarcoma and rhabdomyosarcoma, (e) a tumor of the central and peripheral nervous system selected from astrocytoma, neuroblastoma, glioma and schwannoma, or (f) a melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoacanthoma, thyroid follicular cancer or Kaposi's sarcoma.

[000293] In some embodiments, the cancer is bladder cancer, endometrial cancer, lung squamous cell cancer, breast cancer, colon cancer, kidney cancer, liver cancer, lung cancer, small cell lung cancer, esophagus cancer, gall-bladder cancer, brain cancer, head and neck cancer, ovarian cancer, pancreas cancer, stomach cancer, cervix cancer, thyroid cancer, prostate cancer or skin cancer. In some embodiments, the cancer is leukemia, acute lymphocitic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma or Burkett's lymphoma. In some embodiments, the cancer is acute and chronic myelogenous leukemias, myelodysplastic syndrome or promyelocytic leukemia. In some embodiments, the cancer is fibrosarcoma or rhabdomyosarcoma. In some embodiments, the cancer is melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoacanthoma, thyroid follicular cancer or Kaposi's sarcoma. In some embodiments, the cancer is melanoma,

prostate cancer, ovarian cancer, cervical cancer, breast cancer, colon cancer, sarcoma, or leukemia.

[000294] In treatment methods according to embodiments of the invention, an effective amount of at least one compound described herein is administered to a subject suffering from or diagnosed as having such a disease, disorder, or medical condition. Effective amounts or doses may be ascertained by methods such as modeling, dose escalation studies or clinical trials, *e.g.*, the mode or route of administration or drug delivery, the pharmacokinetics of the agent, the severity and course of the disease, disorder, or condition, the subject's previous or ongoing therapy, the subject's health status and response to drugs, and the judgment of the treating physician.

Definitions

[000295] Unless defined otherwise, all terms of art, notations and other technical and scientific terms or terminology used herein are intended to have the same meaning as is commonly understood by one of ordinary skill in the art to which the claimed subject matter pertains. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference, and the inclusion of such definitions herein should not necessarily be construed to represent a substantial difference over what is generally understood in the art.

[000296] Throughout this application, various embodiments may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the disclosure. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

[000297] As used herein and in the appended claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an agent" includes a plurality of such agents, and reference to "the cell" includes reference to one or more cells (or to a plurality of cells) and equivalents thereof known to those skilled in the art, and so forth. When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. The

term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, may "consist of" or "consist essentially of" the described features.

[000298] "Amino" refers to the $-NH_2$ radical.

[000299] "Cyano" refers to the -CN radical.

[000300] "Nitro" refers to the NO2 radical.

[000301] "Oxo" refers to the =O radical.

[000302] "Hydroxyl" refers to the -OH radical.

[000303] "Alkyl" generally refers to an acyclic (e.g., straight or branched) or cyclic hydrocarbon (e.g., chain) radical consisting solely of carbon and hydrogen atoms, such as having from one to fifteen carbon atoms (*e.g.*, C_1-C_{15} alkyl). Disclosures provided herein of an "alkyl" are intended to include independent recitations of a saturated "alkyl," unless otherwise stated. Alkyl groups described herein are generally monovalent, but may also be divalent (which may also be described herein as "alkylene" or "alkylenyl" groups). In certain embodiments, an alkyl comprises one to thirteen carbon atoms (*e.g.*, C_1-C_{13} alkyl). In certain embodiments, an alkyl comprises one to eight carbon atoms (*e.g.*, C_1-C_8 alkyl). In other embodiments, an alkyl comprises one to five carbon atoms (*e.g.*, C_1-C_5 alkyl). In other embodiments, an alkyl comprises one to four carbon atoms (*e.g.*, C_1-C_4 alkyl). In other embodiments, an alkyl comprises one to three carbon atoms (*e.g.*, C_1-C_3 alkyl). In other embodiments, an alkyl comprises one to two carbon atoms (*e.g.*, C_1-C_2 alkyl). In other embodiments, an alkyl comprises one carbon atom (*e.g.*, C_1 alkyl). In other embodiments, an alkyl comprises five to fifteen carbon atoms (*e.g.*, C_5-C_{15} alkyl). In other embodiments, an alkyl comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkyl). In other embodiments, an alkyl comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkyl). In other embodiments, an alkyl comprises three to five carbon atoms (*e.g.*, C_3-C_5 alkyl). In other embodiments, the alkyl group is selected from methyl, ethyl, 1-propyl (*n*-propyl), 1-methylethyl (*iso*-propyl), 1-butyl (*n*-butyl), 1-methylpropyl (*sec*-butyl), 2-methylpropyl (*iso*-butyl), 1,1-dimethylethyl (*tert*-butyl), 1-pentyl (*n*-pentyl). The alkyl is attached to the rest of the molecule by a single bond. In general, alkyl groups are each independently substituted or unsubstituted. In some

instances, an alkyl group provided herein is substituted or further substituted with one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, -OR^a, -SR^a, -$OC(O)$-R^a, -$N(R^a)_2$, -$C(O)R^a$, -$C(O)OR^a$, -$C(O)N(R^a)_2$, -$N(R^a)C(O)OR^a$, -$OC(O)$-$N(R^a)_2$, -$N(R^a)C(O)R^a$, -$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -$S(O)_tOR^a$ (where t is 1 or 2), -$S(O)_tR^a$ (where t is 1 or 2) and -$S(O)_tN(R^a)_2$ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, carbocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), carbocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl).

[000304] "Alkoxy" refers to a radical bonded through an oxygen atom of the formula –O-alkyl, where alkyl is an alkyl group as defined above.

[000305] "Aminoalkyl" refers to a radical bonded through a nitrogen atom of the formula –NH-alkyl, where alkyl is an alkyl group as defined above.

[000306] "Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon double bond, and having from two to twelve carbon atoms. In certain embodiments, an alkenyl comprises two to eight carbon atoms. In other embodiments, an alkenyl comprises two to four carbon atoms. The alkenyl is attached to the rest of the molecule by a single bond, for example, ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. Unless stated otherwise specifically in the specification, an alkenyl group provided herein is substituted or further substituted as described for "alkyl" hereinabove.

[000307] "Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon triple bond, having from two to twelve carbon atoms. In certain embodiments, an alkynyl comprises two to eight carbon atoms. In other embodiments, an alkynyl comprises two to six carbon atoms. In other embodiments, an alkynyl comprises two to four carbon atoms. The alkynyl is attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise specifically in the specification, an

alkynyl group provided herein is substituted or further substituted as described for "alkyl" hereinabove.

[000308] "Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing no unsaturation, and having from one to twelve carbon atoms, for example, methylene, ethylene, propylene, *n*-butylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group are through one carbon in the alkylene chain or through any two carbons within the chain. In certain embodiments, an alkylene comprises one to eight carbon atoms (*e.g.*, C_1-C_8 alkylene). In other embodiments, an alkylene comprises one to five carbon atoms (*e.g.*, C_1-C_5 alkylene). In other embodiments, an alkylene comprises one to four carbon atoms (*e.g.*, C_1-C_4 alkylene). In other embodiments, an alkylene comprises one to three carbon atoms (*e.g.*, C_1-C_3 alkylene). In other embodiments, an alkylene comprises one to two carbon atoms (*e.g.*, C_1-C_2 alkylene). In other embodiments, an alkylene comprises one carbon atom (*e.g.*, C_1 alkylene). In other embodiments, an alkylene comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkylene). In other embodiments, an alkylene comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkylene). In other embodiments, an alkylene comprises three to five carbon atoms (*e.g.*, C_3-C_5 alkylene). Unless stated otherwise specifically in the specification, an alkylene chain is substituted or further substituted as described for "alkyl" hereinabove.

[000309] "Alkenylene" or "alkenylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one carbon-carbon double bond, and having from two to twelve carbon atoms. The alkenylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. In certain embodiments, an alkenylene comprises two to eight carbon atoms (*e.g.*, C_2-C_8 alkenylene). In other embodiments, an alkenylene comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkenylene). In other embodiments, an alkenylene comprises two to four carbon atoms (*e.g.*, C_2-C_4 alkenylene). In other embodiments, an alkenylene comprises two to three carbon atoms (*e.g.*, C_2-C_3 alkenylene). In other embodiments, an alkenylene comprises two carbon atoms (*e.g.*, C_2 alkenylene). In other embodiments, an alkenylene comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkenylene). In other embodiments, an alkenylene comprises three to five carbon atoms (*e.g.*, C_3-C_5 alkenylene). Unless stated specifically otherwise in the specification, the alkenylene is substituted or further substituted as described for "alkyl" hereinabove.

[000310] "Alkynylene" or "alkynylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one carbon-carbon triple bond, and having from two to twelve carbon atoms. The alkynylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. In certain embodiments, an alkynylene comprises two to eight carbon atoms (*e.g.*, C_2-C_8 alkynylene). In other embodiments, an alkynylene comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkynylene). In other embodiments, an alkynylene comprises two to four carbon atoms (*e.g.*, C_2-C_4 alkynylene). In other embodiments, an alkynylene comprises two to three carbon atoms (*e.g.*, C_2-C_3 alkynylene). In other embodiments, an alkynylene comprises two carbon atoms (*e.g.*, C_2 alkynylene). In other embodiments, an alkynylene comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkynylene). In other embodiments, an alkynylene comprises three to five carbon atoms (*e.g.*, C_3-C_5 alkynylene). Unless stated specifically otherwise in the specification, the alkynylene is substituted or further substituted as described for "alkyl" hereinabove.

[000311] "Aryl" refers to a radical derived from an aromatic monocyclic or multicyclic hydrocarbon ring system by removing a hydrogen atom from a ring carbon atom. The aromatic monocyclic or multicyclic hydrocarbon ring system contains only hydrogen and carbon from five to eighteen carbon atoms, where at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. The ring system from which aryl groups are derived include, but are not limited to, groups such as benzene, fluorene, indane, indene, tetralin and naphthalene. In some instances, an aryl group provided herein is substituted or further substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, cycloalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), cycloalkylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally

substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[000312] "Aralkyl" or "aryl-alkyl" refers to a radical of the formula -R^c-aryl where R^c is an alkylene chain as defined above, for example, methylene, ethylene, and the like. Unless stated specifically otherwise in the specification, the alkylene chain part of the aralkyl radical is substituted or unsubstituted as described above for an alkylene chain. Unless stated specifically otherwise in the specification, the aryl part of the aralkyl radical is substituted or unsubstituted as described above for an aryl group.

[000313] "Carbocyclyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which includes fused or bridged ring systems, having from three to fifteen carbon atoms. In certain embodiments, a carbocyclyl comprises three to ten carbon atoms. In other embodiments, a carbocyclyl comprises five to seven carbon atoms. The carbocyclyl is attached to the rest of the molecule by a single bond. Carbocyclyl is saturated (*i.e.*, containing single C-C bonds only) or unsaturated (*i.e.*, containing one or more double bonds or triple bonds). A fully saturated carbocyclyl radical is also referred to as "cycloalkyl." Examples of monocyclic cycloalkyls include, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. An unsaturated carbocyclyl is also referred to as "cycloalkenyl." Examples of monocyclic cycloalkenyls include, *e.g.*, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Polycyclic carbocyclyl radicals include, for example, adamantyl, norbornyl (*i.e.*, bicyclo[2.2.1]heptanyl), norbornenyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. In some instances, a carbocyclyl group provided herein is substituted or further substituted with one or more substituents independently selected from optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, halo, oxo, thioxo, cyano, nitro, -R^b-OR^a, -R^b-OC(O)-R^a, -R^b-OC(O)-OR^a, -R^b-OC(O)-$N(R^a)_2$, -R^b-$N(R^a)_2$, -R^b-C(O)R^a, -R^b-C(O)OR^a, -R^b-C(O)$N(R^a)_2$, -R^b-O-R^c-C(O)$N(R^a)_2$, -R^b-$N(R^a)$C(O)OR^a, -R^b-$N(R^a)$C(O)R^a, -R^b-$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -R^b-$S(O)_tR^a$ (where t is 1 or 2), -R^b-$S(O)_tOR^a$ (where t is 1 or

2) and -R^b-$S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, cycloalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), cycloalkylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the R^a, R^b, or R^c substituents is unsubstituted unless otherwise indicated.

[000314] "Carbocyclylalkyl" refers to a radical of the formula –R^c-carbocyclyl where R^c is an alkylene chain as defined above. Unless stated specifically otherwise in the specification, the alkylene chain and the carbocyclyl radical are independently substituted or further substituted as defined hereinabove.

[000315] "Carbocyclylalkenyl" refers to a radical of the formula –R^c-carbocyclyl where R^c is an alkenylene chain as defined above. Unless stated specifically otherwise, the alkenylene chain and the carbocyclyl radical are independently substituted or further substituted as defined hereinabove.

[000316] "Carbocyclylalkoxy" refers to a radical bonded through an oxygen atom of the formula –O-R^c-carbocyclyl where R^c is an alkylene chain as defined above. Unless stated specifically otherwise, the alkylene chain and the carbocyclyl radical are independently substituted or further substituted as defined hereinabove.

[000317] "Halo" or "halogen" refers to fluoro, bromo, chloro, or iodo substituents.

[000318] "Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halogen radicals, as defined above, for example, trihalomethyl, dihalomethyl, halomethyl, and the like. In some embodiments, the haloalkyl is a fluoroalkyl, such as, for example, trifluoromethyl, difluoromethyl, fluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. In some embodiments, the alkyl part of the fluoroalkyl radical is substituted or further substituted as defined above for an alkyl group.

[000319] The term "heteroalkyl" refers to an alkyl group as defined above in which one or more skeletal carbon atoms of the alkyl are substituted with a heteroatom (with the appropriate

number of substituents or valencies – for example, -CH_2- may be replaced with -NH- or -O-). For example, each substituted carbon atom is independently substituted with a heteroatom, such as wherein the carbon is substituted with a nitrogen, oxygen, sulfur, or other suitable heteroatom. In some instances, each substituted carbon atom is independently substituted for an oxygen, nitrogen (e.g. -NH-, -N(alkyl)-, or -N(aryl)- or having another substituent contemplated herein), or sulfur (e.g. -S-, -S(=O)-, or -$S(=O)_2$-). In some embodiments, a heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In some embodiments, a heteroalkyl is attached to the rest of the molecule at a heteroatom of the heteroalkyl. In some embodiments, a heteroalkyl is a C_1-C_{18} heteroalkyl. In some embodiments, a heteroalkyl is a C_1-C_{12} heteroalkyl. In some embodiments, a heteroalkyl is a C_1-C_6 heteroalkyl. In some embodiments, a heteroalkyl is a C_1-C_4 heteroalkyl. In some embodiments, heteroalkyl includes alkylamino, alkylaminoalkyl, aminoalkyl, heterocycloalkyl, heterocycloalkyl, heterocyclyl, and heterocycloalkylalkyl, as defined herein. Unless stated otherwise specifically in the specification, heteroalkyl does not include alkoxy as defined herein. Unless stated specifically otherwise, a heteroalkyl group is substituted or further substituted as defined above for an alkyl group.

[000320] "Heteroalkylene" refers to a divalent heteroalkyl group defined above which links one part of the molecule to another part of the molecule. Unless stated specifically otherwise, a heteroalkylene is substituted or further substituted, as defined above for an alkyl group.

[000321] "Heterocyclyl" refers to a stable 3- to 18-membered non-aromatic ring radical that comprises two to twelve carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. Unless stated otherwise specifically in the specification, the heterocyclyl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which optionally includes fused or bridged ring systems. The heteroatoms in the heterocyclyl radical are optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heterocyclyl radical is partially or fully saturated. The heterocyclyl radical is saturated (*i.e.*, containing single C-C bonds only) or unsaturated (e.g., containing one or more double bonds or triple bonds in the ring system). In some instances, the heterocyclyl radical is saturated. In some instances, the heterocyclyl radical is saturated and substituted. In some instances, the heterocyclyl radical is unsaturated. Examples of such heterocyclyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl,

thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. In some instances, a heterocyclyl group is substituted or further substituted with one or more substituents selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, cycloalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), cycloalkylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[000322] "Heterocyclylalkyl" refers to a radical of the formula $-R^c$-heterocyclyl where R^c is an alkylene chain as defined above. If the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heterocyclylalkyl radical is optionally substituted as defined above for an alkylene chain. Unless stated specifically otherwise in the specification, the heterocyclyl part of the heterocyclylalkyl radical is substituted or further substituted as defined above for a heterocyclyl group.

[000323] "Heterocyclylalkoxy" refers to a radical bonded through an oxygen atom of the formula $-O-R^c$-heterocyclyl where R^c is an alkylene chain as defined above. If the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heterocyclylalkoxy radical is optionally

substituted as defined above for an alkylene chain. Unless stated specifically otherwise in the specification, the heterocyclyl part of the heterocyclylalkoxy radical is substituted or further substituted as defined above for a heterocyclyl group.

[000324] "Heteroaryl" or "aromatic heterocycle" refers to a radical derived from a 3- to 18-membered aromatic ring radical that comprises two to seventeen carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. As used herein, the heteroaryl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, wherein at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. Heteroaryl includes fused or bridged ring systems. The heteroatom(s) in the heteroaryl radical is optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl is attached to the rest of the molecule through any atom of the ring(s). Examples of heteroaryls include, but are not limited to, pyrazinone, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[d]thiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, benzo[b][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzothieno[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5,6-dihydrobenzo[h]cinnolinyl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, furo[3,2-c]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridinyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno[2,3-d]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-c]pyridazinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl,

triazinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, thieno[2,3-c]pridinyl, and thiophenyl (*i.e.* thienyl). In some instances, a heteroaryl group is substituted or further substituted with one or more substituents selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, cycloalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), cycloalkylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[000325] "Heteroarylalkyl" refers to a radical of the formula $-R^c$-heteroaryl, where R^c is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkyl radical is optionally substituted as defined above for an alkylene chain. Unless specifically stated otherwise in the specification, the heteroaryl part of the heteroarylalkyl radical is substituted or further substituted as defined above for a heteroaryl group.

[000326] "Heteroarylalkoxy" refers to a radical bonded through an oxygen atom of the formula $-O-R^c$-heteroaryl, where R^c is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkoxy radical is optionally substituted as

defined above for an alkylene chain. Unless specifically stated otherwise in the specification, the heteroaryl part of the heteroarylalkoxy radical is substituted or further substituted as defined above for a heteroaryl group.

[000327] "Adduct" refers to the combined product of two or more compounds and/or proteins to form a larger structure. For example, the adduct may comprise a protein and a compound described herein which forms a new singular structure. The protein and the compound may bind by protein-compound interactions which include, but are not limited to electrostatic interactions, van der Waals forces, hydrophobic interactions, hydrogen bonding, or covalent bonding.

[000328] "Adjacent" refers to being within a specific space and distance of a compound or protein. For example, a compound adjacent to a protein can be within a specific distance such as 20 angstroms or less, or 10 angstroms or less between the compound and protein. In some embodiments, a compound adjacent lies within a distance of about 1 to 6 Angstroms. In some embodiments, a compound adjacent lies within a distance of about 2 to 5 Angstroms. In some embodiments, a compound adjacent lies within a distance of about 3 to 5 Angstroms. In some embodiments, a compound adjacent lies within a distance of about 3 to 6 Angstroms.

[000329] In general, optionally substituted groups are each independently substituted or unsubstituted. Each recitation of a optionally substituted group provided herein, unless otherwise stated, includes an independent and explicit recitation of both an unsubstituted group and a substituted group (e.g., substituted in certain embodiments, and unsubstituted in certain other embodiments). In some instances, a substituted group provided herein (e.g., substituted alkyl) is substituted by one or more substituent, each substituent being independently selected from the group consisting of halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-OC(O)-N(R^a)_2$, $-N(R^a)C(O)R^a$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^a$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl (e.g., optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, carbocyclyl (e.g., optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), carbocyclylalkyl (e.g., optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (e.g., optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (e.g., optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (e.g., optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (e.g., optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (e.g., optionally substituted with halogen,

hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (e.g., optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl).

[000330] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

EXAMPLES

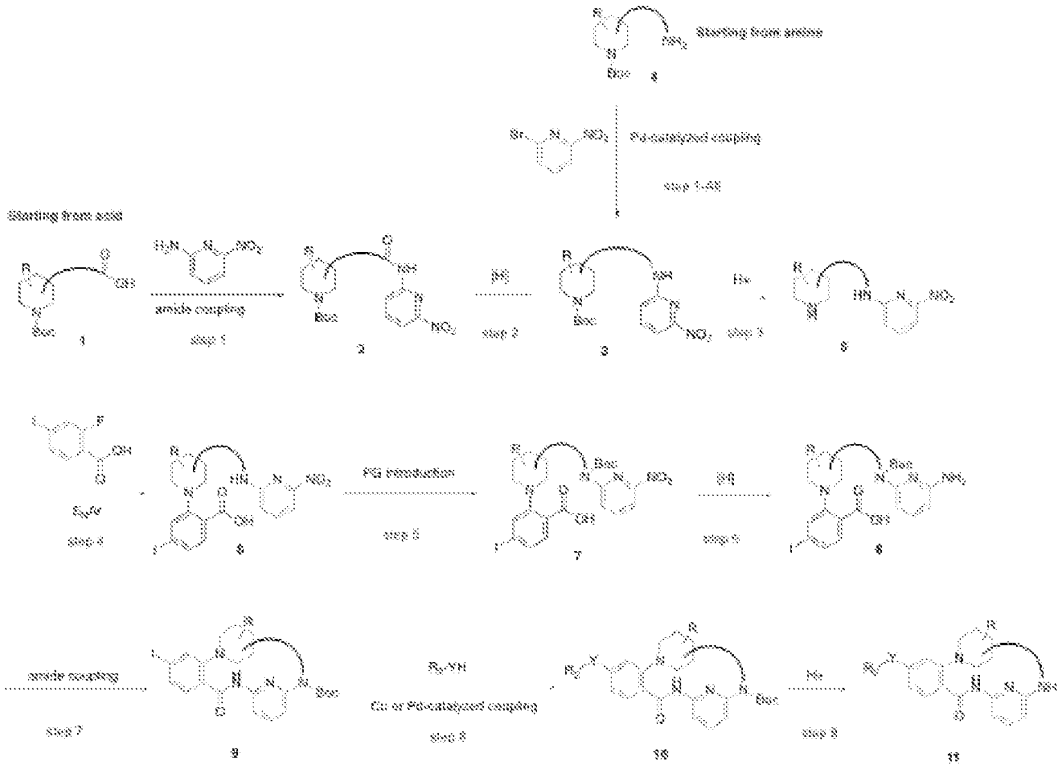
[000331] The following illustrative examples are representative of embodiments of the stimulation, systems, and methods described herein and are not meant to be limiting in any way.

General Synthesis

[000332] In some instances, a compound provided herein (e.g., a compound provided in Table 1) is synthesized as described herein.

General Synthetic Schemes

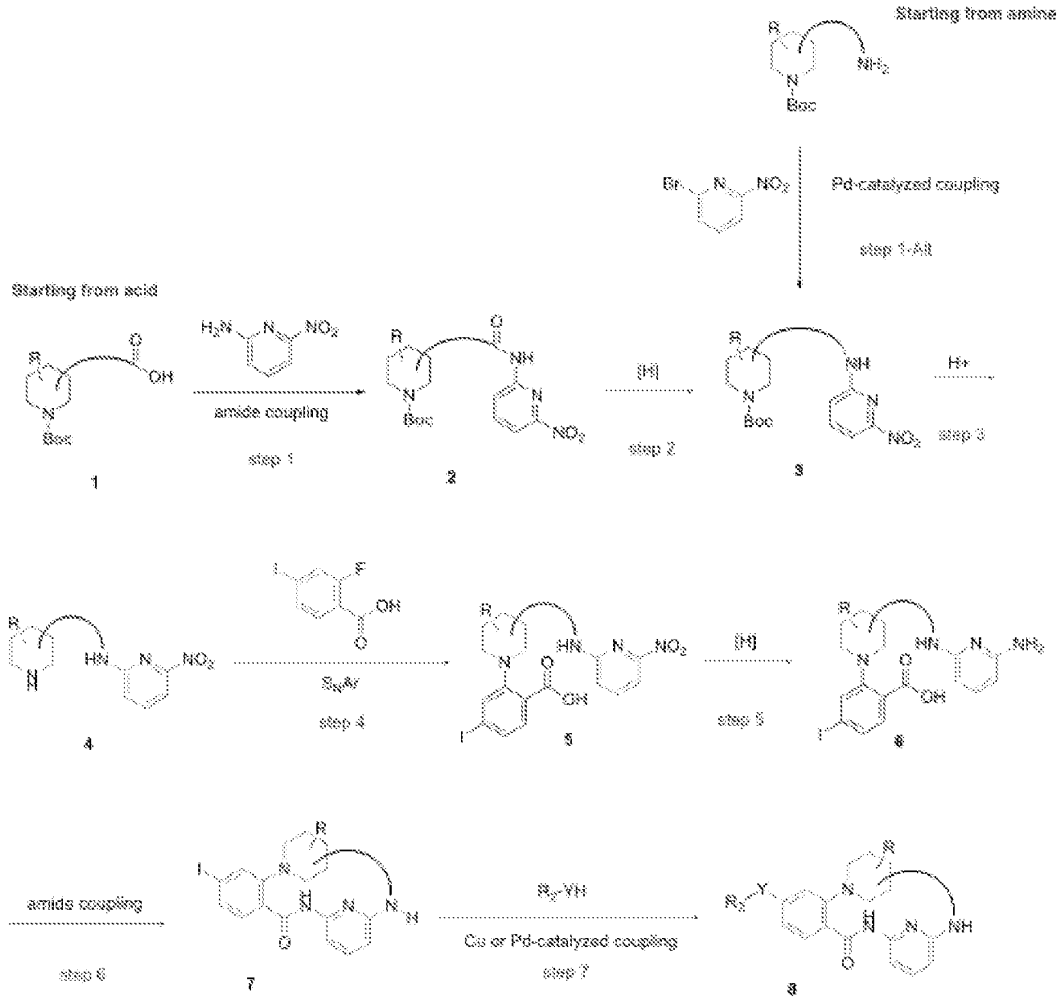
General synthetic route 1A



[000333] In this route key intermediate 3 can be obtained via two alternative approaches. In the first approach starting from acid 1 amide coupling with 6-nitropyridin-2-amine using either a coupling agent, such as HATU, or activating acid by transforming into acid chloride resulted in intermediate 2 which in turn was reduced to aniline 3. In second approach starting from amine 4 and 2-bromo-6-nitopyridine, Pd-catalyzed coupling using PEPPSI and base such as

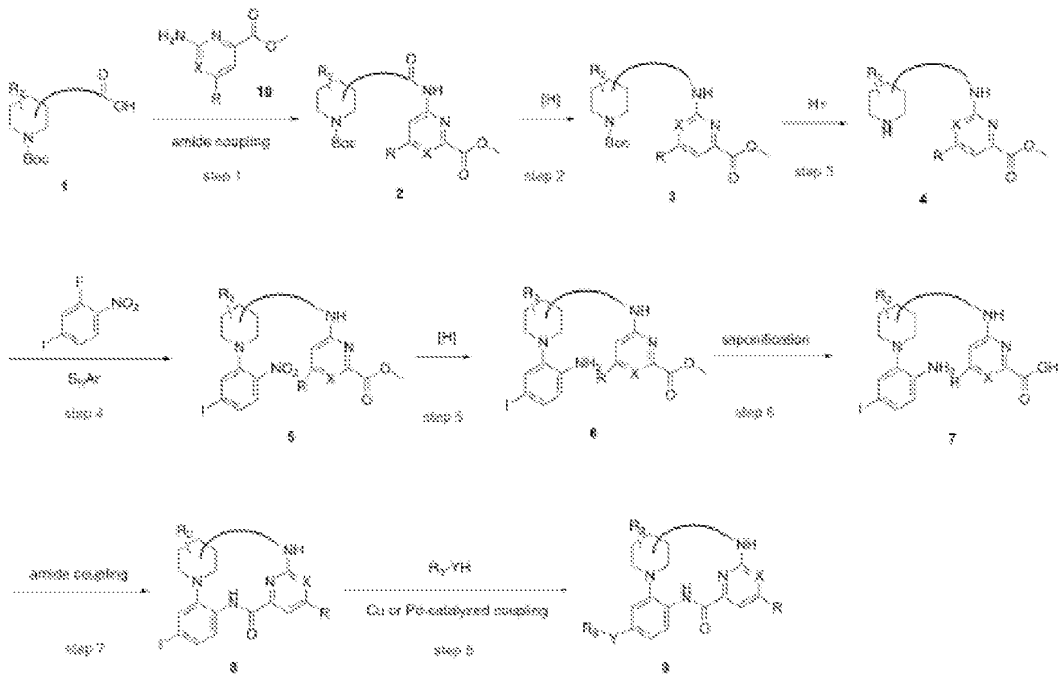
Cesium carbonate or similar reagents produced compound 3. After acid-promoted Boc-group removal compound 5 was produced and further underwent base- or heat-mediated S_NAr coupling with 2-fluoro-4-iodobenzoic acid to give 6. Boc protection of aniline nitrogen followed by iron-mediated nitro group reduction produced compound 8. Next, a macrocyclization via amide bond formation was forged by coupling agents such us T3P, HATU or other suitable agent. Finally, Cu-or Pd-catalyzed coupling with an appropriate nucleophile in Step 8 followed by acid-promoted Boc removal in Step 9 afforded compound 11.

General synthetic route 1B



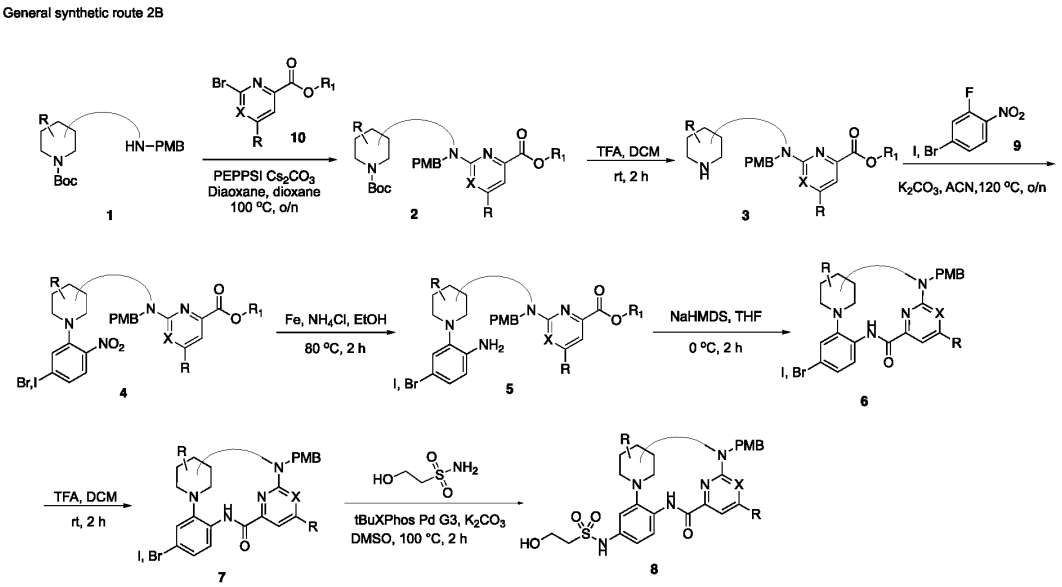
[000334] This route followed the same sequence of transformations as General synthetic route 1A with exception for omitting Boc protection and de-protection of the aniline nitrogen (Steps 5 and 9 in Route 1A).

General synthetic route 2A



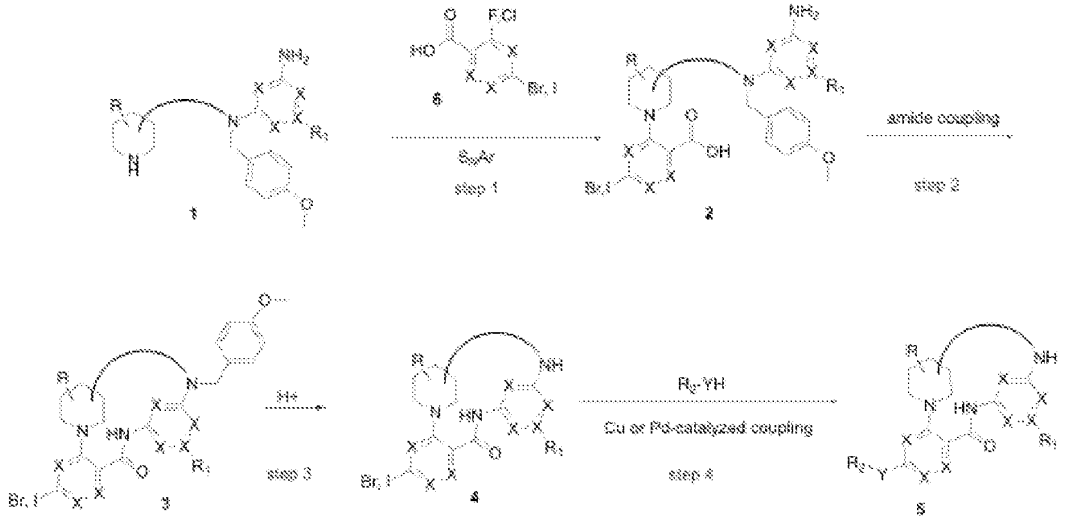
[000335] Acid 1 underwent HATU or other appropriate coupling agent mediated amide coupling with aniline 10 in Step 1 to produce 2. Reduction of amide functionality to aniline 3 followed by acid-catalyzed Boc-protecting group removal yielded intermediate 4. Subsequent S_NAr with 2-fluoro-4-iodo-1-nitrobenzene produced 5 and the nitro group reduction using iron gave intermediate 6. The ester was saponificated to carboxylic acid 7 which was subjected to amide coupling reagent such as HATU or similar agents to produce macrocycle 8. Cu- or Pd-catalyzed coupling afforded target compound 9.

General synthetic route 2B



[000336] Amine 1 and aryl halide 10 underwent base- or heat-mediated SNAr or, alternatively, Pd-catalyzed reaction in Step 1 to produce intermediate 2. Acid-catalyzed selective Boc removal following by base-catalyzed SNAr with fluoro arene 9 gave intermediate 4. Iron-mediated reduction of the nitro group afforded compound 5 which in turn underwent intramolecular amide bond formation facilitated by NaHMDS producing macrocyclic 6. Acid-catalyzed PMB protecting group removal in Step 6 followed by Cu-or Pd-catalyzed coupling in Step 7 with an appropriate nucleophile afforded compound 8.

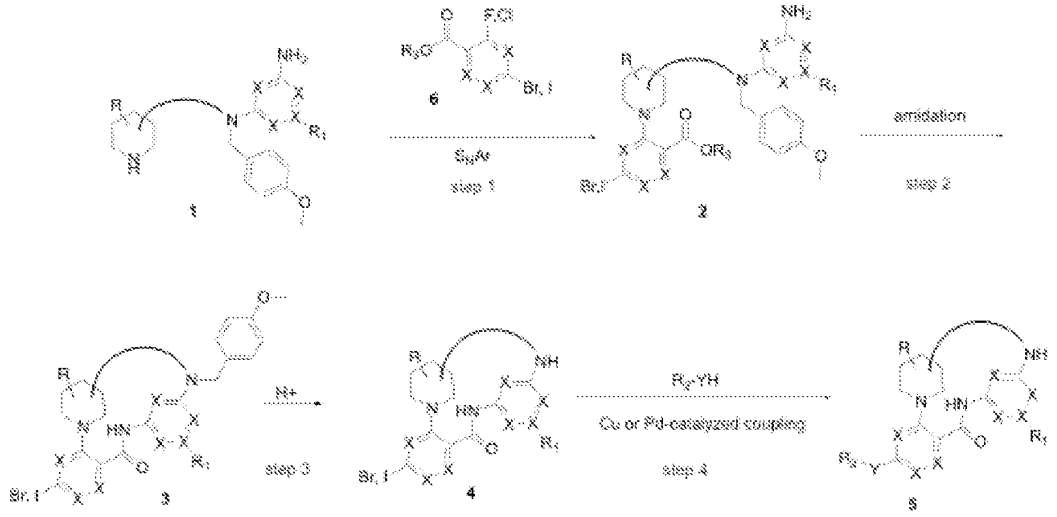
General synthetic route 3A



[000337] Intermediate 1 was employed in base-promoted S_NAr with aryl fluoride or aryl chloride 6 to afford intermediate 2. Intramolecular amide coupling utilizing HATU, TCFH or

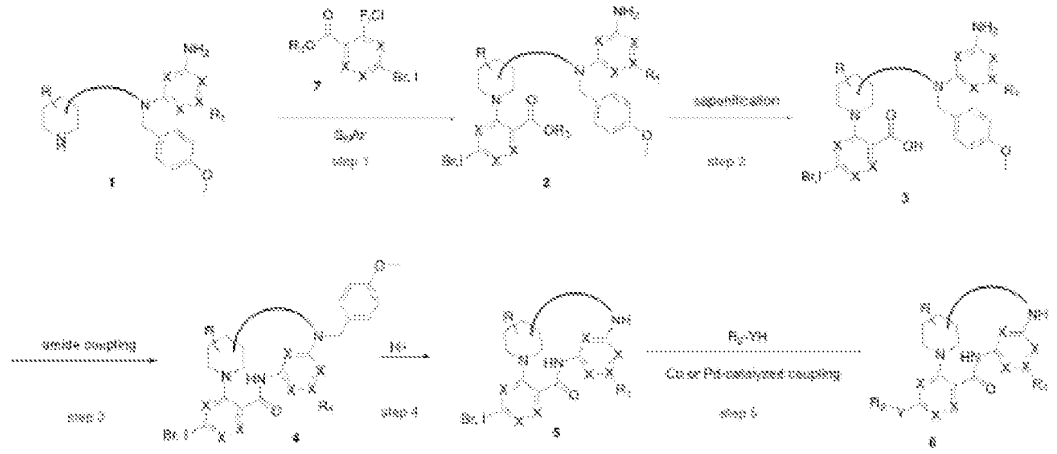
other suitable reagent gave macrocycle 3. Following that PMB group was removed under acidic conditions in Step 3 and Cu-or Pd-catalyzed coupling in Step 4 with an appropriate nucleophile afforded final compound 5.

General synthetic route 3B



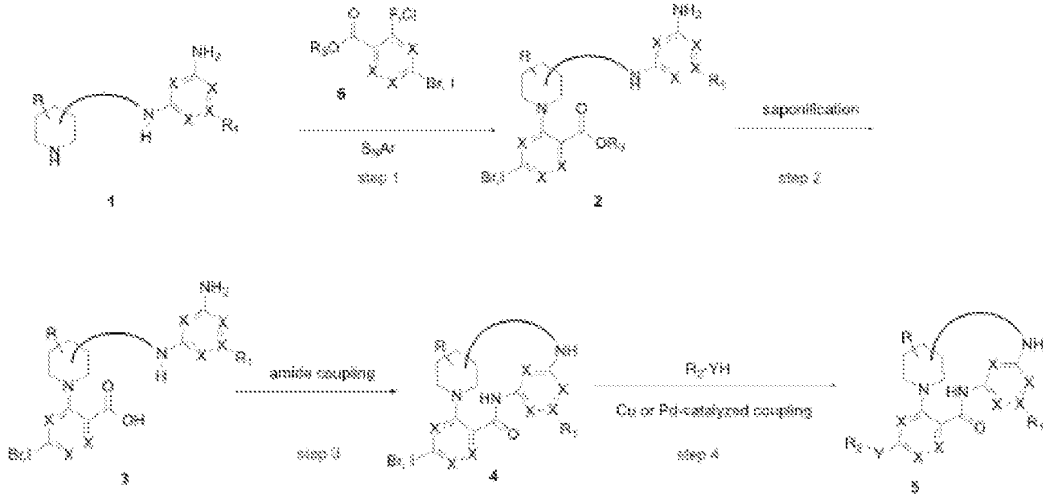
[000338] The route followed the same sequence of transformations as General synthetic route 3A with exception for Step 2 which in this route employed Lewis Acid-catalyzed transformation of an ester to an amid thus forging the macrocycle formation.

General synthetic route 3C



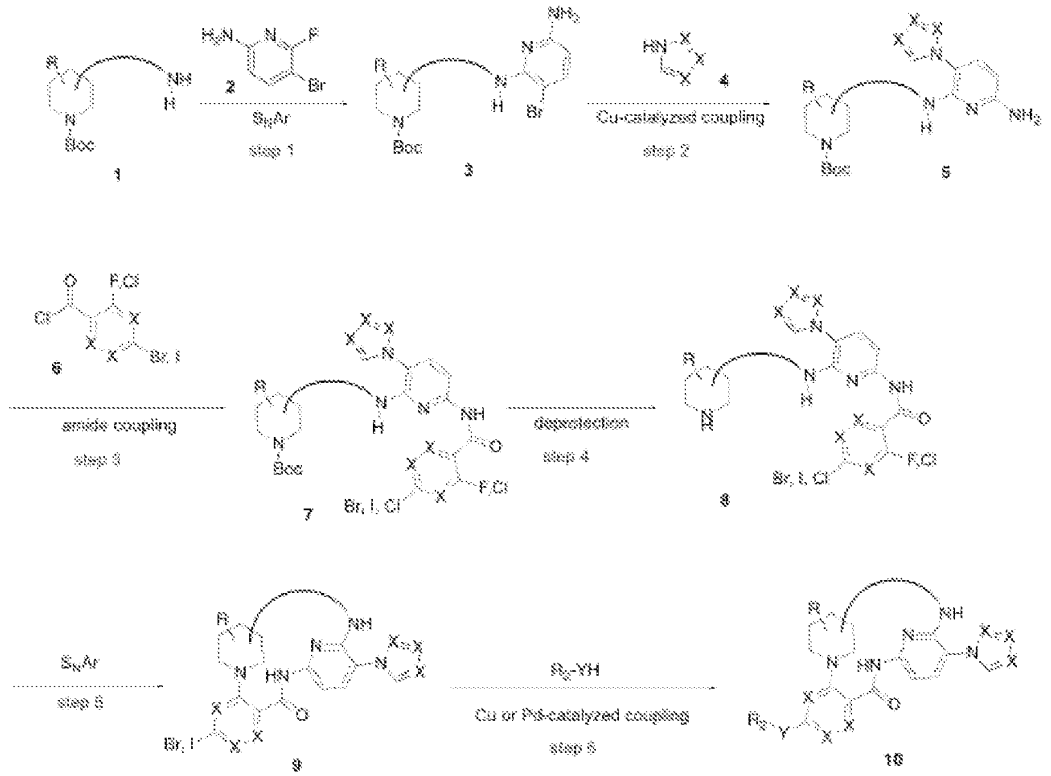
[000339] Intermediate 1 was employed in base-promoted S_NAr with aryl fluoride or aryl chloride 7 to afford intermediate 2. The ester group in 2 was hydrolyzed under basic conditions to produce acid 3. Intramolecular amide coupling utilizing HATU, TCFH or other suitable reagent gave macrocycle 4. Following that PMB group was removed under acidic conditions in Step 4 and Cu-or Pd-catalyzed coupling in Step 5 with an appropriate nucleophile afforded final compound 6.

General synthetic route 3D



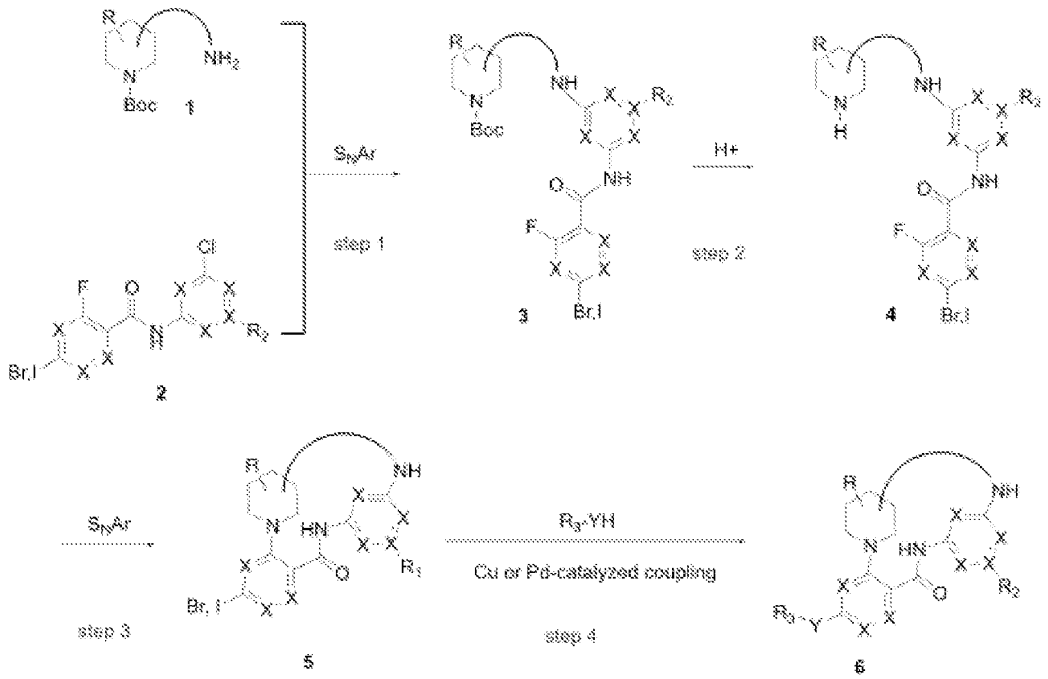
[000340] Intermediate 1 was employed in base-promoted S_NAr with aryl fluoride or aryl chloride 6 to afford intermediate 2. The ester group in 2 was hydrolyzed under basic conditions, such as LiOH in water-THF to produce acid 3. Intramolecular amide coupling utilizing HATU, TCFH or another suitable reagent gave macrocycle 4. Following that Cu-or Pd-catalyzed coupling in Step 5 with an appropriate nucleophile afforded final compound 5.

General synthetic route 3E



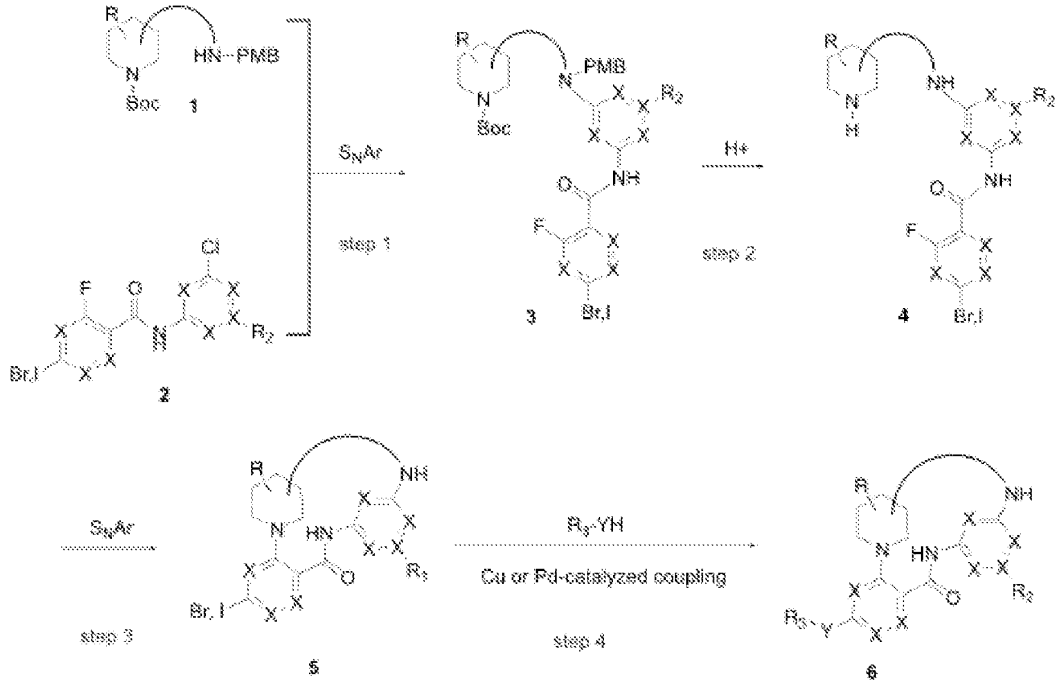
[000341] Intermediate 1 was employed in base-promoted S_NAr with aryl fluoride 2 to afford intermediate 3. Cu-catalyzed reaction with azole 4 resulted in intermediate 5 which was benzylated in with benzoyl chloride 6 to produce amide 7. Deprotection of amine, followed by intramolecular S_NAr produce macrocycle 9. Following that Cu-or Pd-catalyzed coupling in Step 6 with an appropriate nucleophile afforded final compound 10

General synthetic route 4A



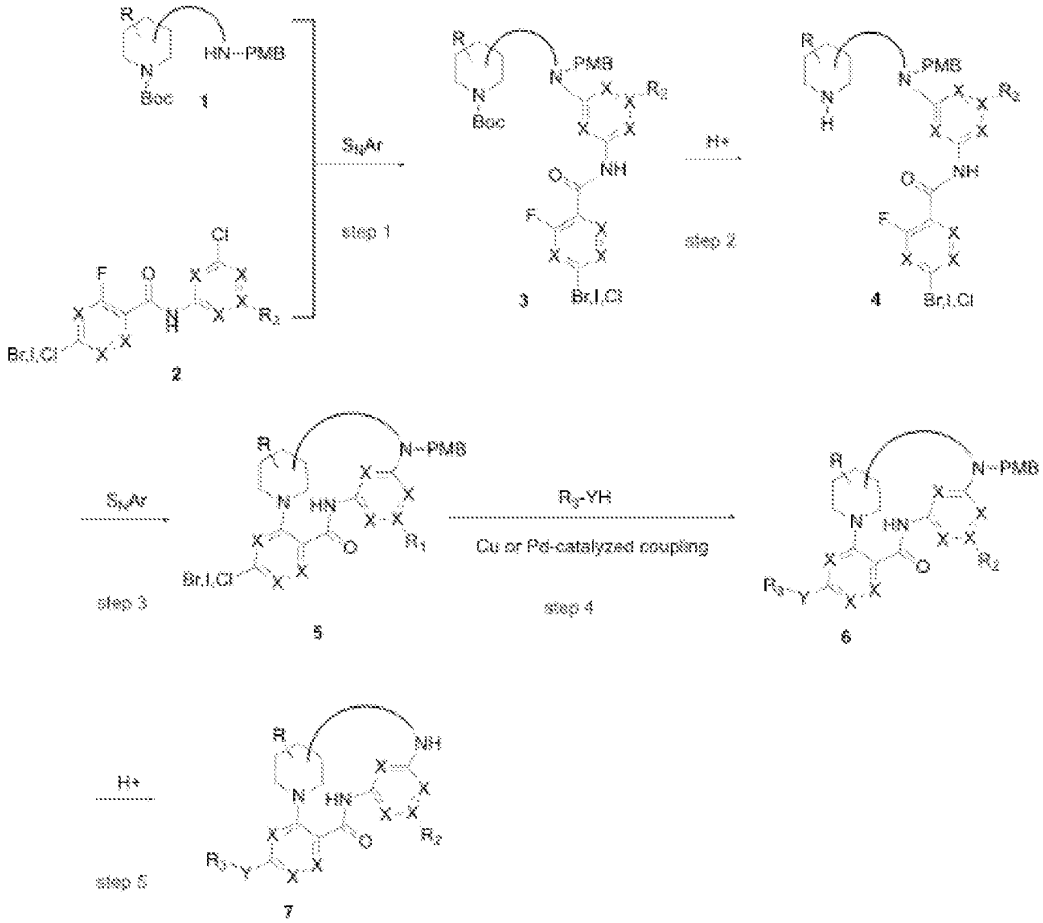
[000342] In Step 1 base- (such as KF and DIPEA) or heat-promoted S_NAr between amine 1 and intermediate 2 produced compound 3. Boc group was removed in step 2 under acidic conditions. For compound 4 intramolecular S_NAr, promoted by a base such as potassium carbonate in ACN or DMSO, was accomplished in Step 3 to produce macrocycle 5. Finally, Cu-or Pd-catalyzed coupling in Step 4 with an appropriate nucleophile afforded final compound 6.

General synthetic route 4B



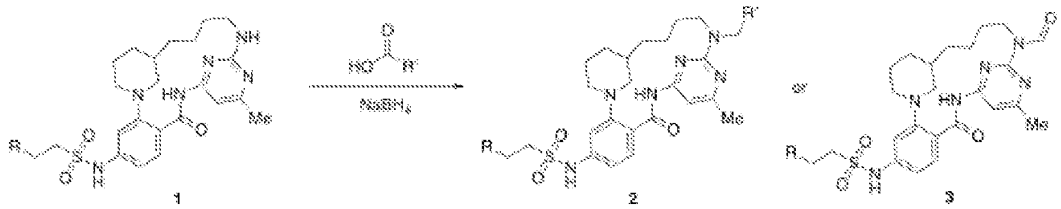
[000343] In Step 1 base-or heat-promoted S_NAr between amine 1 and intermediate 2 produced compound 3. Both PMB and Boc groups were removed in step 2 under acidic conditions. For compound 4 intramolecular S_NAr, promoted by a base such as potassium carbonate in ACN or DMS, was accomplished in Step 3 to produce macrocycle 5. Finally, Cu- or Pd-catalyzed coupling in Step 4 with an appropriate nucleophile afforded final compound 6.

General synthetic route 4C



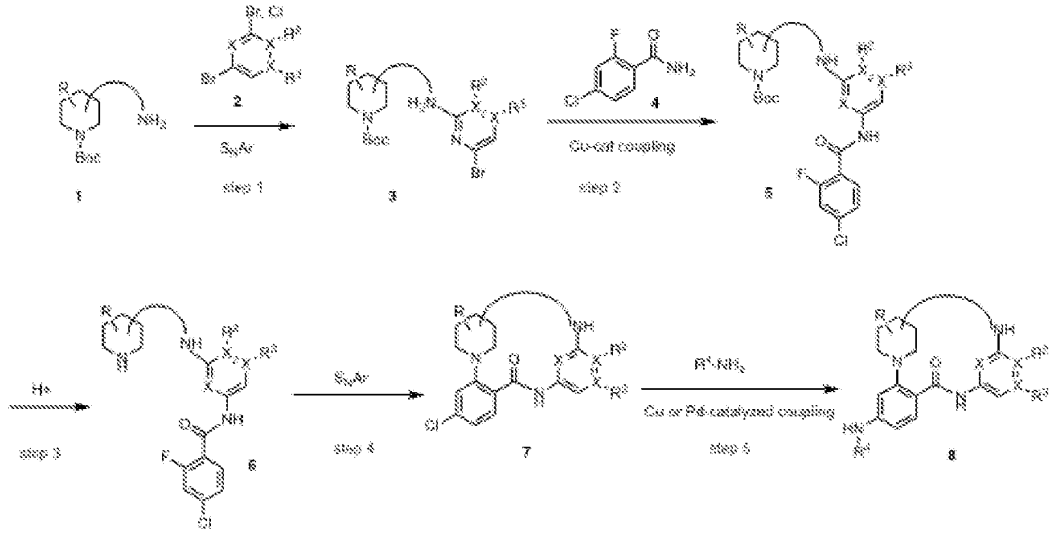
[000344] In Step 1 base-or heat-promoted S_NAr between amine 1 and intermediate 2 produced compound 3. Selective Boc group were removal in step 2 under mild acidic conditions furnished 4. Intramolecular S_NAr, promoted by a base such as potassium carbonate in ACN or DMSO, was accomplished in Step 3 to produce macrocycle 5. Cu-or Pd-catalyzed coupling in Step 4 with an appropriate nucleophile afforded compound 6. PMB group removal in Step 5 lead to final compound 7.

General synthetic route 5



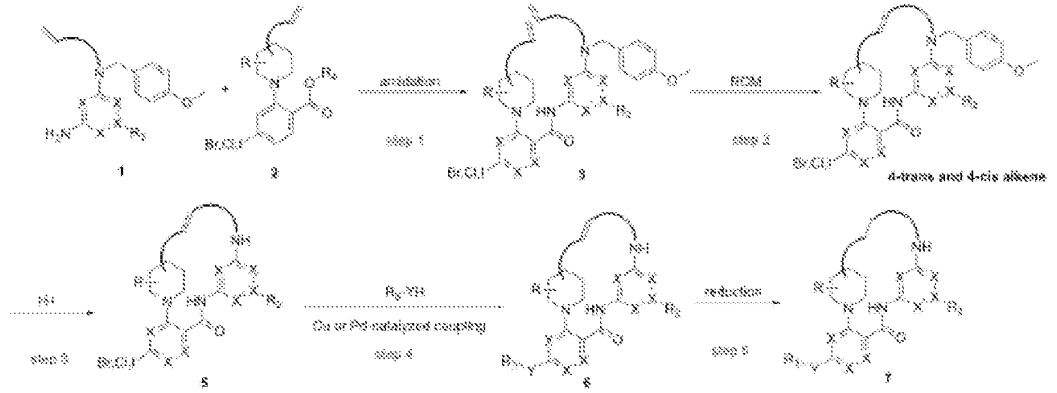
[000345] Fully elaborated compound 1 underwent one pot coupling/reduction sequence with a carboxylic acid in presence of sodium borohydride upon reflux in DCE to yield compound 2 or 3 (when formic acid was used).

General synthetic route 6



[000346] In Step 1 base-or heat-promoted S_NAr between amine 1 and aryl halide 2 produced compound 3. Benzamide 4 was incorporated via Cu-mediated coupling in Step 2. Following that Boc was removed under acidic conditions in Step 3. Compound 7 was prepared via intramolecular S_NAr, promoted by a base such as potassium carbonate in ACN or DMSO. Finally, Cu-or Pd-catalyzed coupling in Step 5 with an appropriate nucleophile afforded final compound 8.

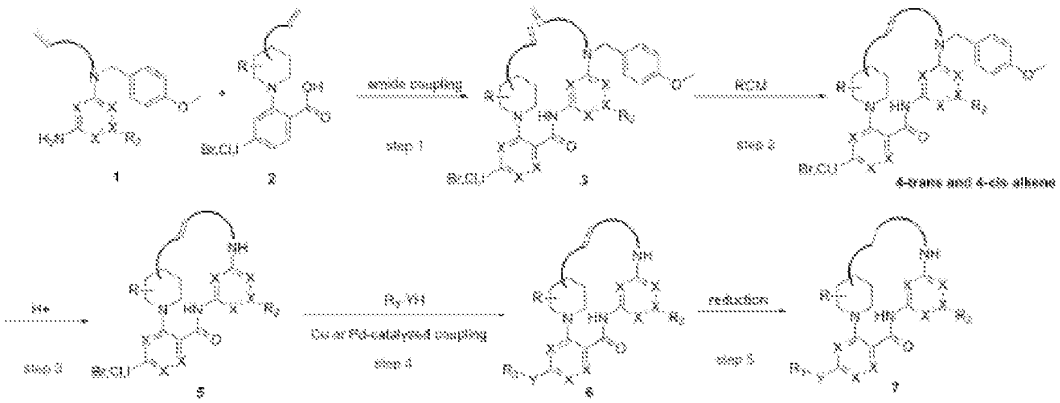
General synthetic route 7A



[000347] In Step 1 aniline 1 and ester 2 undergo base-(such as NaHMDS) or Lewis acid-(such as AlMe3) promoted amidation. Following that compound 3 is subjected to Grubbs or similar catalyst to promote macrocyclization via RCM (ring-closing metathesis) to produce a

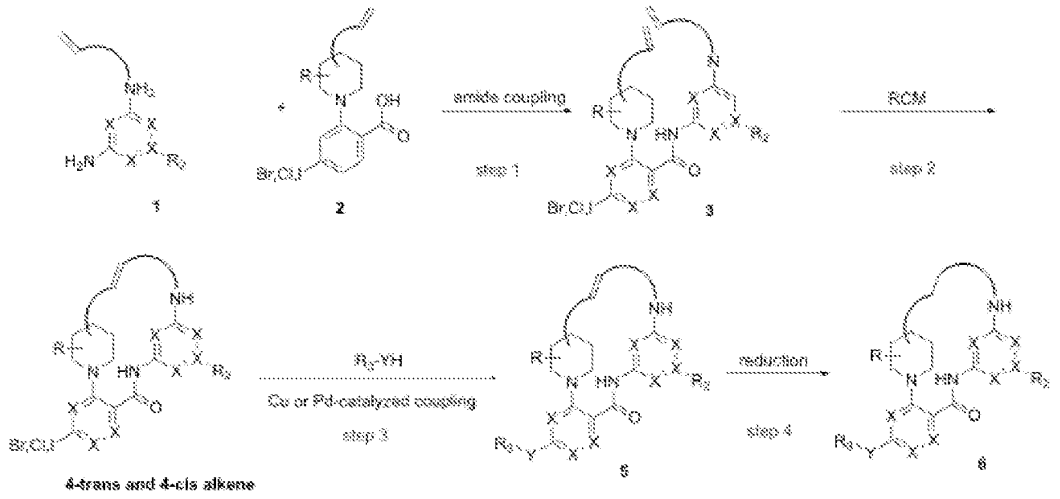
mixture of cis and trans isomers 4 (which can be separated at this step or carried forward and separated after step 4). Acid-catalyzed protecting group removal followed by Cu-or Pd-catalyzed coupling in Step 4 with an appropriate nucleophile afforded compound 6 which can be either 1) used as desired final compound or 2) further hydrogenated in step 5 using hydrogen (gas) over Pd/C or other appropriate reductant (such as tosylhydrazide) to reduce the olefine and produce final compound 7.

General synthetic route 7B



[000348] Same synthetic sequence was employed as in General synthetic route 7A except for in Step 1 amide coupling between aniline 1 and acid 2 was used.

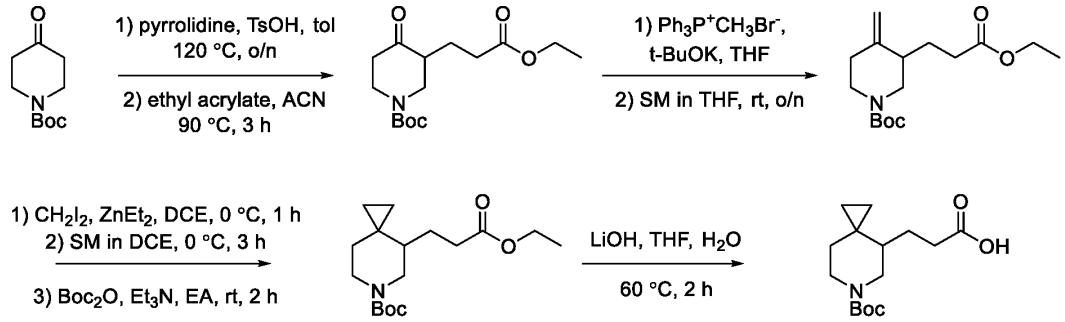
General synthetic route 8



[000349] In Step 1 aniline 1 and acid 2 undergo amide coupling utilizing HATU, TCFH, oxalyl chloride or other coupling agent. Following that compound 3 is subjected to Grubbs or similar catalyst to promote macrocyclization via RCM (ring-closing metathesis) to produce a mixture of cis and trans isomers 4 (which can be separated at this step or carried forward and separated after step 3). Cu-or Pd-catalyzed coupling in Step 4 with an appropriate nucleophile

afforded compound 5 which can be either 1) used as desired final compound or 2) further hydrogenated in step 4 using hydrogen (gas) over Pd/C or other appropriate reductant (such as tosylhydrazide) to reduce the olefine and produce final compound 6.

Intermediate A. 3-(6-(tert-butoxycarbonyl)-6-azaspiro[2.5]octan-4-yl)propanoic acid



Step 1: tert-butyl 3-(3-ethoxy-3-oxopropyl)-4-oxopiperidine-1-carboxylate

[000350] TsOH-H_2O (11.9 g, 62.7 mmol) was added to a mixture of tert-butyl 4-oxopiperidine-1-carboxylate (50 g, 250.9 mmol) and pyrrolidine (71.3 g, 1 mol) in toluene (600 mL). The resulting mixture was heated to 120°C and stirred overnight. After cooling to room temperature, the resulting mixture was concentrated under vacuum to afford the crude product. The residue was dissolved in MeCN (500 mL) and treated with ethyl acrylate (37.7 g, 376 mmol). The resulting mixture was heated to 90 °C and stirred at for 3 hours. After cooling to room temperature, the resulting mixture was concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with PE:EA = 9:1 to afford the desired product tert-butyl 3-(3-methoxy-3-oxopropyl)-4-oxopiperidine-1-carboxylate (20 g, 22.5% yield). LCMS (ESI-MS) m/z = 300.2 $[M+H]^+$.

Step 2: tert-butyl 3-(3-ethoxy-3-oxopropyl)-4-methylenepiperidine-1-carboxylate

[000351] Potassium tert-butoxide (22.5 g, 200 mmol) was added to mixture of methyltriphenylphosphonium bromide (71.6 g, 200 mmol) in THF (210 mL). The resulting mixture was stirred at 25 °C for 1 hour, followed by addition of a mixture of tert-butyl 3-(3-ethoxy-3-oxopropyl)-4-oxopiperidine-1-carboxylate (20 g, 66.8 mmol) in THF (100 mL). The resulting mixture was stirred at room temperature overnight, quenched by addition of water (500 mL) and extracted with EA (3 x 500 mL). The combined organic layers were washed with brine (3 x 1 L), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with PE:EA = 10:1 to afford the desired product tert-butyl 3-(3-ethoxy-3-oxopropyl)-4-methylenepiperidine-1-carboxylate (16 g, 80.5% yield). LCMS (ESI-MS) m/z = 298.2 $[M+H]^+$.

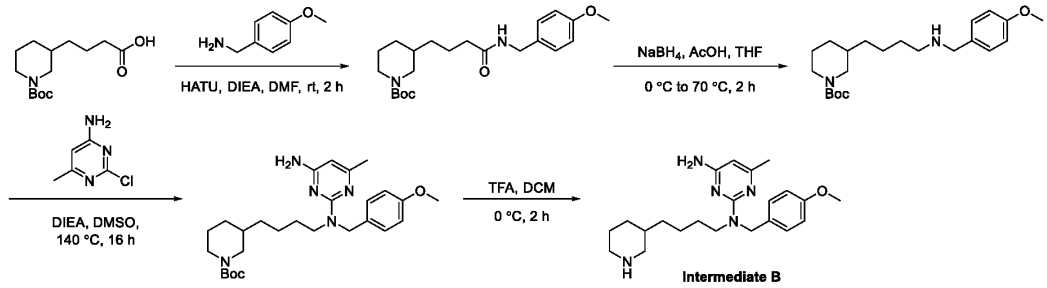
Step 3: tert-butyl 4-(3-ethoxy-3-oxopropyl)-6-azaspiro [2.5] octane-6-carboxylate

[000352] A solution of diethyl zinc in toluene (2 M, 100.1 mL, 200.2 mmol) was added to 1,2-dichloroethane (50 mL) followed by addition of diiodomethane (67.5 g, 252.2 mmol) slowly under nitrogen atmosphere. The resulting mixture was stirred at 0 °C for 1 hour. Then a mixture of tert-butyl 3-(3-ethoxy-3-oxopropyl)-4-methylenepiperidine-1-carboxylate (15 g, 50.4 mmol) in 1,2-dichloroethane (50 mL) was added to the reaction mixture above and the resulting mixture was stirred at room temperature overnight. Then Boc_2O (22.02 g, 100 mmol), Et_3N (20.42 g, 201.7mmol) and EA (100 mL) was added to the resulting mixture above and stirred at room temperature for 2 hours. The reaction mixture was quenched by the addition of water (200 mL) and filtered. The filter cake was washed with EA (3 x 100 mL). The resulting mixture was extracted with EA (2 x 200 mL). The combined organic layers (3 x 100 mL + 2 x 200 mL) were washed with brine (3 x 200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE:EA = 9:1 to afford a mixture of tert-butyl 4-(3-ethoxy-3-oxopropyl)-6-azaspiro[2.5]octane-6-carboxylate and tert-butyl 3-(3-ethoxy-3-oxopropyl)-4-methylidenepiperidine-1-carboxylate (8 g crude with 30% of desired product based on LCMS). LCMS (ESI-MS) m/z = 312.2 $[M+H]^+$.

Step 4: 3-(6-(tert-butoxycarbonyl)-6-azaspiro[2.5]octan-4-yl)propanoic acid

[000353] LiOH (3.7 g, 154.1 mmol) was added to tert-butyl 4-(3-ethoxy-3-oxopropyl)-6-azaspiro[2.5]octane-6-carboxylate (8 g crude, 30% purity based on LCMS) in water (40 mL) and THF (40 mL). The resulting mixture was stirred at 60°C for 2 hours. After removing THF under vacuum, the aqueous phase was acidified to pH 6 by addition of aqueous HCl (1 N). The resulting mixture was extracted with EA (3 x 80 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4, filtered and was concentrated under vacuum to afford a mixture of 3-(6-(tert-butoxycarbonyl)-6-azaspiro[2.5]octan-4-yl)propanoic acid and 3-(1-(tert-butoxycarbonyl)-4-methylenepiperidin-3-yl)propanoic acid, Intermediate A (7.5 g crude with 30% of desired product based on LCMS).

Intermediate B. N^2-(4-methoxybenzyl)-6-methyl-N^2-(4-(piperidin-3-yl)butyl)pyrimidine-2,4-diamine



Step 1: *tert*-butyl 3-(4-((4-methoxybenzyl)amino)-4-oxobutyl)piperidine-1-carboxylate

[000354] DIEA (8.72 g, 67.4 mmol) was added to a stirred mixture of 4-(1-(*tert*-butoxycarbonyl)piperidin-3-yl)butanoic acid (6.1 g, 22.5 mmol), (4-methoxyphenyl)methanamine (3.08 g, 22.5 mmol) and HATU (12.8 g, 33.7 mmol) in DMF (50 mL). The resulting mixture was stirred at room temperature for 2 hours, diluted with EA (500 ml) and washed with brine (3 x 500 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with EA:PE=1:1 to afford *tert*-butyl 3-(4-((4-methoxybenzyl)amino)-4-oxobutyl)piperidine-1-carboxylate (7.4 g, 84.2% yield). LCMS (ESI-MS) m/z = 391.2 $[M+H]^+$.

Step 2: *tert*-butyl 3-(4-((4-methoxybenzyl)amino)butyl)piperidine-1-carboxylate

[000355] $NaBH_4$ (1.74 g, 46.0 mmol) was added to a stirred mixture of *tert*-butyl 3-(4-((4-methoxybenzyl)amino)-4-oxobutyl)piperidine-1-carboxylate (6 g, 15.4 mmol) and AcOH (2.77 g, 46.0 mmol) in THF (60 mL) at 0 °C under nitrogen atmosphere. The resulting mixture was heated to 70 °C and stirred for 2 hours. After cooling to room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ and diluted with water (200 mL). The resulting mixture was extracted with EA (3 x 200 ml). The combined organic layers were dried over anhydrous sodium sulfate, concentrated under vacuum to afford a crude product. The residue was purified by silica gel column chromatography, eluted with EA:PE=3:2 to afford *tert*-butyl 3-(4-((4-methoxybenzyl)amino)butyl)piperidine-1-carboxylate (2.8 g, 48.4% yield). LCMS (ESI-MS) m/z = 377.2 $[M+H]^+$.

Step 3: *tert*-butyl 3-(4-((4-amino-6-methylpyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)piperidine-1-carboxylate

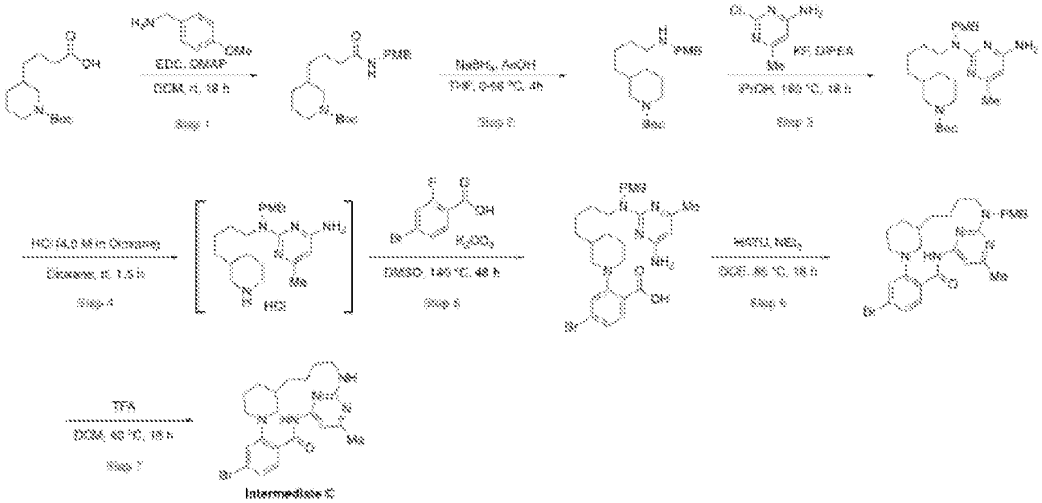
[000356] DIEA (3.84 g, 29.7 mmol) was added to a stirred mixture of *tert*-butyl 3-(4-((4-methoxybenzyl)amino)butyl)piperidine-1-carboxylate (2.8 g, 7.43 mmol) and 2-chloro-6-

methylpyrimidin-4-amine (1.71 g, 11.9 mmol) in DMSO (30 mL). The resulting mixture was heated to 140 °C and stirred for 16 hours. After cooling to room temperature, the resulting mixture was diluted with EA (500 ml) and washed with brine (3 x 500 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with EA:PE=1:3 to afford *tert*-butyl 3-(4-((4-amino-6-methylpyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)piperidine-1-carboxylate (1.7 g, 47.2% yield). LCMS (ESI-MS) m/z = 484.3 $[M+H]^+$.

Step 4: N^2-(4-methoxybenzyl)-6-methyl-N^2-(4-(piperidin-3-yl)butyl)pyrimidine-2,4-diamine

[000357] TFA (1 mL) was added to a stirred solution of *tert*-butyl 3-(4-((4-amino-6-methylpyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)piperidine-1-carboxylate (600 mg, 1.24 mmol) in DCM (10 mL). The resulting mixture was cooled to 0 °C and stirred for 2 hours. The reaction was quenched by addition of aqueous saturated $NaHCO_3$ (100 mL) and extracted with EA (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford a crude product N^2-(4-methoxybenzyl)-6-methyl-N^2-(4-(piperidin-3-yl)butyl)pyrimidine-2,4-diamine, Intermediate B (500 mg crude). The crude product was used for next step without purification. LCMS (ESI-MS) m/z = 384.4 $[M+H]^+$.

Intermediate C. 2-hydroxy-N-(3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphane-25-yl)ethane-1-sulfonamide



Step 1. 4-(1-(*tert*-butoxycarbonyl)piperidin-3-yl)butanoic acid

[000358] To a RBF with stir bar was added 4-(1-boc-piperidin-3-yl)butyric acid (2.00 g, 1 Eq, 7.37 mmol), 3-(((ethylimino)methylene)amino)-N,N-dimethylpropan-1-amine hydrochloride (2.12 g, 1.5 Eq, 11.1 mmol), DMAP (450 mg, 0.5 Eq, 3.69 mmol), DCM (80

mL), and Benzenemethanamine, 4-methoxy (1.21 g, 1.15 mL, 1.2 Eq, 8.84 mmol). The reaction mixture was then stirred at rt overnight. After 18 h, the reaction mixture was washed with sat. aq. NaHCO3 and water, then the aq. layer was extracted with DCM (3 x). The combined organic layers were washed with brine, dried over MgSO4, and concentrated. Purification via Isco column chromatography (0-100% EtOAc in heptane) provided tert-butyl 3-(4-((4-methoxybenzyl)amino)-4-oxobutyl)piperidine-1-carboxylate (2.857 g, 7.316 mmol, 99.3 %). LCMS M+1/Z = 391.1

[000359] 1H NMR (499 MHz, CHLOROFORM-d) δ ppm 7.16 - 7.23 (m, 2 H) 6.83 - 6.88 (m, 2 H) 5.70 (br s, 1 H) 4.36 (d, J=5.5 Hz, 2 H) 3.82 - 3.99 (m, 2 H) 3.79 (s, 3 H) 2.74 (ddd, J=13.1, 11.5, 3.0 Hz, 1 H) 2.43 (br s, 1 H) 2.17 (td, J=7.6, 2.1 Hz, 2 H) 1.59 - 1.87 (m, 4 H) 1.33 - 1.48 (m, 11 H) 1.15 - 1.29 (m, 2 H) 0.97 - 1.10 (m, 1 H).

Step 2. *tert*-butyl 3-(4-((4-methoxybenzyl)amino)-4-oxobutyl)piperidine-1-carboxylate

[000360] To a RBF was added tert-butyl 3-(4-((4-methoxybenzyl)amino)-4-oxobutyl)piperidine-1-carboxylate (1.85 g, 1 Eq, 4.74 mmol), NaBH4 (591 mg, 3.3 Eq, 15.6 mmol), and THF (20 mL). The reaction mixture was cooled to 0 °C stirred 5 min then acetic acid (939 mg, 894 µL, 3.3 Eq, 15.6 mmol) was added slowly. The reaction mixture was then warmed to 66 °C. After 4 h, the reaction mixture was cooled to rt, diluted with DCM, and quenched with aq. NaHCO3. The aq. layer was extracted with DCM (3 x), and the combined organic layers were washed with brine, dried over MgSO4, and concentrated. Purification via Isco column chromatography (0-10% MeOH in DCM with 1% TEA) provided tert-butyl 3-(4-((4-methoxybenzyl)amino)butyl)piperidine-1-carboxylate (1.283 g, 3.407 mmol, 71.9 %). LCMS M+1/Z = 377.2

Step 3. *tert*-butyl 3-(4-((4-amino-6-methylpyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)piperidine-1-carboxylate

[000361] To a vial was added tert-butyl 3-(4-((4-methoxybenzyl)amino)butyl)piperidine-1-carboxylate (2.0 g, 1 Eq, 5.3 mmol), 2-Chloro-6-methylpyrimidin-4-yl-amine (0.76 g, 1 Eq, 5.3 mmol), DIPEA (2.1 g, 2.8 mL, 3 Eq, 16 mmol), and dry Isopropanol (10.0 mL). The reaction mixture was then heated to 160 °C in a microwave reactor. After 18 h, the reaction mixture was concentrated and purified directly via Isco column chromatography (0-100% EtOAc in heptane) to provide tert-butyl 3-(4-((4-amino-6-methylpyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)piperidine-1-carboxylate (1.816 g, 3.755 mmol, 71 %). LCMS M+1/Z = 484.3. 1H NMR (499 MHz, CHLOROFORM-d) δ ppm 7.15 - 7.20 (m, 2 H) 6.79 - 6.84 (m, 2 H) 5.63 (s, 1 H) 4.79 (s, 2 H) 4.40 (br s, 2 H) 3.89 (br d, J=13.1 Hz, 2 H) 3.78 (s, 3

H) 3.40 - 3.52 (m, 2 H) 2.73 (br s, 1 H) 2.19 (s, 3 H) 1.77 (br dd, J=13.3, 3.4 Hz, 1 H) 1.49 - 1.65 (m, 7 H) 1.34 - 1.48 (m, 13 H).

Step 4. N^2-(4-methoxybenzyl)-6-methyl-N^2-(4-(piperidin-3-yl)butyl)pyrimidine-2,4-diamine hydrochloride

[000362] To a vial was added tert-butyl 3-(4-((4-amino-6-methylpyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)piperidine-1-carboxylate (310 mg, 1 Eq, 641 µmol), dioxane (4.0 mL), and Hydrogen chloride in dioxane (117 mg, 801 µL, 4.0 molar, 5 Eq, 3.20 mmol). The reaction mixture was stirred at rt. After 90 min the solvent was removed in vacuo and the crude material was used for the next step without further purification. LCMS M+1/Z = 384.2

Step 5. 2-(3-(4-((4-amino-6-methylpyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)piperidin-1-yl)-4-bromobenzoic acid

[000363] To the crude material from the previous step was added 4-bromo-2-fluorobenzoic acid (211 mg, 1.5 Eq, 961 µmol), K2CO3 (443 mg, 5 Eq, 3.20 mmol), DMSO (4.0 mL) were added. The reaction mixture was heated to 140 °C. After 48 h, the reaction mixture was diluted with EtOAc and washed with brine (5 x), dried over MgSO4, and concentrated. Purification via Isco column chromatography (0-10% MeOH in DCM) provided 2-(3-(4-((4-amino-6-methylpyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)piperidin-1-yl)-4-bromobenzoic acid (180 mg, 309 µmol, 48.2 % over 2 steps). LCMS M+1/Z = 582.2. 1H NMR (499 MHz, CHLOROFORM-d) δ ppm 8.15 (d, J=8.5 Hz, 1 H) 7.49 - 7.55 (m, 2 H) 7.13 - 7.20 (m, 2 H) 6.78 - 6.83 (m, 2 H) 5.62 (s, 1 H) 4.72 - 4.82 (m, 2 H) 4.43 (br s, 2 H) 3.77 (s, 3 H) 3.39 - 3.52 (m, 2 H) 2.95 - 3.10 (m, 2 H) 2.79 (br t, J=11.4 Hz, 1 H) 2.61 (s, 2 H) 2.40 - 2.54 (m, 1 H) 2.16 (s, 3 H) 1.87 - 1.95 (m, 2 H) 1.74 - 1.84 (m, 2 H) 1.53 (br dd, J=12.6, 6.3 Hz, 2 H) 1.18 - 1.32 (m, 4 H).

Step 6. 2^5-bromo-6-(4-methoxybenzyl)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one

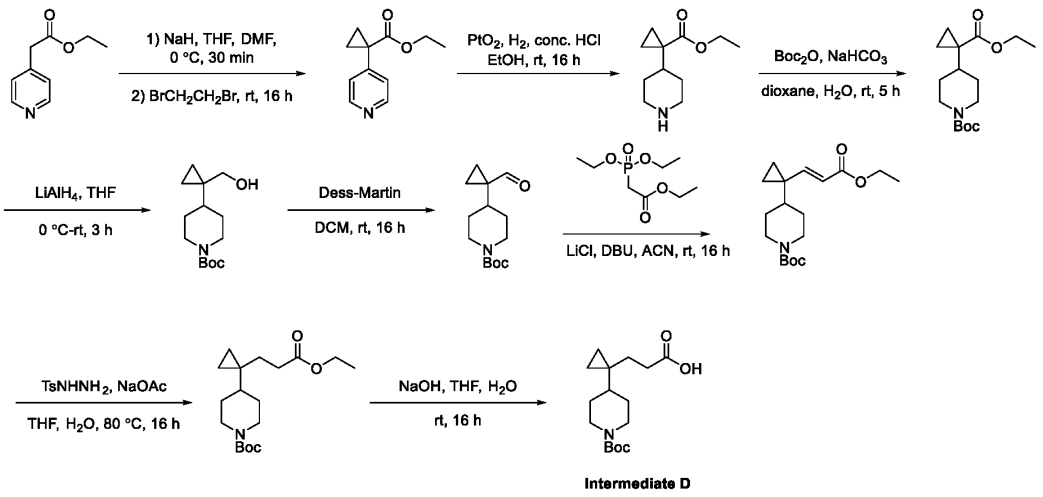
[000364] To a vial was added 2-(3-(4-((4-amino-6-methylpyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)piperidin-1-yl)-4-bromobenzoic acid (150 mg, 1 Eq, 257 µmol), triethylamine (104 mg, 144 µL, 4 Eq, 1.03 mmol), DCE (8.0 mL), and HATU (196 mg, 2 Eq, 515 µmol). The reaction mixture was then stirred at 85 °C. After 18 h, the reaction mixture was concentrated and purified directly via Isco column chromatography (0-50% EtOAc in heptane) to provide25-bromo-6-(4-methoxybenzyl)-56-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (50.5 mg, 89.5 µmol, 34.7 %). LCMS M+1/Z = 564.1. 1H NMR (499 MHz, CHLOROFORM-d) δ ppm 13.32 - 13.80 (m, 1 H) 11.98 - 12.47 (m, 1 H) 8.03 - 8.31 (m, 1 H) 7.47 (br d, J=5.7 Hz, 1 H) 7.32 - 7.41 (m, 1 H) 7.24 (d, J=8.5 Hz,

3 H) 6.84 (d, J=8.5 Hz, 2 H) 5.05 - 5.25 (m, 1 H) 4.84 (br d, J=17.2 Hz, 1 H) 4.41 - 4.59 (m, 1 H) 3.79 (s, 3 H) 2.84 - 3.84 (m, 2 H) 2.27 - 2.62 (m, 4 H) 2.04 - 2.20 (m, 1 H) 1.86 (br s, 2 H) 1.69 (br s, 2 H) 1.54 (s, 2 H) 0.85 - 1.58 (m, 5 H).

Step 7. 2^5-bromo-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one

[000365] To a solution of 25-bromo-6-(4-methoxybenzyl)-56-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (1.32 g, 1 Eq, 2.34 mmol) in DCM (4.0 mL) was added TFA (5.33 g, 3.60 mL, 20 Eq, 46.8 mmol). The reaction mixture was stirred at rt. After 18 hours, the reaction mixture was concentrated in vacuo and directly purified via Isco column chromatography (0-70% EtOAc in heptane) to provide 25-bromo-56-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one, Intermediate C (541 mg, 1.22 mmol, 52.1 %). LCMS M+1/Z = 444.0

Intermediate D. 3-(1-(1-(tert-butoxycarbonyl) piperidin-4-yl)cyclopropyl)propanoic acid



Intermediate D

Step 1. ethyl 1-(pyridin-4-yl)cyclopropane-1-carboxylate

[000366] NaH (60% in mineral oil, 7.26 g, 303 mmol) was added to a stirred mixture of ethyl 2-(pyridin-4-yl)acetate (10 g, 60.5 mmol) in DMF (100 mL) and THF (100 mL) at 0 °C. After stirring for 30 minutes, dibromoethane (34.1 g, 182 mmol) was added. The resulting mixture was stirred at room temperature for 16 hours, quenched by addition of saturated aqueous NH_4Cl (200 mL) and extracted with EA (2 x 200 mL). The combined organic layers were washed with brine (200 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified with silica gel column, eluted with EA:PE = 1:1 to afford the desired

product ethyl 1-(pyridin-4-yl)cyclopropane-1-carboxylate (8 g, 64.7%, yield). LCMS (ESI-MS) m/z =192.2 [M+H]+.

Step 2. ethyl 1-(piperidin-4-yl)cyclopropane-1-carboxylate

[000367] PtO_2 (0.95 g, 4.18 mmol) was added to a stirred mixture of ethyl 1-(pyridin-4-yl)cyclopropane-1-carboxylate (8 g, 41.8 mmol) and conc. HCl (5 mL, 165 mmol) in EtOH (100 mL) under nitrogen atmosphere. The resulting mixture stirred at room temperature for 16 hours under hydrogen atmosphere, filtered and the filtrate was concentrated under vacuum to afford the crude product ethyl 1-(piperidin-4-yl)cyclopropane-1-carboxylate (6.2 g crude). The crude product was used for next step without further purification. LCMS (ESI-MS) m/z = 198.2 $[M+H]^+$.

Step 3. tert-butyl 4-(1-(ethoxycarbonyl)cyclopropyl)piperidine-1-carboxylate

[000368] A solution of $NaHCO_3$ (7.92 g, 94.3 mmol) in water (50 mL) was added to a stirred mixture of ethyl 1-(piperidin-4-yl)cyclopropane-1-carboxylate (6.2 g, 31.4 mmol) and Boc_2O (6.86 g, 31.4 mmol) in dioxane (100 mL). The resulting mixture was stirred at room temperature for 5 hours, diluted with water (100 mL) and extracted with EA (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried with anhydrous Na2SO4, filtered and concentrated under vacuum to afford the crude product. The residue was purified with silica gel column, eluted with PE:EA = 3:1 to afford the desired product tert-butyl 4-(1-(ethoxycarbonyl)cyclopropyl)piperidine-1-carboxylate (4.2 g, 42.7% yield). LCMS (ESI-MS) m/z = 298.3 $[M+H]^+$.

Step 4. tert-butyl 4-(1-(hydroxymethyl)cyclopropyl)piperidine-1-carboxylate

[000369] $LiAlH_4$ (1.61 g, 42.4 mmol) was added to stirred mixture of tert-butyl 4-(1-(ethoxycarbonyl)cyclopropyl) piperidine-1-carboxylate (4.2 g, 14.1 mmol) in THF (80 mL) portionwise at 0 °C. The resulting mixture was stirred at room temperature for 3 hours, carefully quenched by addition of saturated aqueous NH_4Cl (50 mL) dropwise at 0 °C and then extracted with EA (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, evaporated to afford the crude product tert-butyl 4-(1-(hydroxymethyl)cyclopropyl)piperidine-1-carboxylate (3.2 g crude). The crude product was used for next step without further purification. LCMS (ESI-MS) m/z = 256.3 $[M+H]^+$.

Step 5. tert-butyl 4-(1-formylcyclopropyl)piperidine-1-carboxylate

[000370] Dess-Martin periodinane (11.5 g, 27.0 mmol) was added to a stirred mixture of tert-butyl 4-(1-(hydroxymethyl)cyclopropyl)piperidine-1-carboxylate (3.2 g, 13.5 mmol) in DCM

(60 mL). The resulting mixture was stirred at room temperature for 16 hours and concentrated directly under vacuum. The residue was purified with silica gel column, eluted with PE:EA = 1:1 to afford the desired product tert-butyl 4-(1-formylcyclopropyl)piperidine-1-carboxylate (3 g, 78.9% yield). LCMS (ESI-MS) m/z = 254.2 $[M+H]^+$.

Step 6. tert-butyl (E)-4-(1-(3-ethoxy-3-oxoprop-1-en-1-yl)cyclopropyl)piperidine-1-carboxylate

[000371] LiCl (0.65 g, 15.4 mmol) and DBU (5.00 g, 32.8 mmol) was added to a stirred mixture of tert-butyl 4-(1-formylcyclopropyl)piperidine-1-carboxylate (2.6 g, 10.3 mmol) and triethyl phosphonoacetate (2.76 g, 12.6 mmol) in MeCN (50 mL). The resulting mixture was stirred at room temperature for 16 hours and concentrated under vacuum. The residue was purified with silica gel column, eluted with PE:EA = 1:1 to afford the desired product tert-butyl (E)-4-(1-(3-ethoxy-3-oxoprop-1-en-1-yl)cyclopropyl)piperidine-1-carboxylate (2.4 g, 67.9% yield). LCMS (ESI-MS) m/z = 324.2 $[M+H]^+$.

Step 7. tert-butyl 4-(1-(3-ethoxy-3-oxopropyl)cyclopropyl)piperidine-1-carboxylate

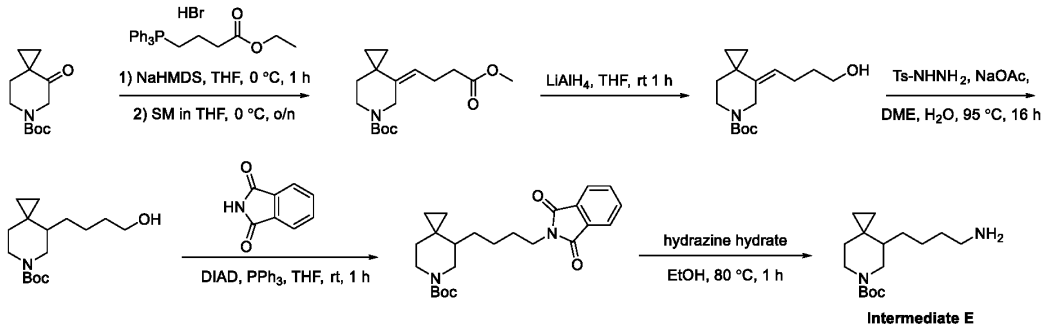
[000372] A solution of NaOAc (1.83 g, 22.3 mmol) in water (20 mL) was added to a stirred mixture of tert-butyl (E)-4-(1-(3-ethoxy-3-oxoprop-1-en-1-yl)cyclopropyl)piperidine-1-carboxylate (2.4 g, 7.42 mmol) and 4-toluenesulfonyl hydrazide (2.76 g, 14.8 mmol) in THF (20 mL). The resulting mixture was heated to 80 °C for 16 hours. After cooling to room temperature, the reaction mixture was diluted with water (50 mL) and extracted with EA (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product tert-butyl 4-(1-(3-ethoxy-3-oxopropyl)cyclopropyl)piperidine-1-carboxylate (2.4 g crude). The crude product was used for next step without further purification. LCMS (ESI-MS) m/z = 326.2 $[M+H]^+$.

Step 8. 3-(1-(1-(tert-butoxycarbonyl)piperidin-4-yl)cyclopropyl)propanoic acid

[000373] A solution of NaOH (0.88 g, 22.1 mmol) in water (40 mL) was added to stirred mixture of tert-butyl 4-(1-(3-ethoxy-3-oxopropyl)cyclopropyl)piperidine-1-carboxylate (2.4 g, 7.37 mmol) in THF (40 mL). The resulting mixture was stirred at room temperature for 16 hours and THF was evaporated off under vacuum. The PH value of the aqueous phase was adjusted to around 5~6 by addition of aqueous HCl (1 M). Then the resulting mixture was extracted with EA (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified with silica gel column, eluted with DCM:MeOH = 10:1 to afford the desired product

3-(1-(1-(tert-butoxycarbonyl) piperidin-4-yl)cyclopropyl)propanoic acid, Intermediate D (2.1 g, 91.8% yield). LCMS (ESI-MS) m/z = 298.3 $[M+H]^+$.

Intermediate E. tert-butyl 4-(4-aminobutyl)-6-azaspiro[2.5]octane-6-carboxylate



Step 1. tert-butyl (Z)-4-(4-ethoxy-4-oxobutylidene)-6-azaspiro[2.5]octane-6-carboxylate

[000374] A solution of 1M NaHMDS in THF (44.5 ml) was added to (4-ethoxy-4-oxobutyl)triphenylphosphanium bromide (20.3 g, 44.5 mmol) in THF (50 mL) under nitrogen atmosphere at 0°C. The mixture was stirred at 0°C for 1 hour. Tert-butyl 4-oxo-6-azaspiro[2.5]octane-6-carboxylate (5 g, 22.1 mmol) was added to the reaction mixture and the resulting solution was stirred at room temperature overnight. The reaction was quenched with sat. NH_4Cl (aq.) (100 mL) at room temperature. The resulting mixture was extracted with EA (3 x 100 mL). The combined organic layers were washed with brine (3 x 300 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/ EA (10:1) to afford tert-butyl (4Z)-4-(4-ethoxy-4-oxobutylidene)-6-azaspiro[2.5]octane-6-carboxylate(2 g, 27.8% yield). LCMS (ESI-MS) m/z = 223.2 $[M+H\text{-}Boc]^+$.

Step 2. tert-butyl (Z)-4-(4-hydroxybutylidene)-6-azaspiro[2.5]octane-6-carboxylate

[000375] $LiAlH_4$ (0.65 g, 17 mmol) was added to tert-butyl (4Z)-4-(4-ethoxy-4-oxobutylidene)-6-azaspiro[2.5]octane-6-carboxylate in THF (60 mL) under nitrogen atmosphere at 0°C. The reaction mixture was stirred at room temperature for 1 hour. The reaction was quenched with sat. NH_4Cl (aq.) (120mL) at 0°C. The resulting mixture was extracted with EA (3 x 300 mL). The combined organic layers were washed with brine (3x1 L), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford the crude product tert-butyl (Z)-4-(4-hydroxybutylidene)-6-azaspiro[2.5]octane-6-carboxylate(4.6 g crude). LCMS (ESI-MS) m/z = 282.2 $[M+H]^+$.

Step 3. tert-butyl 4-(4-hydroxybutyl)-6-azaspiro[2.5]octane-6-carboxylate

[000376] NaOAc (4 g, 49 mmol) in water (40 mL) was added to a mixture of tert-butyl (Z)-4-(4-hydroxybutylidene)-6-azaspiro[2.5]octane-6-carboxylate (4.6 g, 16.3 mmol) and $TsNHNH_2$ (18.3 g, 98 mmol) in DME (40 mL). The resulting mixture was heated to 95℃ and stirred for 16 h. The mixture was allowed to cool down to room temperature. The reaction was quenched with water (40 mL) at room temperature. The resulting mixture was extracted with EA (3 x 40mL). The combined organic layers were washed with brine (3 x 40 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (9:1) to afford tert-butyl 4-(4-hydroxybutyl)-6-azaspiro[2.5]octane-6-carboxylate (4.2 g, 90% yield). LCMS (ESI-MS) m/z = 284.2 $[M+H]^+$.

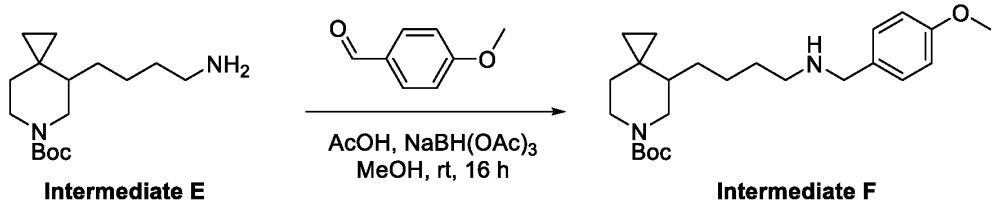
Step 4. tert-butyl 4-(4-(1,3-dioxoisoindolin-2-yl)butyl)-6-azaspiro[2.5]octane-6-carboxylate

[000377] DIAD (10.1 g, 50.2 mmol) was added to a mixture of tert-butyl 4-(4-hydroxybutyl)-6-azaspiro[2.5]octane-6-carboxylate (9.5 g, 33.5 mmol), phthalimide (5.4 g, 36.8 mmol) and PPh_3 (13.2 g, 50.3 mmol) in THF (100 mL) under nitrogen atmosphere at 0°C. The mixture was stirred at room temperature for 1 hour. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford tert-butyl 4-[4-(1,3-dioxoisoindol-2-yl)butyl]-6-azaspiro[2.5]octane-6-carboxylate (12 g, 82.4% yield). LCMS (ESI-MS) m/z = 413.2 $[M+H]^+$.

Step 5. tert-butyl 4-(4-aminobutyl)-6-azaspiro[2.5]octane-6-carboxylate

[000378] Hydrazine hydrate (0.61 g, 12.1 mmol) was added to a stirred mixture of tert-butyl 4-[4-(1,3-dioxoisoindol-2-yl)butyl]-6-azaspiro[2.5]octane-6-carboxylate (2 g, 4.85 mmol) in EtOH (30 mL) at rt. The resulting mixture was stirred heated to 80 °C and stirred for 1 hours. The resulting mixture was filtered. The filtrate was concentrated under reduced pressure to give the crude product (700 mg crude), intermediate E. The crude product was used in the next step directly without further purification. LCMS (ESI-MS) m/z = 283.2 $[M+H]^+$.

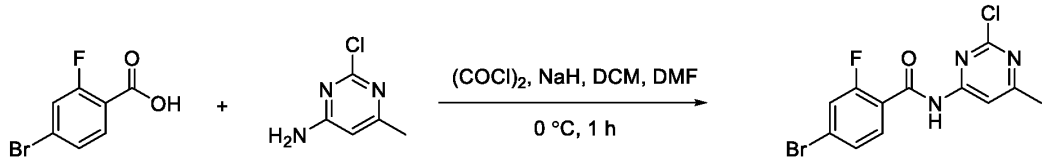
Intermediate F. *tert*-butyl 4-(4-((4-methoxybenzyl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate



Intermediate E Intermediate F

[000379] To a solution of Intermediate E (22.00 g, 77.898 mmol, 1.0 eq) in MeOH (220 mL) was added p-Anisaldehyde (11.14 g, 81.793 mol, 1.05 eq) and CH_3COOH (46.78 mg, 0.779 mmol, 0.01 eq). The reaction was stirred at 20 °C for 1 h, then STAB (41.27 g, 194.745 mmol, 2.5 eq) was added at 10 °C. The reaction was condensed under reduced pressure. The crude residue was added to NaOH aqueous solution (200 mL, 8% in water) and MTBE (200 mL), stirred well for 10 min, separated the solution, extracted the aqueous phase with MTBE (200 mL). Combined the organic phase, washed with saturated saline (50 mL), dried over $MgSO_4$, filtered and the filtrate was concentrated under vacuum. The crude residue was purified by silica gel flash chromatography (Heptane:THF=20:1~5:1~1:1) to afford *tert*-butyl 4-(4-((4-methoxybenzyl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate, Intermediate F (22.06 g, 54.798 mmol, 70.35% yield). LC-MS$[M+H]^+$=403.4. ^{1}HNMR ($CDCl_3$, 400 MHz) 6.86-7.28 (m, 4H), 3.77-4.05 (m, 6H), 2.60-3.14 (m, 7H), 1.79-2.01 (m, 1H), 1.22-1.65 (m, 14H), 0.58-0.95 (m, 2H), 0.20-0.41 (m, 4H).

Intermediate G. 4-bromo-*N*-(2-chloro-6-methylpyrimidin-4-yl)-2-fluorobenzamide

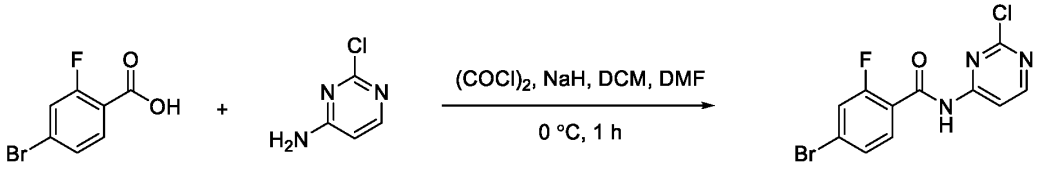


Intermediate G

[000380] $(COCl)_2$ (1.51 g, 11.9 mmol) was added to a stirred mixture of 4-bromo-2-fluorobenzoic acid (2 g, 9.13 mmol) in DCM (20 mL) at 0 °C, followed by addition of DMF (0.1 mL). After stirring for 1 hour, the reaction mixture was evaporated under vacuum and dissolved in DMF (5 mL). At the same time, NaH (60% in mineral oil, 280 mg, 11.9 mmol) was added to a stirred mixture of 2-chloro-6-methylpyrimidin-4-amine (1.31 g, 9.13 mmol) in DMF (20 mL) at 0 °C. After stirring for 1 hours, the former solution was added. The resulting mixture was stirred at 0 °C for 1 hours, quenched by addition of saturated aqueous NH_4Cl (20 mL) and extracted with EA (2 x 50 mL). The combined organic layers were washed with brine

(20 x 2mL), dried with anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified with silica gel column, eluted with EA:PE = 3:1 to afford the desired product 4-bromo-N-(2-chloro-6-methylpyrimidin-4-yl)-2-fluorobenzamide (1.3 g, 41.3 % yield). LCMS (ESI-MS) m/z = 344.1 $[M+H]^+$.

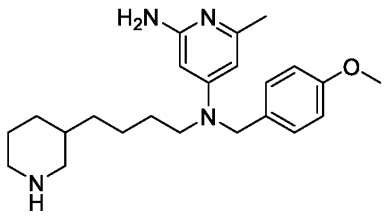
Intermediate H. 4-bromo-*N*-(2-chloropyrimidin-4-yl)-2-fluorobenzamide



Intermediate H

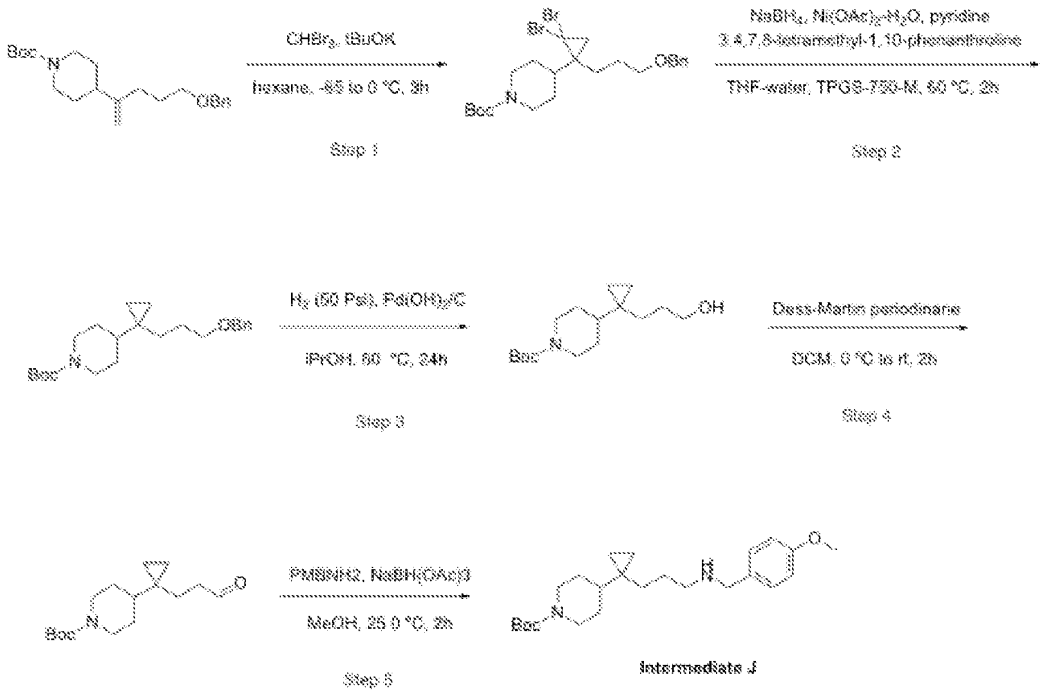
[000381] Intermediate H was synthesized via the same procedure as Intermediate G using 2-chloropyrimidin-4-amine in place of 2-chloro-6-methylpyrimidin-4-amine.

Intermediate I. N4-(4-methoxybenzyl)-6-methyl-N4-(4-(piperidin-3-yl)butyl)pyridine-2,4-diamine



[000382] Intermediate I was synthesized via the same procedure as Intermediate B using 4-chloro-6-methylpyridin-2-amine in place of 2-chlro-6-methylpyrimidin-4-amine in Step 3.

Intermediate J. *tert*-butyl 4-(1-(3-((4-methoxybenzyl)amino)propyl)cyclopropyl)piperidine-1-carboxylate



Step 1. tert-butyl 4-(1-(3-(benzyloxy)propyl)-2,2-dibromocyclopropyl)piperidine-1-carboxylate

[000383] In two batches to a solution of *tert*-butyl 4-(5-(benzyloxy)pent-1-en-2-yl)piperidine-1-carboxylate (90.0 g, 250 mmol, 1.00 *eq*) and t-BuOK (140 g, 1.25 mol, 5.00 *eq*) in hexane (900 mL) was slowly added $CHBr_3$ (316 g, 1.25 mol, 5.00 *eq*) at 0 °C. The mixture was stirred at 0 °C for 2 hr. The reaction was quenched by addition Sat.NH_4Cl 500 mL for 2 hrs, then extracted with EtOAc 500 mL x 3. The combined organic layers were washed with brine 500 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by reversed-phase HPLC(0.1% FA condition) to produce *tert*-butyl 4-(1-(3-(benzyloxy)propyl)-2,2-dibromocyclopropyl)piperidine-1-carboxylate (64.9 g, 123 mmol, 49.0% yield). LCMS: m/z = 271.0 ($M+H^+$-100)

Step 2. *tert*-butyl 4-(1-(3-(benzyloxy)propyl)cyclopropyl)piperidine-1-carboxylate

[000384] Two batches: To a solution of *tert*-butyl 4-(1-(3-(benzyloxy)propyl)-2,2-dibromocyclopropyl)piperidine-1-carboxylate (60.0 g, 113 mmol, 1.00 *eq*), $Ni(OAc)_2$-H_2O (1.41 g, 5.67 mmol, 0.05 *eq*), 3.4,7,8-tetramethyl-1,10-phenanthroline (2.67 g, 11.3 mmol, 0.10 *eq*), pyridine (13.4 g, 171 mmol, 1.50 *eq*) and TPGS-750-M (2.00% *w/w*) in THF (600 mL) and H_2O (120 mL) was slowly $NaBH_4$ (21.5 g, 565 mmol, 5.00 *eq*) added under Ar atmosphere. The mixture was stirred at 60 °C for 2 hr. The reaction mixture was quenched by addition 1M

HCl to adjust pH to 7, then extracted with EtOAc 200 mL x 3. The combined organic layers were washed with brine 300 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=50/1 to 10/1, Rf of P1 = 0.6) to produce *tert*-butyl 4-(1-(3-(benzyloxy)propyl)cyclopropyl)piperidine-1-carboxylate (27.3 g, 73.1 mmol, 64.3% yield). LCMS: m/z = 274.1 ($M+H^+$-100)

Step 3.*tert*-butyl 4-(1-(3-hydroxypropyl)cyclopropyl)piperidine-1-carboxylate

[000385] Two batches: To a solution of *tert*-butyl 4-(1-(3-(benzyloxy)propyl)cyclopropyl)piperidine-1-carboxylate (21.0 g, 56.3 mmol, 1.00 *eq*) in i-PrOH (210 mL) was added $Pd(OH)_2/C$ (20% purity, 20% *w/w*) under Ar atmosphere. The suspension was degassed and purged with H_2 for **3** times. The mixture was stirred under H_2 (50.0 Psi) at 60 °C for 24 hr. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl 4-(1-(3-hydroxypropyl)cyclopropyl)piperidine-1-carboxylate (12.8 g, 45.2 mmol, 80.5% yield). LCMS: m/z = 184 ($M+H^+$-100)

Step 4.*tert*-butyl 4-(1-(3-oxopropyl)cyclopropyl)piperidine-1-carboxylate

[000386] Two batches: To a solution of *tert*-butyl 4-(1-(3-hydroxypropyl)cyclopropyl)piperidine-1-carboxylate (20.0 g, 70.6 mmol, 1.00 *eq*) in DCM (200 mL) was slowly added DMP (59.8 g, 141 mmol, 2.00 *eq*) at 0 °C. The mixture was stirred at 25 °C for 2 hrs. TLC (Petroleum ether : Ethyl acetate = 3:1, Rf of R1 = 0.4, Rf of P1 = 0.6) indicated Reactant 1 was consumed completely and one new spots formed. The reaction was quenched by addition Sat.$Na_2S_2O_3$ 300 mL, then extracted with DCM 150 mL x 3. The combined organic layers were washed with brine 300 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 5/1, R_f of P1 = 0.6) to produce *tert*-butyl 4-(1-(3-oxopropyl)cyclopropyl)piperidine-1-carboxylate (14.6 g, 50.1 mmol, 73.7%yield) was obtained.

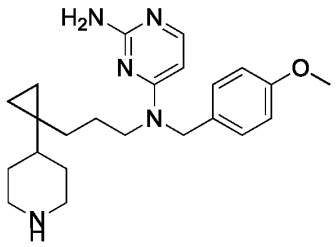
Step 5.*tert*-butyl 4-(1-(3-((4-methoxybenzyl)amino)propyl)cyclopropyl)piperidine-1-carboxylate

[000387] Two batches: To a solution of *tert*-butyl 4-(1-(3-oxopropyl)cyclopropyl)piperidine-1-carboxylate (18.0 g, 64.0 mmol, 1.00 *eq*) and $PMBNH_2$ (9.65 g, 70.4 mmol, 1.1 eq) in MeOH (180 mL) was added $NaBH(OAc)_3$ (27.1 g, 128mmol, 2.00 eq) at 0 °C, then the reaction mixture was stirred at 25 °C for 1 hr. TLC (Petroleum ether : Ethyl acetate = 3:1, Rf of R1 = 0.6, Rf of P1 = 0.05) indicated Reactant 1 was consumed completely and one new spots formed. The reaction was concentrated under reduced pressure to remove EtOH. The residue was

quenched by addition Sat.$NaHCO_3$ 200 mL , then extracted with EtOAc 100 mL * 3. The combined organic layers were washed with brine 100 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC, column: Welch Ultimate XB-CN 250*70*10um;mobile phase: [Hexane-EtOH（0.1% NH3.H2O）];gradient:5%-45% B over 15 min to afford *tert*-butyl 4-(1-(3-((4-methoxybenzyl)amino)propyl)cyclopropyl)piperidine-1-carboxylate, Intermediate J (11.0 g, 27.3 mmol, 42.7% yield). LCMS: m/z = 403.3 ($M+H^+$)

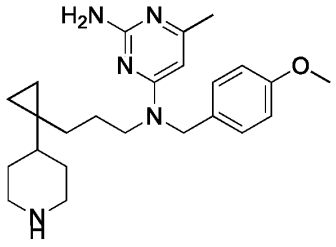
[000388] ^1H NMR (400 MHz, DMSO-*d6)* δ 7.19 - 7.24 (m, 2H), 6.83 - 6.88 (m, 2H), 3.91 - 4.01 (m, 2H), 3.72 (s, 3H), 3.57 - 3.63 (m, 2H), 2.54 (s, 1H), 2.41 (t, J=6.82 Hz, 2H), 1.50 (br d, J=11.88 Hz,2 H), 1.38 (s, 9H), 1.30 - 1.36 (m, 2H), 1.21 - 1.30 (m, 3H), 1.12 (br d, J=11.88 Hz, 1H), 1.04 (td, J=12.2, 4.00 Hz, 2H), 0.23 - 0.29 (m, 2H), 0.13 - 0.20 (m, 2H).

Intermediate K. N4-(4-methoxybenzyl)-N4-(3-(1-(piperidin-4-yl)cyclopropyl)propyl)pyrimidine-2,4-diamine



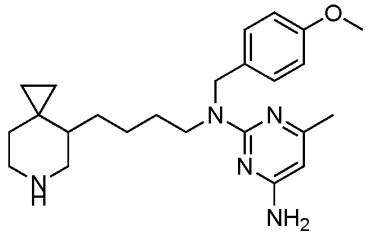
[000389] Intermediate K was synthesized from Intermediate J via the same procedure as for Intermediate B steps 3 and 4 using 4-chloropyrimidin-2-amine in place of 2-chlro-6-methylpyrimidin-4-amine in Step 3.

Intermediate L. N4-(4-methoxybenzyl)-6-methyl-N4-(3-(1-(piperidin-4-yl)cyclopropyl)propyl)pyrimidine-2,4-diamine



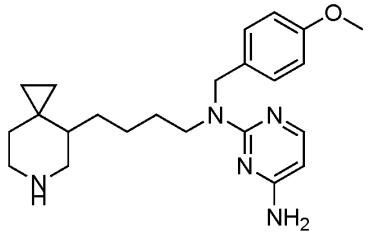
[000390] Intermediate L was synthesized from Intermediate J via the same procedure as Intermediate B steps 3 and 4.

Intermediate M. N^2-(4-(6-azaspiro[2.5]octan-4-yl)butyl)-N^2-(4-methoxybenzyl)-6-methylpyrimidine-2,4-diamine



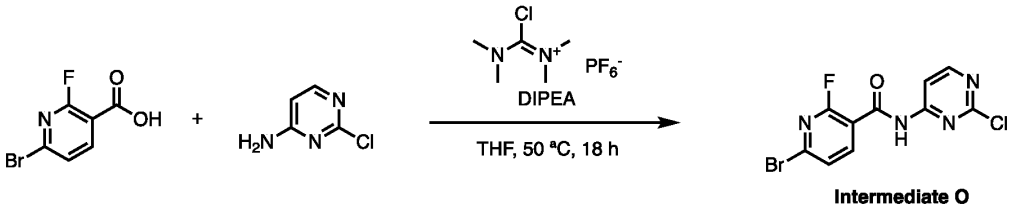
[000391] Intermediate M was synthesized from Intermediate F via the same procedure as Intermediate B steps 3 and 4.

Intermediate N. *N*^{2}-(4-(6-azaspiro[2.5]octan-4-yl)butyl)-*N*^{2}-(4-methoxybenzyl)pyrimidine-2,4-diamine



[000392] Intermediate N was synthesized from Intermediate F and 2-chloropyrimidin-4-amine via the same procedure as Intermediate B steps 3 and 4.

Intermediate O. 6-bromo-*N*-(2-chloropyrimidin-4-yl)-2-fluoronicotinamide was prepared following the synthetic scheme outlined below.

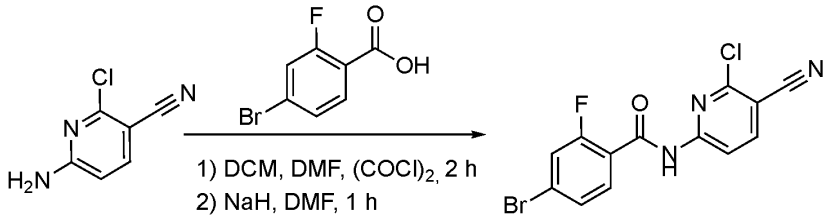


Intermediate O

[000393] To a vial was added 2-Chloro-pyrimidin-4-ylamine (1.18 g, 4 Eq, 9.09 mmol), 6-bromo-2-fluoronicotinic acid (500 mg, 1 Eq, 2.27 mmol), N-(chloro(dimethylamino)methylene)-N-methylmethanaminium hexafluorophosphate(V) (765 mg, 1.2 Eq, 2.73 mmol), DIPEA (1.18 g, 1.58 mL, 4 Eq, 9.09 mmol), and THF (10 mL). The reaction mixture was then heated to 50 °C. After 18 h, the reaction mixture was diluted with water and extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine, dried over MgSO4, and concentrated. Purification via Isco column chromatography (0-40% EtOAc in heptanes) followed by purification via prepHPLC (10-100% MeCN in 0.1%

TFA water) provided 6-bromo-N-(2-chloropyrimidin-4-yl)-2-fluoronicotinamide (214 mg, 645 μmol, 28.4 %) as a white solid after neutralization and extraction. LCMS M+1/Z = 332.9

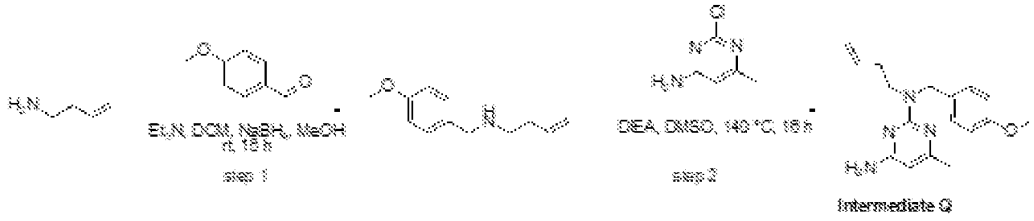
Intermediate P. 4-bromo-N-(6-chloro-5-cyanopyridin-2-yl)-2-fluorobenzamide



Intermediate P

[000394] To a stirred solution of 4-bromo-2-fluorobenzoic acid (856 mg, 3.91 mmol) in DCM (2 mL) were added $(COCl)_2$ (645 mg, 5.08 mmol) and DMF (2 mL) dropwise at 0 °C. Then the reaction mixture was stirred for 2 hours. After completion of reaction, the reaction mixture was concentrated under reduced pressure to give the crude acid chloride. To a stirred solution of 6-amino-2-chloropyridine-3-carbonitrile (600 mg, 3.91 mmol) in anhydrous DMF (2 mL) was added NaH (281 mg, 11.7 mmol) at 0 °C and the resulting was stirred for 1 hour before being treated with a solution of the acid chloride in DMF (1mL). The resulting mixture was stirred for 2 hours and then was quenched with H_2O (10 mL) and the aqueous layer was extracted with EA (2 x 10 mL). The residue was purified by silica gel column chromatography, eluted with PE / EA 4 : 1 to afford 4-bromo-N-(6-chloro-5-cyanopyridin-2-yl)-2-fluorobenzamide (470 mg, 29.5% yield). LCMS (ESI-MS) m/z =353.9 $[M+H]^+$.

Intermediate Q. N^2-(but-3-en-1-yl)-N^2-(4-methoxybenzyl)-6-methylpyrimidine-2,4-diamine.



Step 1. N-(4-methoxybenzyl)but-3-en-1-amine

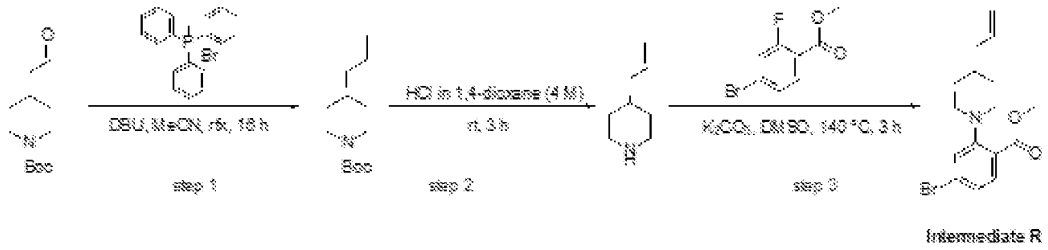
[000395] To a solution of 3-buten-1-amine (10 g, 140 mmol) in DCM (150 mL) was added anisaldehyde (19.1 g, 140 mmol) and TEA (42.7 g, 422 mmol). The resulting solution was stirred at room temperature for 16 hours. Then the reaction mixture was cooled to 0 °C. MeOH (50 mL) and $NaBH_4$ (5.32 g, 140 mmol) were added. The resulting mixture was stirred at 0 °C for 2 hours and pH of the mixture was adjusted to 2.0 by adding 1 N HCl (aq). The reaction mixture was extracted with DCM (100 mL x 2) and the water phase was collected. The pH of

the water phase was adjusted to 8.0 by adding aq. $NaHCO_3$ solution and extracted with DCM (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under vacuum to afford N-(4-methoxybenzyl)but-3-en-1-amine (6.7 g crude). LCMS (ESI-MS) m/z = 192.1 $[M+H]^+$.

Step 2. N^2-(but-3-en-1-yl)-N^2-(4-methoxybenzyl)-6-methylpyrimidine-2,4-diamine

[000396] DIEA (8.11 g, 62.7 mmol) was added to a mixture of N-(4-methoxybenzyl)but-3-en-1-amine (3 g, 15.7 mmol) and 2-chloro-6-methylpyrimidin-4-amine (2.25 g, 15.7 mmol) in DMSO (50 mL). The resulting solution was heated to 140 °C and stirred for 16 hours. After cooling to room temperature, the reaction mixture was diluted with water (100 mL) and extracted with EA (100 mL x 2). The combined organic layers were washed with brine (100 mLx2), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA/PE 1:1 to afford the desired product N^2-(but-3-en-1-yl)-N^2-(4-methoxybenzyl)-6-methylpyrimidine-2,4-diamine (1.4 g, 28.6% yield). LCMS (ESI-MS) m/z = 299.0 $[M+H]^+$.

Intermediate R. Methyl 2-(4-allylpiperidin-1-yl)-4-bromobenzoate.



Step 1. tert-butyl 4-allylpiperidine-1-carboxylate

[000397] DBU (13.4 g, 88.0 mmol) was added to a mixture of tert-butyl 4-(2-oxoethyl)piperidine-1-carboxylate (10 g, 44.0 mmol) and methyltriphenylphosphonium bromide (31.4 g, 88.0 mmol) in ACN (100 mL). The resulting solution was heated to reflux and stirred for 16 hours. After cooling to room temperature, the reaction mixture was diluted with water (100 mL) and extracted with EA (2 x 200 mL). The combined organic layers were washed with brine (200 mL x 2) and water (150 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA/ PE 5:1 to afford the desired product tert-butyl 4-allylpiperidine-1-carboxylate (8 g, 79.1% yield). LCMS (ESI-MS) m/z = 226.1 $[M+H]^+$.

Step 2. 4-allylpiperidine

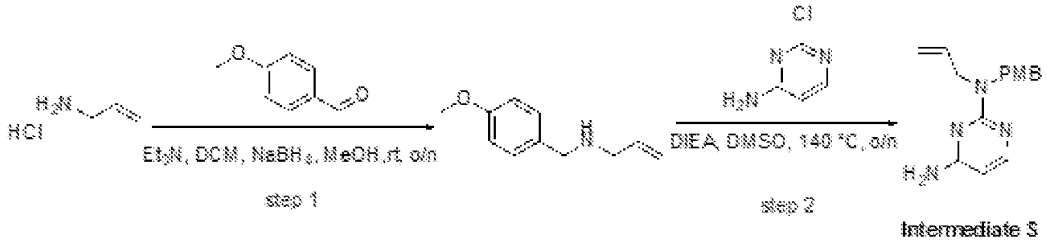
[000398] Into a 250-mL round-bottom flask, was placed tert-butyl 4-allylpiperidine-1-carboxylate (8 g, 35.5 mmol) and HCl in 1,4-dioxane (4M, 100 mL, 400 mmol). The resulting

solution was stirred at room temperature for 3 hours. The residue was evaporated and dried under vacuum to afford 4-allylpiperidine (4.2 g crude). LCMS (ESI-MS) m/z = 126.1 $[M+H]^+$.

Step 3. methyl 2-(4-allylpiperidin-1-yl)-4-bromobenzoate

[000399] K_2CO_3 (11.0 g, 79.9 mmol) was added to a mixture of 4-allylpiperidine (2 g, 16.0 mmol) and methyl 4-bromo-2-fluorobenzoate (3.72 g, 16.0 mmol) in DMSO (40 mL, 563 mmol). The resulting solution was heated to 140 °C and stirred for 3 hours. After cooling to room temperature, the reaction mixture was diluted with water (100 mL) and extracted with EA (100 mL x 2). The combined organic layers were washed with brine (100 mL x 2), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA/PE 1:2 to afford methyl 2-(4-allylpiperidin-1-yl)-4-bromobenzoate (5 g, 72.8% yield). LCMS (ESI-MS) m/z = 338.0 $[M+H]^+$.

Intermediate S. N^2-allyl-N^2-(4-methoxybenzyl)pyrimidine-2,4-diamine



Step 1. *N*-(4-methoxybenzyl)prop-2-en-1-amine

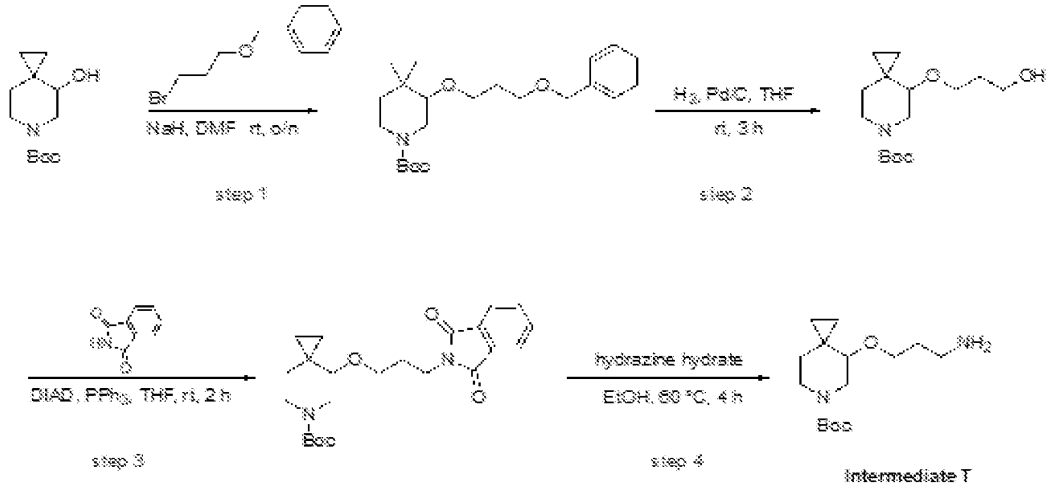
[000400] Et_3N (5.41 g, 53.4 mmol) was added to a mixture of 4-methoxybenzaldehyde (7.28 g, 53.4 mmol) and prop-2-en-1-amine hydrochloride (5 g, 53.4 mmol) in DCM (150 mL). The mixture was stirred at room temperature overnight. $NaBH_4$ (13.6 g, 64.1 mmol) and MeOH (150 mL) were added to the reaction mixture at 0 °C and the resulting was stirred at room temperature for 1 hour. The mixture was concentrated under vacuum. The resulting mixture was quenched with sat. $NaHCO_3$ (aq.) (400 mL) at room temperature. The resulting mixture was extracted with EA (3 x 500 mL). The combined organic layers were washed with brine (1 L), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (7:1) to afford *N*-(4-methoxybenzyl)prop-2-en-1-amine (5 g, 47.5% yield). LCMS (ESI-MS) m/z =178.1 $[M+H]^+$.

Step 2. N^2-allyl-N^2-(4-methoxybenzyl)pyrimidine-2,4-diamine

[000401] DIEA (5.99 g, 46.3 mmol) was added to a mixture of 2-chloropyrimidin-4-amine (2 g, 15.4 mmol) and N-(4-methoxybenzyl)prop-2-en-1-amine (2.74 g, 15.4 mmol) in DMSO (20 mL). The mixture was stirred at 140 °C overnight. The reaction was quenched with water

(100 mL) at room temperature. The resulting mixture was extracted with EA (3 x 150 mL). The combined organic layers were washed with brine (450 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford N^2-allyl-N^2-(4-methoxybenzyl)pyrimidine-2,4-diamine (1.2 g, 25.8% yield). LCMS (ESI-MS) m/z = 271.1 $[M+H]^+$.

Intermediate T. tert-butyl 4-(3-aminopropoxy)-6-azaspiro[2.5]octane-6-carboxylate



Step 1. tert-butyl 4-(3-(benzyloxy)propoxy)-6-azaspiro[2.5]octane-6-carboxylate

[000402] A solution of tert-butyl 4-hydroxy-6-azaspiro[2.5]octane-6-carboxylate (4.6 g, 20.2 mmol) in DMF (50 mL) was treated with NaH (728 mg, 30.4 mmol) for 1 hour at 0 °C under nitrogen atmosphere followed by the addition of ((3-bromopropoxy)methyl)benzene (5.1 g, 22.3 mmol). The resulting solution was stirred at room temperature overnight. The reaction mixture was diluted with EA (500 ml) and washed with brine (3 x 500 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with EA/PE 1:8 to afford *tert*-butyl 4-(3-(benzyloxy)propoxy)-6-azaspiro[2.5]octane-6-carboxylate (1.5 g, 19.7% yield). LCMS (ESI-MS) m/z = 376.2 $[M+H]^+$.

Step 2. tert-butyl 4-(3-hydroxypropoxy)-6-azaspiro[2.5]octane-6-carboxylate

[000403] Pd/C (1 g, 9.39 mmol) was added to a stirred solution of tert-butyl 4-(3-(benzyloxy)propoxy)-6-azaspiro[2.5]octane-6-carboxylate (1.5 g, 3.99 mmol) in MeOH (20 mL). The mixture was stirred at room temperature for 3 hours under hydrogen atmosphere. The reaction mixture was filtered off and the filtrate was concentrated to afford tert-butyl 4-(3-hydroxypropoxy)-6-azaspiro[2.5]octane-6-carboxylate (1 g crude). LCMS (ESI-MS) m/z = 286.2 $[M+H]^+$.

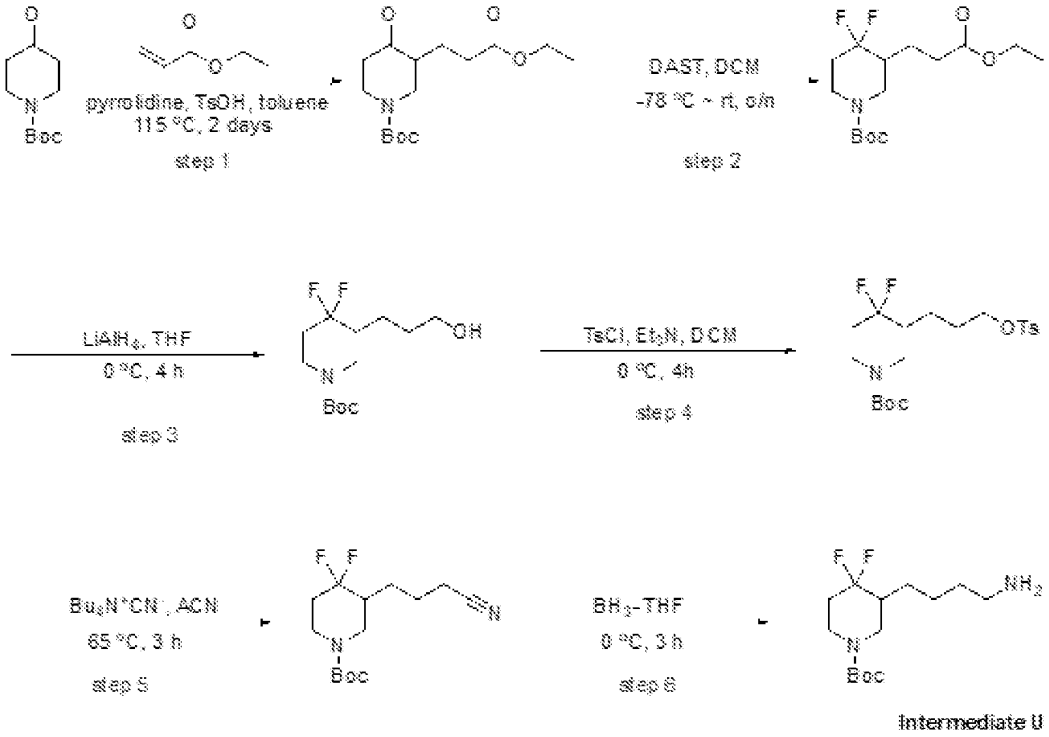
Step 3. tert-butyl 4-(3-(1,3-dioxoisoindolin-2-yl)propoxy)-6-azaspiro[2.5]octane-6-carboxylate

[000404] DIAD (1.06 g, 5.25 mmol) was added to a stirred mixture of tert-butyl 4-(3-hydroxypropoxy)-6-azaspiro[2.5]octane-6-carboxylate (1 g, 3.50 mmol), isoindoline-1,3-dione (620 mg, 4.20 mmol) and PPh_3 (1.38 g, 5.25 mmol) in THF (15 mL) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 2 hours. The reaction solution was concentrated under vacuum and the residue was purified by silica gel column chromatography, eluted with EA/PE 2:3 to afford tert-butyl 4-(3-(1,3-dioxoisoindolin-2-yl)propoxy)-6-azaspiro[2.5]octane-6-carboxylate (1.2 g, 82.6% yield). LCMS (ESI-MS) m/z = 415.1 $[M+H]^+$.

Step 4. tert-butyl 4-(3-aminopropoxy)-6-azaspiro[2.5]octane-6-carboxylate

[000405] Hydrazine hydrate (15 mL) was added to a solution of tert-butyl 4-(3-(1,3-dioxoisoindolin-2-yl)propoxy)-6-azaspiro[2.5]octane-6-carboxylate (1.2 g, 2.89 mmol) in EtOH (20 mL). The resulting mixture was heated to 60 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was filtered off and the filtrate was concentrated under vacuum. The residue was dissolved in EA (200 ml) and washed with brine (3 x 200 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford tert-butyl 4-(3-aminopropoxy)-6-azaspiro[2.5]octane-6-carboxylate (700 mg crude). LCMS (ESI-MS) m/z = 285.3 $[M+H]^+$.

Intermediate U. tert-butyl 3-(4-aminobutyl)-4,4-difluoropiperidine-1-carboxylate.



Step 1. tert-butyl 3-(3-ethoxy-3-oxopropyl)-4-oxopiperidine-1-carboxylate

[000406] Pyrrolidine (21.4 g, 301 mmol) was added to a mixture of tert-butyl 4-oxopiperidine-1-carboxylate (20 g, 100 mmol) and 4-methylbenzenesulfonic acid (2.6 g, 15.1 mmol) in toluene (1 L). The resulting solution was heated to 120 °C and stirred for 2 hours under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was concentrated under vacuum to afford a crude product. The residue was dissolved in ACN (200 mL) and ethyl acrylate (10 g, 100 mmol). The resulting solution was heated to 90 °C and stirred for 2 hours. Then water (66.6 mL) was added. The resulting solution was heated to 100 °C and stirred for 20 hours. After cooling to room temperature, the reaction mixture was extracted with EA (2 x 200 mL). The combined organic layers were washed with brine (2 x 200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the desired product tert-butyl 3-(3-ethoxy-3-oxopropyl)-4-oxopiperidine-1-carboxylate (18 g crude) as a yellow oil. LCMS (ESI-MS) m/z =300.1 $[M+H]^+$.

Step 2. tert-butyl 3-(3-ethoxy-3-oxopropyl)-4,4-difluoropiperidine-1-carboxylate

[000407] DAST (29.1 g, 180 mmol) was added to a mixture of tert-butyl 3-(3-ethoxy-3-oxopropyl)-4-oxopiperidine-1-carboxylate (18 g, 60.1 mmol) in DCM (240 mL). The resulting

solution was stirred for 10 h at -78 °C under nitrogen atmosphere, quenched by addition of 10 % sodium bicarbonate (1000 mL) at 0 °C and then extracted with DCM (2 x 1000 mL). The combined organic layers were washed with brine (2 x 1000 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE/EA 8:1 to afford the desired product tert-butyl 3-(3-ethoxy-3-oxopropyl)-4,4-difluoropiperidine-1-carboxylate (11 g, 57 % yield). LCMS (ESI-MS) m/z = 322.1 $[M+H]^+$.

Step 3. tert-butyl 4,4-difluoro-3-(3-hydroxypropyl)piperidine-1-carboxylate

[000408] $LiAlH_4$ (2.6 g, 68.5 mmol) was added to a mixture of tert-butyl 3-(3-ethoxy-3-oxopropyl)-4,4-difluoropiperidine-1-carboxylate (11 g, 34.2 mmol) and in THF (110 mL). The resulting mixture was stirred for 4 h at 0 °C under nitrogen atmosphere. The reaction was quenched by the addition of water (300 mL) at 0 °C. The resulting mixture was extracted with EA (2 x 300 mL). The combined organic layers were washed with brine (2 x 200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford tert-butyl 4,4-difluoro-3-(3-hydroxypropyl)piperidine-1-carboxylate (6 g crude). LCMS (ESI-MS) m/z = 280.2 $[M+H]^+$.

Step 4. tert-butyl 4,4-difluoro-3-(3-(tosyloxy)propyl)piperidine-1-carboxylate

[000409] TsCl (4.91 g, 25.7 mmol) was added to a mixture of tert-butyl 4,4-difluoro-3-(3-hydroxypropyl)piperidine-1-carboxylate (6 g, 21.5 mmol) , and Et_3N (6.52 g, 64.4 mmol) in DCM (120 mL) at 0 °C. The resulting mixture was stirred for 4 h at 0 °C under nitrogen atmosphere. The reaction mixture was diluted with water (120 mL) ,extracted with EA (2 x 120 mL). The combined organic layers were washed with brine (2 x 120 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE/EA 8:1 to afford the desired product tert-butyl 4,4-difluoro-3-(3-(tosyloxy)propyl)piperidine-1-carboxylate (6 g, 64.4 % yield). LCMS (ESI-MS) m/z = 434.1 $[M+H]^+$.

Step 5. tert-butyl 3-(3-cyanopropyl)-4,4-difluoropiperidine-1-carboxylate

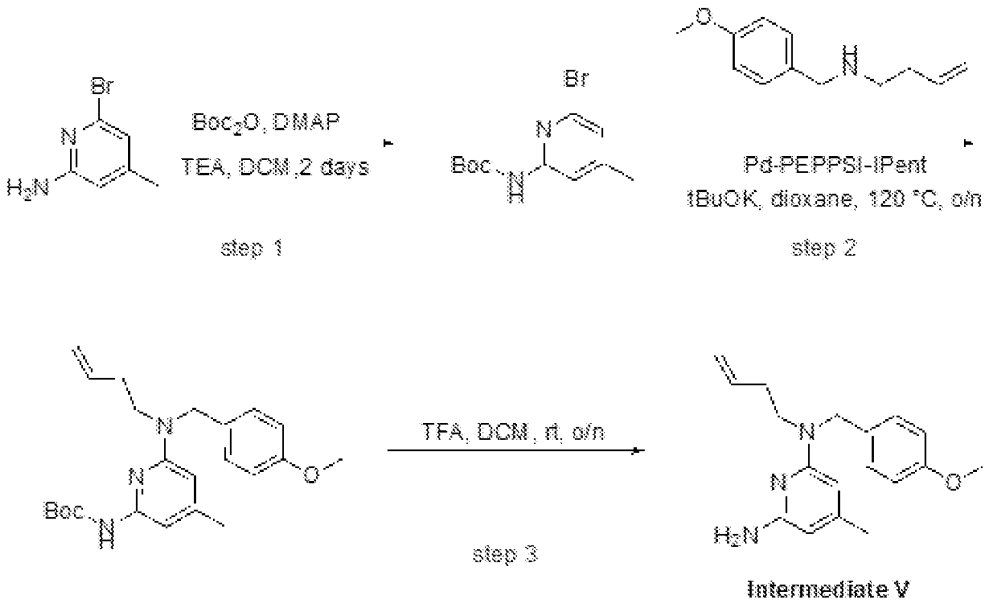
[000410] $Bu4N^+CN^-$(3.06 g, 11.4 mmol) was added to a mixture of tert-butyl 4,4-difluoro-3-(3-(tosyloxy)propyl)piperidine-1-carboxylate (6 g, 13.8 mmol) in ACN (150 mL). The resulting mixture was heated to 65 °C and stirred for 3 hours under nitrogen atmosphere. After cooling to room temperature, the resulting mixture was diluted with water (300 mL) and extracted with EA (2 x 250 mL). The combined organic layers were washed with brine (5 x 200 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford tert-

butyl 3-(3-cyanopropyl)-4,4-difluoropiperidine-1-carboxylate (4.2 g crude). LCMS (ESI-MS) m/z = 289.1 $[M+H]^+$.

Step 6. tert-butyl 3-(4-aminobutyl)-4,4-difluoropiperidine-1-carboxylate

[000411] BH_3 in THF (1 M, 36.4 mL, 36.4 mmol) was added to a mixture of tert-butyl 3-(3-cyanopropyl)-4,4-difluoropiperidine-1-carboxylate (4.2 g, 14.6 mmol) in THF (50 mL). The resulting mixture was stirred for 3 h at room temperature under nitrogen atmosphere. The reaction was quenched with MeOH (20 ml) at 0 °C. The residue was diluted with water (300 mL) and extracted with EA (2 x 300 mL). The combined organic layers were washed with brine (2 x 300 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH 7:2 to afford the desired product tert-butyl 3-(4-aminobutyl)-4,4-difluoropiperidine-1-carboxylate (1.7 g, 39.9 % yield). LCMS (ESI-MS) m/z = 293.2 $[M+H]^+$.

Intermediate V. tert-butyl (6-(but-3-en-1-yl(4-methoxyphenyl)methyl)amino)-4-methylpyridin-2-yl)carbamate



Step 1. tert-butyl (6-bromo-4-methylpyridin-2-yl)carbamate

[000412] Boc_2O (13.7 mL, 64.2 mmol) was added to a mixture of 6-bromo-4-methylpyridin-2-amine (10 g, 53.5 mmol) and DMAP (1.31 g, 10.7 mmol) and TEA (9.7mL, 69.5 mmol) in DCM (100 mL) at room temperature. The resulting mixture was stirred for 2 days at room temperature. The reaction was quenched with water at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were washed with brine

(3 x 200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA 1 : 1 to afford tert-butyl (6-bromo-4-methylpyridin-2-yl)carbamate (11.3 g, 73.6% yield). LCMS (ESI-MS) m/z =287.0 $[M+H]^+$.

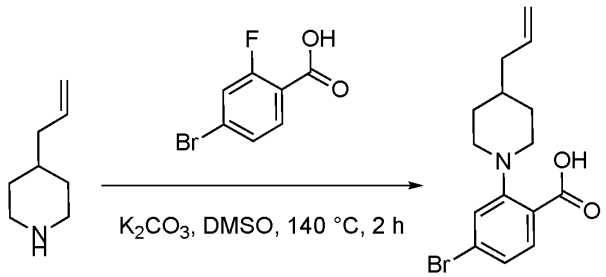
Step 2. tert-butyl (6-(but-3-en-1-yl(4-methoxyphenyl)methyl)amino)-4-methylpyridin-2-yl)carbamate

[000413] To a stirred mixture of tert-butyl (6-bromo-4-methylpyridin-2-yl)carbamate (3.0 g, 10.4 mmol) and but-3-en-1-yl[(4-methoxyphenyl)methyl]amine (2.0 g, 10.4 mmol) in dioxane (30 mL) was added Pd-PEPPSI-IPent catalyst (414 mg, 0.52 mmol) and t-BuOK (3.5 g, 31.2 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was heated to 120 °C and stirred for overnight. After cooling to room temperature. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with EA (3 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE : EA = 5 : 1 to afford tert-butyl (6-(but-3-en-1-yl(4-methoxyphenyl)methyl)amino)-4-methylpyridin-2-yl)carbamate (1.5 g, 36.1% yield) LCMS (ESI-MS) m/z = 398.2 $[M+H]^+$.

Step 3. N^2-(but-3-en-1-yl)-N^2-(4-methoxybenzyl)-4-methylpyridine-2,6-diamine

[000414] TFA (0.5 mL) was added to a stirred mixture of tert-butyl (6-(but-3-en-1-yl(4-methoxyphenyl)methyl)amino)-4-methylpyridin-2-yl)carbamate (500 mg, 1.26 mmol) in DCM (5 mL). The resulting mixture was stirred for overnight at room temperature, and concentrated to afford the crude product N^2-(but-3-en-1-yl)-N^2-(4-methoxybenzyl)-4-methylpyridine-2,6-diamine (300 mg, crude). LCMS (ESI-MS) m/z = 298.2 $[M+H]^+$.

Intermediate W. 2-(4-allylpiperidin-1-yl)-4-bromobenzoic acid.

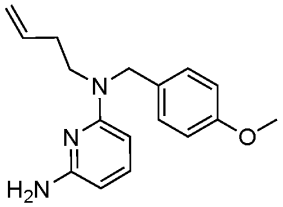


Intermediate W

[000415] K_2CO_3 (7.12 g, 51.5 mmol) was added to a mixture of 4-allylpiperidine (4.57 g, 17.2 mmol) and 4-bromo-2-fluorobenzoic acid (4.3 g, 17.2 mmol) in DMSO (80 mL). The

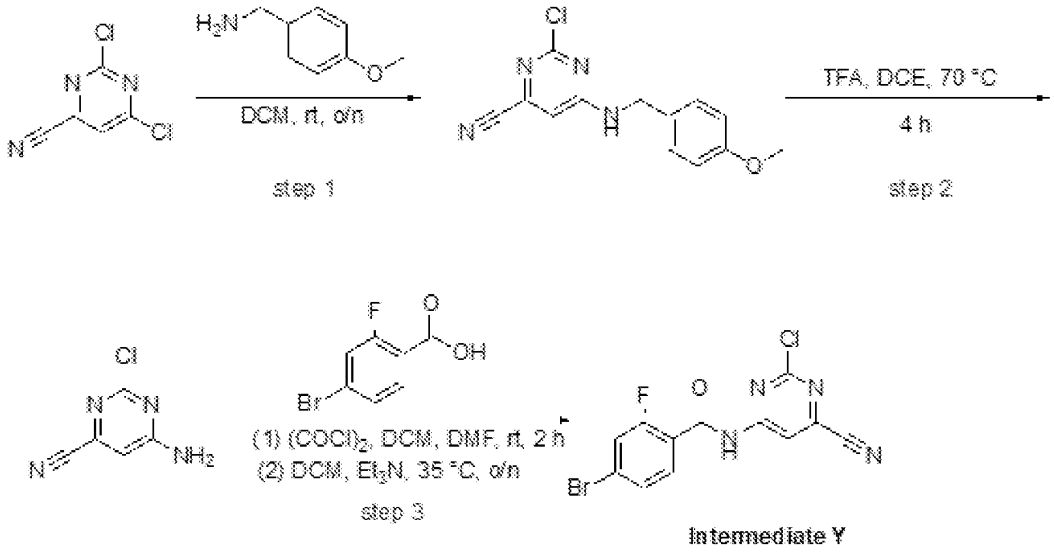
resulting mixture was heated to 140 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was diluted with water (100 mL) and extracted with EA (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with PE/EA 4 : 1 to afford the desired product 2-(4-allylpiperidin-1-yl)-4-bromobenzoic acid (2.6 g, 30.5% yield). LCMS (ESI-MS) m/z = 324.1 $[M+H]^+$.

Intermediate X. N^2-(but-3-en-1-yl)-N^2-(4-methoxybenzyl)pyridine-2,6-diamine.



[000416] Intermediate X was synthesized using the same procedure as Intermediate V, steps 1-3 using 6-bromopyridin-2-amine in step 1.

Intermediate Y. 4-bromo-N-(2-chloro-6-cyanopyrimidin-4-yl)-2-fluorobenzamide



Step 1. 2-chloro-6-((4-methoxybenzyl)amino)pyrimidine-4-carbonitrile

[000417] (4-methoxyphenyl)methanamine (6.3 g, 45.98 mmol) was added to a solution of 2,6-dichloropyrimidine-4-carbonitrile (4 g, 22.99 mmol) in DCM (80 mL) and the resulting mixture was stirred at room temperature overnight. After cooling to room temperature, the reaction mixture was diluted with DCM (300 mL) and washed with 1 N HCl (3 x 200 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA/PE 1

: 3 to afford 2-chloro-6-((4-methoxybenzyl)amino)pyrimidine-4-carbonitrile (4.6 g, 72.8% yield). LCMS (ESI-MS) m/z =274.9 $[M+H]^+$.

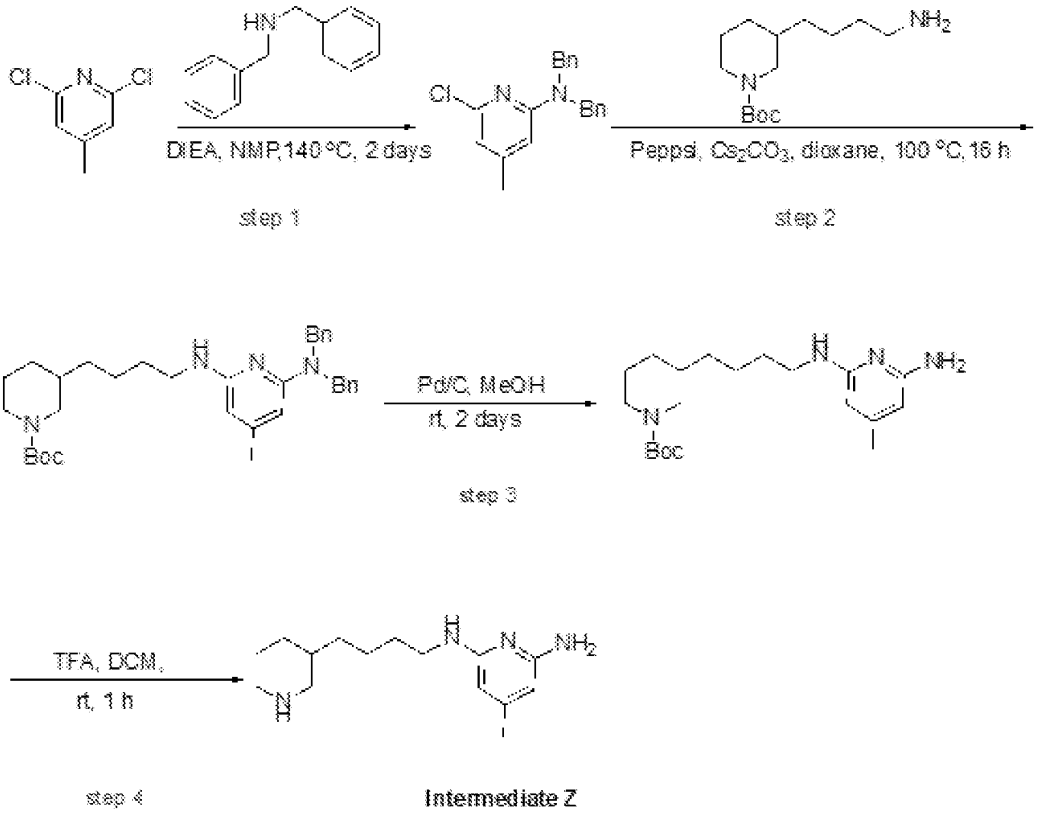
Step 2. 6-amino-2-chloropyrimidine-4-carbonitrile

[000418] TFA (20 mL) was added to a solution of 2-chloro-6-((4-methoxybenzyl)amino)pyrimidine-4-carbonitrile (4.6 g, 16.74 mmol) in DCE (50 mL). The resulting solution was heated to 70 °C and stirred for 4 hours. After cooling to room temperature, the reaction mixture was concentrated under vacuum and the residue was purified by silica gel column chromatography, eluted with EA /PE 1 : 2 to afford 6-amino-2-chloropyrimidine-4-carbonitrile (1.8 g, 65.7% yield). LCMS (ESI-MS) m/z =154.9 $[M+H]^+$.

Step 3. 4-bromo-N-(2-chloro-6-cyanopyrimidin-4-yl)-2-fluorobenzamide

[000419] A solution of 4-bromo-2-fluorobenzoic acid (1.25 g, 5.69 mmol) in DCM (20 mL) was treated with oxalic dichloride (985.45 mg, 7.76 mmol) at room temperature for 2 hours. The mixture was concentrated under vacuum, the residue was re-dissolved in DCM (10 mL) and added to a mixture of Et_3N (2.1 g, 20.70 mmol) and 6-amino-2-chloropyrimidine-4-carbonitrile (800 mg, 5.17 mmol) in DCM (20 mL). The resulting mixture was heated to 35 °C and stirred overnight. After cooling to room temperature, the reaction mixture was concentrated under vacuum and the residue was purified by silica gel column chromatography, eluted with EA/PE 1 : 8 to afford 4-bromo-N-(2-chloro-6-cyanopyrimidin-4-yl)-2-fluorobenzamide (550 mg, 29.9% yield). LCMS (ESI-MS) m/z =354.8 $[M+H]^+$.

Intermediate Z. 4-methyl-N^2-(4-(piperidin-3-yl)butyl)pyridine-2,6-diamine



Step 1. N,N-dibenzyl-6-chloro-4-methylpyridin-2-amine

[000420] DIEA (16.0 g, 123 mmol) was added to a stirred mixture of 2,6-dichloro-4-methylpyridine (10 g, 61.7 mmol) and dibenzylamine (12.2 g, 61.7 mmol) in NMP (100 mL). The resulting mixture was heated to 140 °C and stirred for 2 days. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with DCM/ PE 10:1 to afford *N,N*-dibenzyl-6-chloro-4-methylpyridin-2-amine (1.7 g, 8.1% yield). LCMS (ESI-MS) m/z =543.8 $[M+H]^+$.

Step 2. tert-butyl 3-(4-((6-(dibenzylamino)-4-methylpyridin-2-yl)amino)butyl)piperidine-1-carboxylate

[000421] Pd-PEPPSI-IPentCl 2-methylpyridine (o-picoline) (0.22 g, 0.26 mmol) was added to a stirred mixture of N,N-dibenzyl-6-chloro-4-methylpyridin-2-amine (1.7 g, 5.27 mmol) and *tert*-butyl 3-(4-aminobutyl)piperidine-1-carboxylate (1.62 g, 6.32 mmol) in dioxane (20 mL). The resulting mixture was heated to 100 °C and stirred for 16 hours. After cooling to room

temperature, the reaction mixture was filtered and the filtrate was concentrated under vacuum to afford the residue. The residue was purified by silica gel column chromatography, eluted with PE/EA 5:1 to afford tert-butyl 3-(4-((6-(dibenzylamino)-4-methylpyridin-2-yl)amino)butyl)piperidine-1-carboxylate (2.0 g, 66.8% yield). LCMS (ESI-MS) m/z = 379.2 $[M+H]^+$.

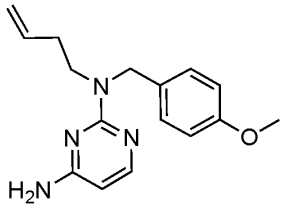
Step 3. tert-butyl 3-(4-((6-amino-4-methylpyridin-2-yl)amino)butyl)piperidine-1-carboxylate

[000422] Pd/C (500 mg, 10% Pd on carbon) was added to a stirred mixture of *tert*-butyl 3-(4-((6-(dibenzylamino)-4-methylpyridin-2-yl)amino)butyl)piperidine-1-carboxylate (2.0 g, 1.84 mmol) in MeOH (20 mL) under nitrogen atmosphere. The mixture was stirred for 2 days at room temperature under hydrogen atmosphere. The reaction mixture was filtered, the filter cake was washed with MeOH (3 x 30 mL). The filtrate was concentrated under reduced pressure to afford the crude product tert-butyl 3-(4-((6-amino-4-methylpyridin-2-yl)amino)butyl)piperidine-1-carboxylate (1.2 g crude)The crude product mixture was used in the next step directly without further purification. LCMS (ESI-MS) m/z = 363.3 $[M+H]^+$.

Step 4. 4-methyl-N^2-(4-(piperidin-3-yl)butyl)pyridine-2,6-diamine

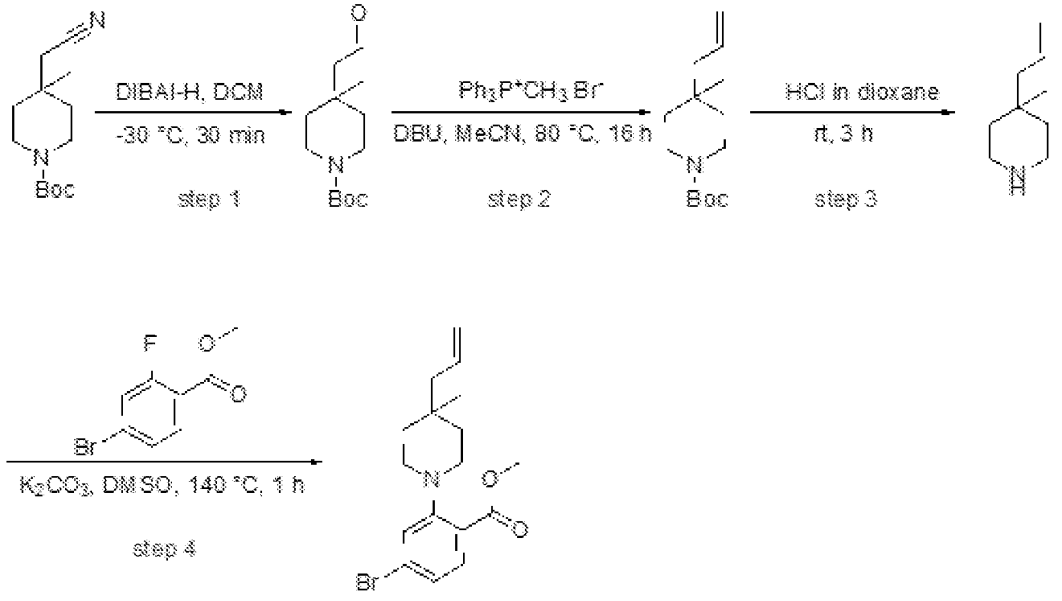
[000423] TFA (10 mL) was added to a stirred mixture of tert-butyl 3-(4-((6-amino-4-methylpyridin-2-yl)amino)butyl)piperidine-1-carboxylate (1.2 g, 3.31 mmol) in DCM (20 mL). The resulting mixture was stirred for 1 hour at room temperature. The reaction was quenched with sat. $NaHCO_3$ (20 mL) at room temperature. The resulting mixture was diluted with EA (2 x 50 ml) and washed with brine (100 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product 4-methyl-N^2-(4-(piperidin-3-yl)butyl)pyridine-2,6-diamine (600 mg crude). LCMS (ESI-MS) m/z = 263.4 $[M+H]^+$.

Intermediate AA. N^2-(but-3-en-1-yl)-N^2-(4-methoxybenzyl)pyrimidine-2,4-diamine.



[000424] Intermediate AA was synthesized following the same procedure as Intermediate Q and using 2-chloropyrimidin-4-amine in step 2 in place of 2-chloro-6-methylpyrimidin-4-amine.

Intermediate AB. Methyl 2-(4-allyl-4-methylpiperidin-1-yl)-4-bromobenzoate



Intermediate AB

Step 1. tert-butyl 4-methyl-4-(2-oxoethyl)piperidine-1-carboxylate

[000425] DIBAl-H (1 M in hexane, 20.98 mL, 21 mmol) was added to a solution of tert-butyl 4-(cyanomethyl)-4-methylpiperidine-1-carboxylate (2 g, 8.39 mmol) in DCM (50 mL) dropwise at -30 °C. The resulting solution was stirred at -30 °C for 30 min. The reaction was quenched with MeOH and filtered. The filtrated was diluted with DCM (50 mL), washed with brine (50 mL x 2), dried with anhydrous Na_2SO_4 and evaporated under vacuum to give tert-butyl 4-methyl-4-(2-oxoethyl)piperidine-1-carboxylate (1 g, crude). LCMS (ESI-MS) m/z = 242.0 $[M+H]^+$.

Step 2. tert-butyl 4-allyl-4-methylpiperidine-1-carboxylate

[000426] DBU (1.26 g, 8.29 mmol) was added to a solution of tert-butyl 4-methyl-4-(2-oxoethyl)piperidine-1-carboxylate (1 g, 4.14 mmol) and methyltriphenylphosphanium bromide (2.96 g, 8.29 mmol) in ACN (20 mL) . The resulting solution was heated to reflux and stirred for 16 hours. The reaction mixture was diluted with water (30 mL), extracted with EA (30 mL x 2). The combined organic layers were combined, washed with brine (30 mL x 2), dried with anhydrous Na_2SO_4, filtered and evaporated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA/PE 3 : 1 to afford tert-butyl 4-allyl-4-methylpiperidine-1-carboxylate (500 mg, 47.9%). LCMS (ESI-MS) m/z = 140.4 $[M-Boc]^+$.

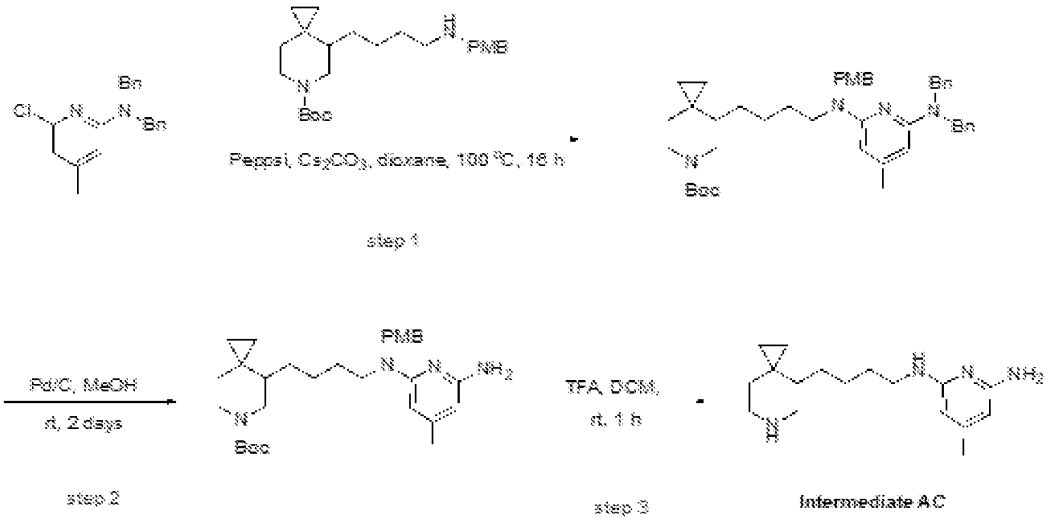
Step 3. 4-allyl-4-methylpiperidine

[000427] Into a 25-mL round-bottom flask, was placed tert-butyl 4-allyl-4-methylpiperidine-1-carboxylate (500 mg, 2.09 mmol) and HCl in 1,4-dioxane (4 M, 5 mL, 20 mmol). The resulting solution was stirred at room temperature for 3 hours. The mixture was evaporated and dried under vacuum to give 4-allyl-4-methylpiperidine (280 mg, crude). LCMS (ESI-MS) m/z = 140.1 $[M+H]^+$.

Step 4. methyl 2-(4-allyl-4-methylpiperidin-1-yl)-4-bromobenzoate

[000428] K_2CO_3 (834 mg, 6.03 mmol) was added to a solution of 4-allyl-4-methylpiperidine (280 mg, 2.01 mmol) and methyl 4-bromo-2-fluorobenzoate (469 mg, 2.01 mmol) in DMSO (3 mL). The resulting solution was heated to 140 °C and stirred for 1 hour. After cooling to room temperature, the reaction mixture was diluted with water (10 mL), extracted with EA (10 mL x 2). The combined organic layers were washed with brine (10 mL x 2), dried with anhydrous Na_2SO_4, filtered and evaporated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA/PE 1 : 2 to give methyl 2-(4-allyl-4-methylpiperidin-1-yl)-4-bromobenzoate (400 mg, 55.7%). LCMS (ESI-MS) m/z = 352.0 $[M+H]^+$.

Intermediate AC. N^2-(4-(6-azaspiro[2.5]octan-4-yl)butyl)-4-methylpyridine-2,6-diamine



Step 1. tert-butyl 4-(4-((6-(dibenzylamino)-4-methylpyridin-2-yl)(4-methoxybenzyl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate

[000429] Pd-PEPPSI-IPent catalyst (260 mg, 0.310 mmol) was added to a stirred mixture of N,N-dibenzyl-6-chloro-4-methylpyridin-2-amine (2 g, 6.12 mmol) , Intermediate F (2.49 g, 6.20 mmol) and Cs_2CO_3 (4.04 g, 12.4 mmol) in dioxane (30 mL). The resulting mixture was

heated to 100 °C and stirred for 16 hours. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated under vacuum to afford the residue. The residue was purified by silica gel column chromatography, eluted with PE/EA 5:1 to afford tert-butyl 4-(4-((6-(dibenzylamino)-4-methylpyridin-2-yl)(4-methoxybenzyl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate (2.1 g, 49.2% yield). LCMS (ESI-MS) m/z = 689.9 $[M+H]^+$.

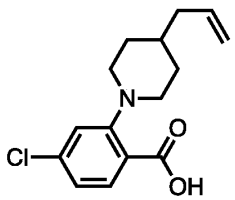
Step 2. tert-butyl 3-(4-((6-amino-4-methylpyridin-2-yl)amino)butyl)piperidine-1-carboxylate

[000430] Pd/C (1 g, 9.39 mmol) was added to a stirred mixture of tert-butyl 4-(4-((6-(dibenzylamino)-4-methylpyridin-2-yl)(4-methoxybenzyl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate (1 g, 1.45 mmol) in MeOH (20 mL) under nitrogen atmosphere. The mixture was stirred for 2 days at room temperature under hydrogen atmosphere. The reaction mixture was filtered, the filter cake was washed with MeOH (3 x 30 mL). The filtrate was concentrated under reduced pressure to afford the crude product tert-butyl 3-(4-((6-amino-4-methylpyridin-2-yl)amino)butyl)piperidine-1-carboxylate (500 mg crude). The crude product mixture was used in the next step directly without further purification. LCMS (ESI-MS) m/z =509.3 $[M+H]^+$.

Step 3. N^2-(4-(6-azaspiro[2.5]octan-4-yl)butyl)-4-methylpyridine-2,6-diamine

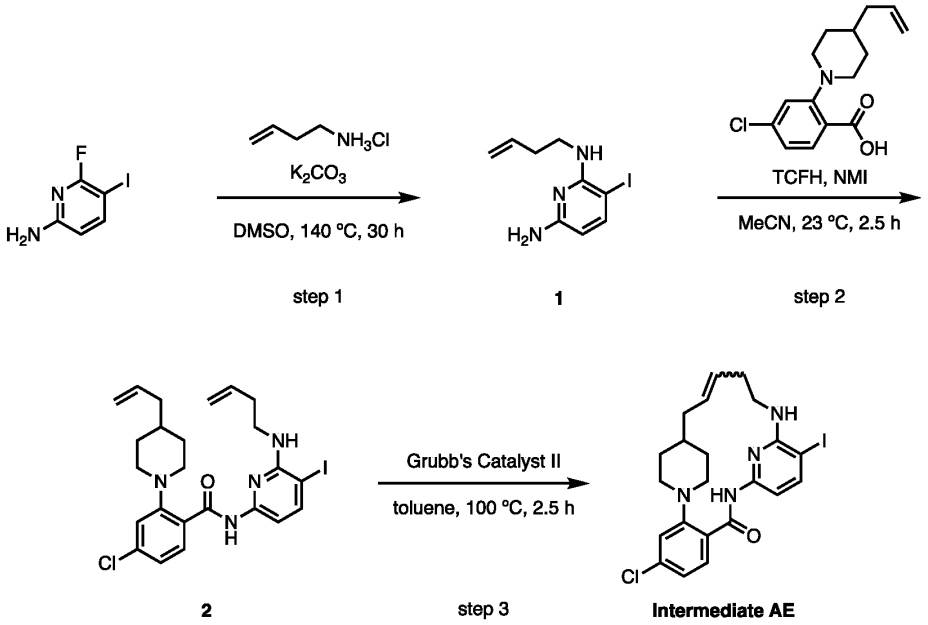
[000431] TFA (5 mL) was added to a stirred mixture of tert-butyl 4-(4-((6-amino-4-methylpyridin-2-yl)(4-methoxybenzyl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate (500 mg, 0.983 mmol) in DCM (5 mL). The resulting mixture was stirred for 1 hour at room temperature. The resulting mixture was stirred at room temperature for 2 hours and concentrated to afford the crude product N^2-(4-(6-azaspiro[2.5]octan-4-yl)butyl)-4-methylpyridine-2,6-diamine (200 mg crude) as yellow oil. LCMS (ESI-MS) m/z = 289.2 $[M+H]^+$.

Intermediate AD. 2-(4-allylpiperidin-1-yl)-4-chlorobenzoic acid



[000432] Intermediate AD was synthesized using the same procedure as intermediate W using 4-chloro-2-fluorobenzoic acid. LCMS (ESI-MS) m/z =280.1 $[M+H]^+$.

Intermediate AE. 25-chloro-55-iodo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one



Step 1. N2-(but-3-en-1-yl)-3-iodopyridine-2,6-diamine

[000433] To a vial was added 3-Buten-1-amine, hydrochloride (90.4 mg, 840 μmol), 6-fluoro-5-iodopyridin-2-amine (100 mg, 420 μmol), DMSO (0.50 mL), and K_2CO_3 (232 mg, 1.68 mmol). The reaction mixture was then heated to 140 °C. After 18 hour, the reaction mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-100% EtOAc in heptane) provided *N*²-(but-3-en-1-yl)-3-iodopyridine-2,6-diamine (30 mg, 25 %). LCMS (ESI-MS) m/z = 290.0 $[M+H]^+$.

Step 2. 2-(4-allylpiperidin-1-yl)-N-(6-(but-3-en-1-ylamino)-5-iodopyridin-2-yl)-4-chlorobenzamide

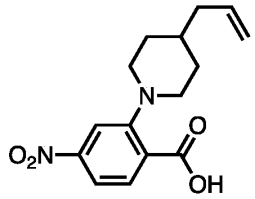
[000434] To a vial was added 2-(4-allylpiperidin-1-yl)-4-chlorobenzoic acid (80 mg, 0.29 mmol), *N*²-(but-3-en-1-yl)-3-iodopyridine-2,6-diamine (91 mg, 0.31 mmol), *N*-(chloro(dimethylamino)methylene)-*N*-methylmethanaminium hexafluorophosphate(V) (0.10 g, 0.37 mmol), 1-Methylimidazole (82 mg, 1.0 mmol), and MeCN (1.5 mL). The reaction was then stirred at rt. After 2.5 hour the reaction mixture was quenched with water and diluted with EtOAc. The organic layer was separated and washed with brine, dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-20% EtOAc on heptane)

provided 2-(4-allylpiperidin-1-yl)-*N*-(6-(but-3-en-1-ylamino)-5-iodopyridin-2-yl)-4-chlorobenzamide (80 mg, 51 %). LCMS (ESI-MS) m/z =551.0 $[M+H]^+$.

Step 3. 25-chloro-55-iodo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one, Intermediate AE

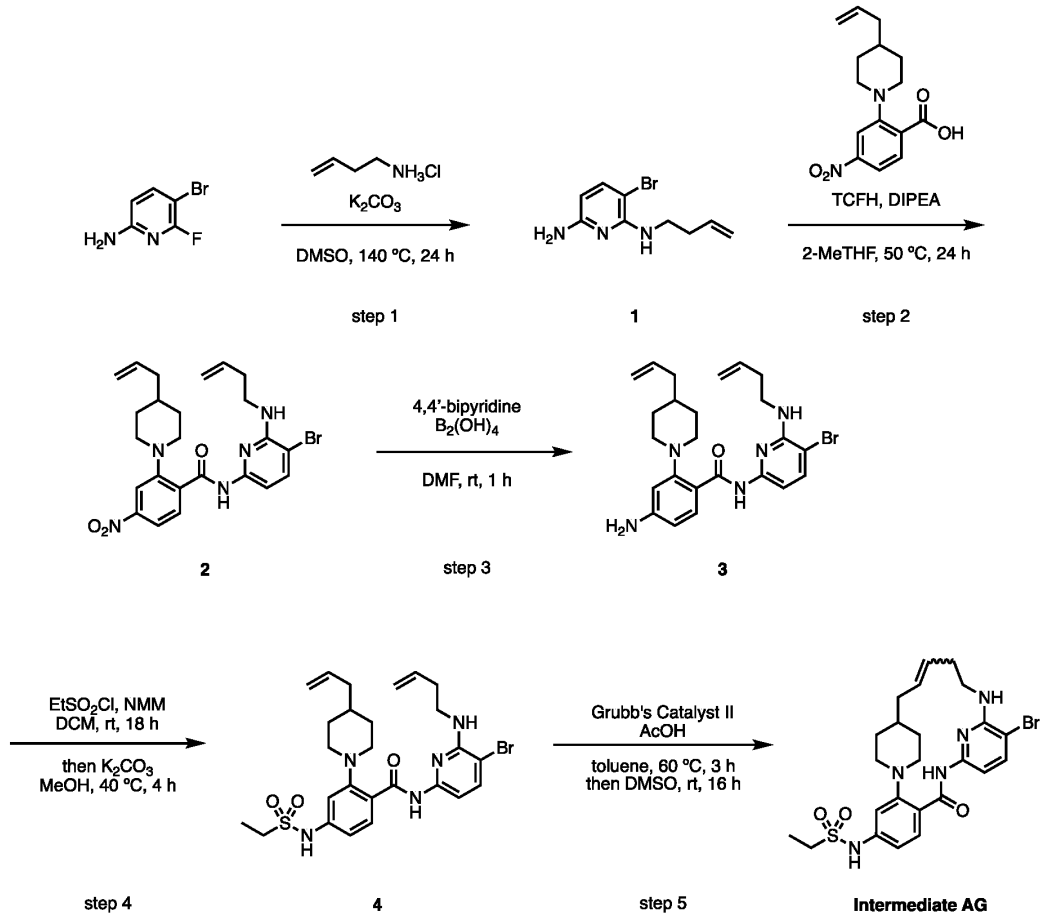
[000435] To a vial was added 2-(4-allylpiperidin-1-yl)-*N*-(6-(but-3-en-1-ylamino)-5-iodopyridin-2-yl)-4-chlorobenzamide (80 mg, 0.15 mmol) and Benzylidene(dichloro)(1,3-dimesityl-2-imidazolidinylidene)ruthenium - tricyclohexylphosphine (1:1) (25 mg, 29 µmol). The reaction was placed under a N_2 atmosphere, then toluene (4.0 mL) was added via syringe. The reaction was then heated to 100 °C. After 2.5 hour the reaction was quenched with water and diluted with EtOAc. The organic layer was separated and washed with brine, dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-20% EtOAc on heptane) provided 2^5-chloro-5^5-iodo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one, intermediate AE (32 mg, 42 %). LCMS (ESI-MS) m/z =523.0 $[M+H]^+$.

Intermediate AF. 2-(4-allylpiperidin-1-yl)-4-nitrobenzoic acid



[000436] Intermediate AF was synthesized using the same procedure as intermediate W using 4-nitro-2-fluorobenzoic acid. LCMS (ESI-MS) m/z =291.1 $[M+H]^+$.

Intermediate AG. N-(55-bromo-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)ethanesulfonamide



Step 1. 3-bromo-N^2-(but-3-en-1-yl)pyridine-2,6-diamine

[000437] To a flask was added 3-Buten-1-amine, hydrochloride (5.63 g, 52.4 mmol) and 5-Bromo-6-fluoro-pyridin-2-ylamine (5.00 g, 26.2 mmol). The vial was placed under a N_2 atmosphere and DMSO (100 mL) and K_2CO_3 (12.7 g, 91.6 mmol) were added. The reaction was then heated to 120 °C. After 24 hour, the reaction mixture was diluted with EtOAc and washed with brine (5 x), dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-20%EtOAc in heptane) provided 3-bromo-N^2-(but-3-en-1-yl)pyridine-2,6-diamine (4.29 g, 67.7 %). LCMS (ESI-MS) m/z = 242.0 $[M+H]^+$.

Step 2. 2-(4-allylpiperidin-1-yl)-N-(5-bromo-6-(but-3-en-1-ylamino)pyridin-2-yl)-4-nitrobenzamide

[000438] To a flask was added 2-(4-allylpiperidin-1-yl)-4-nitrobenzoic acid (5.00 g, 17.2 mmol), 3-bromo-N^2-(but-3-en-1-yl)pyridine-2,6-diamine (5.00 g, 20.7 mmol), *N*-

(chloro(dimethylamino)methylene)-*N*-methylmethanaminium hexafluorophosphate(V) (6.28 g, 22.4 mmol), DIPEA (6.00 mL, 34.4 mmol), and 2-MeTHF (90.0 mL). The reaction was then stirred at rt. After 24 hour the reaction mixture was quenched with 1 M aq. NaOH, diluted with water, and extracted with EtOAc (3 x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-20% EtOAc on heptane) provided 2-(4-allylpiperidin-1-yl)-*N*-(5-bromo-6-(but-3-en-1-ylamino)pyridin-2-yl)-4-nitrobenzamide (5.77 g, 65.1 %). LCMS (ESI-MS) m/z = 514.1 $[M+H]^+$.

Step 3. 2-(4-allylpiperidin-1-yl)-4-amino-N-(5-bromo-6-(but-3-en-1-ylamino)pyridin-2-yl)benzamide

[000439] To a flask was added 2-(4-allylpiperidin-1-yl)-*N*-(5-bromo-6-(but-3-en-1-ylamino)pyridin-2-yl)-4-nitrobenzamide (6.99 g, 13.6 mmol), Hypodiboric acid (4.87 g, 54.4 mmol) and 4,4'-Dipyridyl (53.1 mg, 340 μmol). The reaction vial was placed under a N_2 atmosphere, then DMF (60 mL) was added. The reaction was then stirred at 23 °C. After 1 hour the reaction mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were washed with sat. aq. $NaHCO_3$, then brine, dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-100% EtOAc on heptane) provided 2-(4-allylpiperidin-1-yl)-4-amino-*N*-(5-bromo-6-(but-3-en-1-ylamino)pyridin-2-yl)benzamide (6.00 g, 91.1 %). LCMS (ESI-MS) m/z = 484.1 $[M+H]^+$.

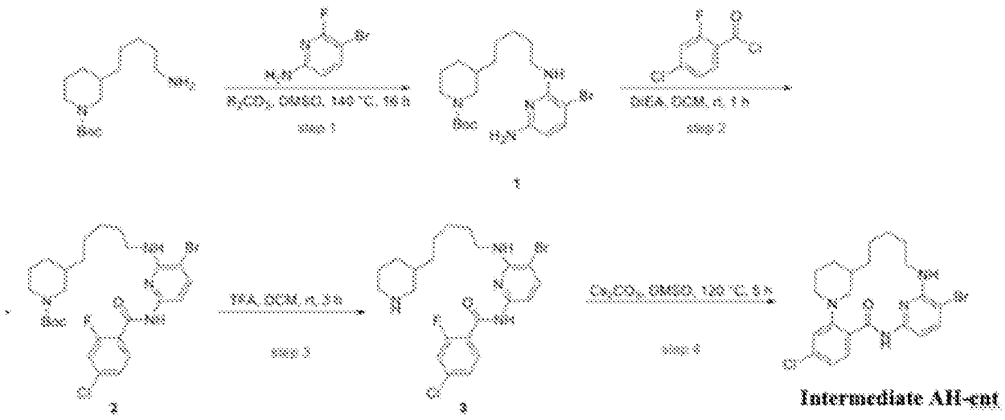
Step 4. 2-(4-allylpiperidin-1-yl)-N-(5-bromo-6-(but-3-en-1-ylamino)pyridin-2-yl)-4-(ethylsulfonamido)benzamide

[000440] To a flask was added 2-(4-allylpiperidin-1-yl)-4-amino-*N*-(5-bromo-6-(but-3-en-1-ylamino)pyridin-2-yl)benzamide (6.0 g, 12 mmol), THF (50 mL), and 4-methylmorpholine (8.2 mL, 74 mmol). Ethylsulfonyl Chloride (6.4 g, 4.7 mL, 50 mmol) in THF (10 mL) was added slowly and the reaction was stirred at rt. After 18 hour, K_2CO_3 (17 g, 0.12 mol) and MeOH (30 mL) were added and the reaction mixture heated to 40 °C. After 4 hour, the reaction mixture was diluted with brine and extracted with DCM (5 x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-10% MeOH in DCM) provided 2-(4-allylpiperidin-1-yl)-*N*-(5-bromo-6-(but-3-en-1-ylamino)pyridin-2-yl)-4-(ethylsulfonamido)benzamide (2.1 g, 29 %). LCMS (ESI-MS) m/z = 577.6 $[M+H]^+$.

Step 5. N-(55-bromo-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)ethanesulfonamide

[000441] To a flask was added 2-(4-allylpiperidin-1-yl)-*N*-(5-bromo-6-(but-3-en-1-ylamino)pyridin-2-yl)-4-(ethylsulfonamido)benzamide (2.1 g, 3.6 mmol), toluene (300 mL) and Benzylidene(dichloro)(1,3-dimesityl-2-imidazolidinylidene)ruthenium - tricyclohexylphosphine (1:1) (0.62 g, 0.73 mmol) under a N_2 atmosphere. The reaction was then heated to 60 °C. After 3 hour the reaction mixture was cooled to rt and DMSO (5.2 mL, 73 mmol) was added and stirred at rt. After 18 h, reaction mixture was concentrated in vacuo. Purification via Isco column chromatography (0-100% EtOAc on heptane) provided *N*-(5^5-bromo-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide, intermediate AG (1.5 g, 75 %). LCMS (ESI-MS) m/z = 548.1 $[M+H]^+$.

Intermediate AH-rac. 5^5-bromo-2^5-chloro-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-3-one



Step 1. *tert*-butyl 3-(5-((6-amino-3-bromopyridin-2-yl)amino)pentyl)piperidine-1-carboxylate

[000442] K_2CO_3 (21 g, 0.16 mol) was added to a solution of *tert*-butyl 3-(5-aminopentyl)piperidine-1-carboxylate (14 g, 52 mmol) and 5-bromo-6-fluoropyridin-2-amine (9.9 g, 52 mmol) in DMSO (150 mL). The resulting solution was stirred at 140 °C for 16 hours. After cooling to room temperature, the reaction was diluted with water (200 mL), extracted with EA (3 x 200 mL). The combined layers were washed with brine (2 x 200 mL), dried with anhydrous Na_2SO_4, filtered and evaporated to give a crude. The crude was purified with silica gel column, eluted with EA / PE 1 : 2 to afford *tert*-butyl 3-(5-((6-amino-3-bromopyridin-2-

yl)amino)pentyl)piperidine-1-carboxylate (15 g, 66 % yield), LCMS (ESI-MS) m/z =441.2 $[M+H]^+$.

Step 2.*tert*-butyl 3-(5-((3-bromo-6-(4-chloro-2-fluorobenzamido)pyridin-2-yl)amino)pentyl)piperidine-1-carboxylate

[000443] Into a solution of *tert*-butyl 3-(5-((6-amino-3-bromopyridin-2-yl)amino)pentyl)piperidine-1-carboxylate (15 g, 34 mmol)in DCM (300 mL)was added DIEA (13 g, 18 mL, 0.10 mol) . The mixture was cooled to 0 °C, 4-chloro-2-fluorobenzoyl chloride (6.6 g, 34 mmol) was added dropwise. The resulting solution was stirred at room temperature for 1 hours. The reaction mixture was evaporated and purified with silica gel column, eluted with EA : PE= 1 : 2 to afford *tert*-butyl 3-(5-((3-bromo-6-(4-chloro-2-fluorobenzamido)pyridin-2-yl)amino)pentyl)piperidine-1-carboxylate (14.5 g, 71 % yield), LCMS (ESI-MS) m/z =597.2 $[M+H]^+$.

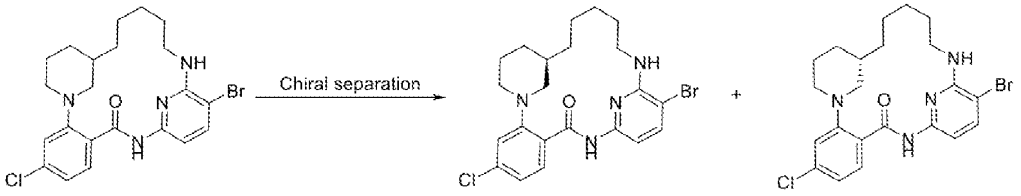
Step 3.*N*-(5-bromo-6-((5-(piperidin-3-yl)pentyl)amino)pyridin-2-yl)-4-chloro-2-fluorobenzamide

[000444] TFA (13.7 g, 120 mmol) was added to a solution of *tert*-butyl 3-(5-((3-bromo-6-(4-chloro-2-fluorobenzamido)pyridin-2-yl)amino)pentyl)piperidine-1-carboxylate (14.4 g, 24.1 mmol) in DCM (150 mL). The resulting solution was stirred at room temperature for 3 hours. The reaction mixture was evaporated to afford *N*-(5-bromo-6-((5-(piperidin-3-yl)pentyl)amino)pyridin-2-yl)-4-chloro-2-fluorobenzamide (10 g, crude), LCMS (ESI-MS) m/z =497.1 $[M+H]^+$.

Step 4.5^5-bromo-2^5-chloro-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-3-one

[000445] Cs_2CO_3 (19 g, 58 mmol) was added to a solution of *N*-(5-bromo-6-((5-(piperidin-3-yl)pentyl)amino)pyridin-2-yl)-4-chloro-2-fluorobenzamide (9.7 g, 19 mmol) in DMSO (100 mL). The resulting solution was stirred at 120 °C for 5 hours. After cooling to room temperature, the mixture was diluted with water (150 mL) and extracted with EA (3 x 150 mL). The combined organic layers were washed with brine (3 x 150 mL), dried with anhydrous Na_2SO_4, filtered and evaporated to give 5^5-bromo-2^5-chloro-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-3-one (4 g, crude), LCMS (ESI-MS) m/z =477.1 $[M+H]^+$.

Intermediate AH and Intermediate AH-1. Enantiopure 55-bromo-25-chloro-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-3-one



[000446] 5^5-bromo-2^5-chloro-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-3-one (4 g, 8 mmol) was dissolved in DCM (60 mL) and purified with the following conditions: Column: CHIRALPAK IG 3*25 cm, 5um; Mobile Phase A: CO2, Mobile Phase B: DCM: MeOH=1: 1(0.1% 2M NH3-MEOH); Flow rate: 85 mL/min; Gradient: isocratic 40% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 7.2; RT2(min): 8.15; Sample Solvent: MEOH; Injection Volume: 3 mL; Number Of Runs: 40. The fractions were collected, evaporated and lyophilized to afford:

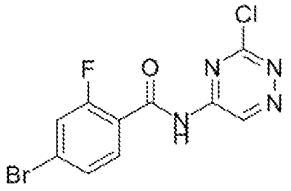
First eluting isomer (Intermediate AH):

[000447] Enantiopure 5^5-bromo-2^5-chloro-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-3-one (1.2 g, 30 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.69 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.72 (dd, J = 8.4, 0.8 Hz, 1H), 7.51 (d, J =8.4 Hz, 1H), 7.40 (s, 1H), 7.35 (dd, J = 8.4, 2.0 Hz, 1H), 6.62 (s, 1H), 3.54-3.47 (m, 1H), 3.32-3.26 (m, 1H), 3.17-3.09 (m, 1H), 3.09-2.89 (m, 2H), 2.68-2.64 (m, 1H), 2.22-2.09 (m, 1H), 2.08-1.91 (m, 2H), 1.81-1.72 (m, 1H), 1.59-1.39 (m, 6H), 1.39-1.20 (m, 2H), 1.19-1.08 (m, 1H). LCMS (ESI-MS) m/z = 477.1 [M+H]+.

Second eluting isomer (Intermediate AH-1):

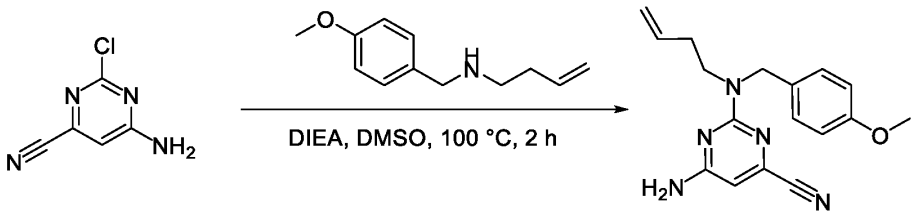
[000448] (1^3S)-5^5-bromo-2^5-chloro-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-3-one (1.1 g, 30 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.51 (d, J =8.4 Hz, 1H), 7.40 (s, 1H), 7.35 (dd, J = 8.4, 2.0 Hz, 1H), 6.62 (s, 1H), 3.59-3.45 (m, 1H), 3.32-3.26 (m, 1H), 3.18-3.09 (m, 1H), 3.03-2.95 (m, 1H), 2.94-2.88 (m, 1H), 2.68-2.59 (m, 1H), 2.23-2.08 (m, 1H), 2.07-1.88 (m, 2H), 1.87-1.72 (m, 1H), 1.65-1.38 (m, 6H), 1.37-1.21 (m, 2H), 1.20-1.05 (m, 1H). LCMS (ESI-MS) m/z = 477.1 [M+H]+.

Intermediate AI. 4-bromo-N-(3-chloro-1,2,4-triazin-5-yl)-2-fluorobenzamide



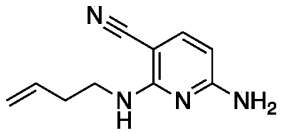
[000449] Intermediate AI was synthesized via the same procedure as Intermediate G using 3-chloro-1,2,4-triazin-5-amine in place of 2-chloro-6-methylpyrimidin-4-amine. LCMS (ESI-MS) m/z = 330.9 $[M+H]^+$.

Intermediate AJ. 6-amino-2-(but-3-en-1-yl(4-methoxybenzyl)amino)pyrimidine-4-carbonitrile



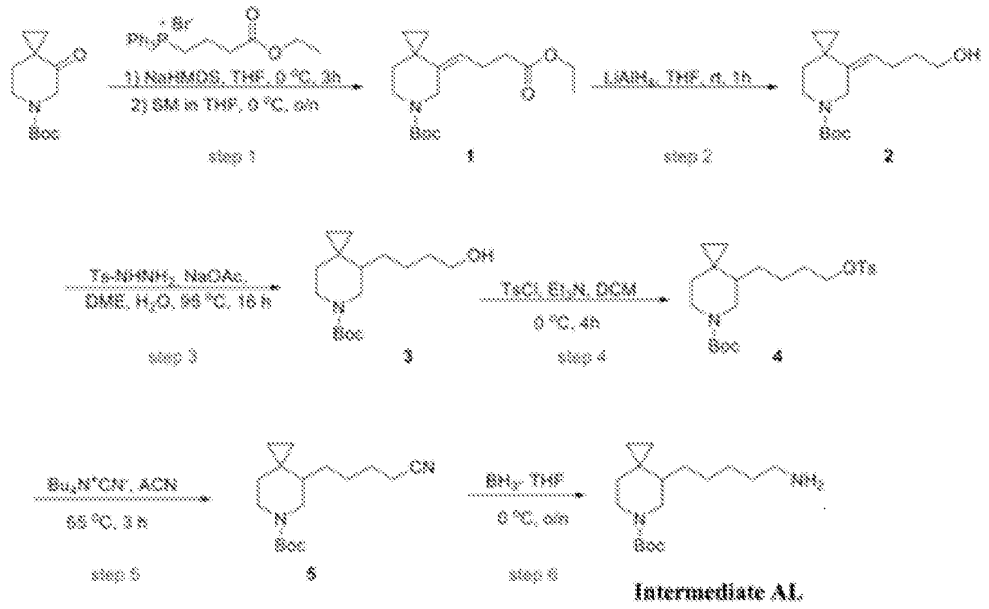
[000450] DIEA (2.5 g, 19.4 mmol) was added to a mixture of 6-amino-2-chloropyrimidine-4-carbonitrile (1 g, 6.47 mmol) and N-(4-methoxybenzyl)but-3-en-1-amine (1.24 g, 6.47 mmol) in DMSO (15 mL). The resulting mixture was heated to 100 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (300 ml) and washed with brine (3 x 300 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA / PE 1 : 3 to afford 6-amino-2-(but-3-en-1-yl(4-methoxybenzyl)amino)pyrimidine-4-carbonitrile (700 mg, 34.9% yield). LCMS (ESI-MS) m/z =310.1 $[M+H]^+$.4A

Intermediate AK. 6-amino-2-(but-3-en-1-ylamino)nicotinonitrile



[000451] Intermediate AK was synthesized via the same procedure as Intermediate AJ using 6-amino-2-chloronicotinonitrile in place of 6-amino-2-chloropyrimidine-4-carbonitrile.

Intermediate AL. tert-butyl 4-(5-aminopentyl)-6-azaspiro[2.5]octane-6-carboxylate.



Step 1. tert-butyl (Z)-4-(4-ethoxy-4-oxobutylidene)-6-azaspiro[2.5]octane-6-carboxylate

[000452] NaHMDS (34 mL, 2.0M in THF) was added to (4-ethoxy-4-oxobutyl)triphenylphosphonium bromine (12.57 g, 33.30 mmol) in THF (50 mL) in THF (50 mL) under nitrogen atmosphere. The mixture was stirred at 0 °C for 3 hours. Tert-butyl 4-oxo-6-azaspiro[2.5]octane-6-carboxylate (5 g, 22.19 mmol) was added to the reaction mixture and stirred at room temperature overnight. The reaction was poured into aq. NH_4Cl (200 mL) at room temperature. The resulting mixture was extracted with EA (3 x 200 mL). The combined organic layers were washed with brine (3 x 200mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA 10 : 1 to afford tert-butyl (Z)-4-(4-ethoxy-4-oxobutylidene)-6-azaspiro[2.5]octane-6-carboxylate (2.6 g, 32.6% yield). LCMS (ESI-MS) m/z =324.2 $[M+H]^+$.

Step 2. tert-butyl (Z)-4-(4-hydroxybutylidene)-6-azaspiro[2.5]octane-6-carboxylate

[000453] $LiAlH_4$ (0.46 g, 12.06 mmol) was added to tert-butyl (Z)-4-(4-ethoxy-4-oxobutylidene)-6-azaspiro[2.5]octane-6-carboxylate (2.6 g, 8.04 mmol in THF (50 mL) under nitrogen atmosphere at 0°C. The mixture was stirred at room temperature for 1 hour. The reaction was quenched with sat. NH_4Cl (aq.) at 0 °C. The resulting mixture was extracted with EA (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried

over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford the crude product tert-butyl (Z)-4-(4-hydroxybutylidene)-6-azaspiro[2.5]octane-6-carboxylate (2.2 g, 97.3%yield), LCMS (ESI-MS) m/z =282.2 $[M+H]^+$.

Step 3. tert-butyl 4-(4-hydroxybutyl)-6-azaspiro[2.5]octane-6-carboxylate

[000454] NaOAc (3.85 g, 46.91 mmol) was added to a mixture of 4-methylbenzene-1-sulfonohydrazide (17.47 g, 93.81 mmol) and tert-butyl (Z)-4-(4-hydroxybutylidene)-6-azaspiro[2.5]octane-6-carboxylate (2.2 g, 7.82 mmol) in DME (40 mL). The mixture was stirred at 95°C for 16 hours. The resulting mixture was concentrated under vacuum to afford the residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford tert-butyl 4-(4-hydroxybutyl)-6-azaspiro[2.5]octane-6-carboxylate (1 g, 45.1%yield), LCMS (ESI-MS) m/z =284.2 $[M+H]^+$.

Step 4. tert-butyl 4-(4-(tosyloxy)butyl)-6-azaspiro[2.5]octane-6-carboxylate

[000455] Et_3N (0.27 g, 2.65 mmol) was added to tert-butyl 4-(4-hydroxybutyl)-6-azaspiro[2.5]octane-6-carboxylate (0.25 g, 0.88 mmol) and 4-Methylbenzenesulfonyl chloride (0.42 g, 2.20 mmol) in DCM (50 mL). The mixture was stirred at room temperature overnight. The mixture was concentrated and purified by silica gel column chromatography, eluted with PE / EA 10 : 1 to afford tert-butyl 4-(4-(tosyloxy)butyl)-6-azaspiro[2.5]octane-6-carboxylate (150 mg, 38.9%yield), LCMS (ESI-MS) m/z =438.2 $[M+H]^+$.

Step 5. tert-butyl 4-(4-cyanobutyl)-6-azaspiro[2.5]octane-6-carboxylate

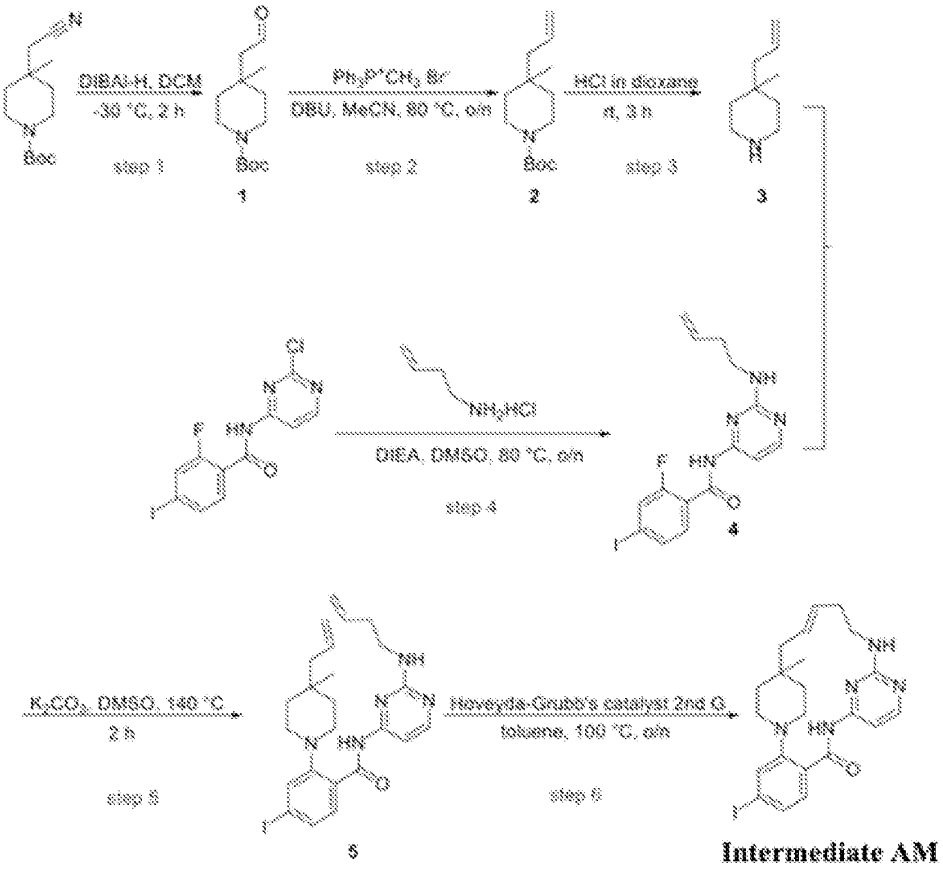
[000456] formonitrile; tetrabutylamine (138 mg, 0.52 mmol) was added to tert-butyl 4-(4-(tosyloxy)butyl)-6-azaspiro[2.5]octane-6-carboxylate (150 mg, 0.34 mmol) in ACN (5 mL) . The mixture was stirred at 65 °C for 2 hour. The reaction was poured into aq.$NaHCO_3$(50 mL) at room temperature. The resulting mixture was extracted with EA (3 x 50 mL). dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford the crude product tert-butyl 4-(4-cyanobutyl)-6-azaspiro[2.5]octane-6-carboxylate (110 mg, crude), LCMS (ESI-MS) m/z =293.2 $[M+H]^+$.

Step 6. tert-butyl 4-(5-aminopentyl)-6-azaspiro[2.5]octane-6-carboxylate

[000457] Borane-tetrahydrofuran complex (4.7 mL, 1.0M in THF) was added to tert-butyl 4-(4-cyanobutyl)-6-azaspiro[2.5]octane-6-carboxylate (110 mg, 0.38 mmol) in THF (1 mL). The mixture was stirred at room temperature overnight. The reaction was poured into MeOH(5mL) at room temperature. The resulting mixture was concentrated under vacuum to afford the crude

product tert-butyl 4-(5-aminopentyl)-6-azaspiro[2.5]octane-6-carboxylate (90 mg, crude), LCMS (ESI-MS) m/z =297.2 $[M+H]^+$.

Intermediate AM. 25-iodo-14-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one



Step 1. tert-butyl 4-methyl-4-(2-oxoethyl)piperidine-1-carboxylate

[000458] Diisobutylaluminum hydride (53 mL, 1.0 M in DCM) was added dropwise to a solution of tert-butyl 4-(cyanomethyl)-4-methylpiperidine-1-carboxylate (5 g, 20.98 mmol) in DCM (200 mL) under nitrogen atmosphere at -30 °C. The mixture was stirred at -30 °C for 2 hours. The reaction was quenched with MeOH (8 mL) and 15 mL of saturated citric acid aqueous solution and then stirred for 15 minutes. The resulting mixture was filtered and the filtrate was washed with brine (3 x 200 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated under vacuum to afford tert-butyl 4-methyl-4-(2-oxoethyl)piperidine-1-carboxylate (2.8 g crude), LCMS (ESI-MS) m/z = 142.1 $[M\text{-boc}+H]^+$.

Step 2. tert-butyl 4-allyl-4-methylpiperidine-1-carboxylate

[000459] Methyltriphenylphosphonium bromide (8.3 g, 23.20 mmol) was added to a solution of tert-butyl 4-methyl-4-(2-oxoethyl)piperidine-1-carboxylate (2.8 g, 11.60 mmol) and DBU (3.5 g, 23.20 mmol) in MeCN (40 mL). The resulting mixture was heated to 80 °C and stirred overnight. After cooling to room temperature, the reaction mixture was concentrated under vacuum, then the residue was diluted with ethyl acetate (300 ml) and washed with brine (3 x 300 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA / PE (1 : 4) to afford tert-butyl 4-allyl-4-methylpiperidine-1-carboxylate (1.4 g, 50.4% yield), LCMS (ESI-MS) m/z = 140.2 $[M\text{-boc}+H]^+$.

Step 3. 4-allyl-4-methylpiperidine

[000460] A solution of tert-butyl 4-allyl-4-methylpiperidine-1-carboxylate (1.3 g, 5.43 mmol) in HCl in 1,4-dioxane (15 mL 4.0 M) was stirred at room temperature for 3 hours. The resulting mixture was concentrated under vacuum to afford 4-allyl-4-methylpiperidine (1 g crude) as a white solid. LCMS (ESI-MS) m/z = 140.1 $[M+H]^+$.

Step 4. N-(2-(but-3-en-1-ylamino)pyrimidin-4-yl)-2-fluoro-4-iodobenzamide

[000461] DIEA (8.22 g, 63.57 mmol) was added to a solution of N-(2-chloropyrimidin-4-yl)-2-fluoro-4-iodobenzamide (3 g, 7.95 mmol) and but-3-en-1-amine hydrochloride (4.27 g, 39.73 mmol) in DMSO (40 mL). The resulting mixture was heated to 80 °C and stirred overnight. After cooling to room temperature, the reaction mixture was diluted with EA (500 ml) and washed with brine (3 x 500 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA / PE (1:2) to afford N-(2-(but-3-en-1-ylamino)pyrimidin-4-yl)-2-fluoro-4-iodobenzamide (1.5 g, 45.8% yield), LCMS (ESI-MS) m/z = 413.3 $[M+H]^+$.

Step 5. 2-(4-allyl-4-methylpiperidin-1-yl)-N-(2-(but-3-en-1-ylamino)pyrimidin-4-yl)-4-iodobenzamide

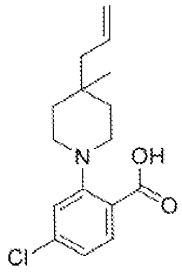
[000462] K_2CO_3 (2.1 g, 15.08 mmol) was added to a solution of 4-allyl-4-methylpiperidine (700 mg, 5.02 mmol) and N-(2-(but-3-en-1-ylamino)pyrimidin-4-yl)-2-fluoro-4-iodobenzamide (1.5 g, 5.02 mmol) in DMSO (15 mL). The resulting mixture was heated to 140 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was diluted with EA (500 ml) and washed with brine (3 x 500 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA / PE (1:4) to afford 2-(4-allyl-4-methylpiperidin-

1-yl)-N-(2-(but-3-en-1-ylamino)pyrimidin-4-yl)-4-iodobenzamide (600 mg, 22.5% yield), LCMS (ESI-MS) m/z = 532.1 $[M+H]^+$.

Step 6. (E)-2^5-iodo-14-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one

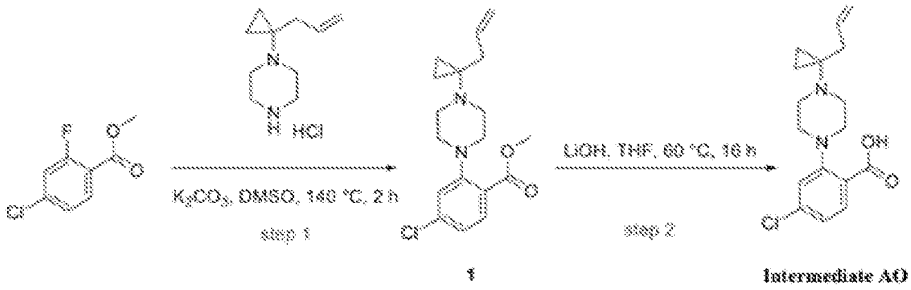
[000463] Hoveyda-Grubb's catalyst 2nd G (3.3 g, 5.27 mmol) was added to a solution of 2-(4-allyl-4-methylpiperidin-1-yl)-N-(2-(but-3-en-1-ylamino)pyrimidin-4-yl)-4-iodobenzamide (560 mg, 1.05 mmol) in toluene (10 mL) and the resulting mixture was heated to 100 °C and stirred overnight. After cooling to room temperature, the resulting mixture was concentrated under vacuum and the residue was purified by silica gel column chromatography, eluted with EA / PE 1 : 2 to afford (E)-2^5-iodo-14-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (200 mg crude). LCMS (ESI-MS) m/z = 504.1 $[M+H]^+$.

Intermediate AN. 2-(4-allyl-4-methylpiperidin-1-yl)-4-chlorobenzoic acid



[000464] Intermediate AN was synthesized from 4-allyl-4-methylpiperidine (described in synthesis of Intermediate AB) and 4-chloro-2-fluorobenzoic acid following the same procedure as used in synthesis of intermediate AO, LCMS (ESI-MS) m/z = 294.1 $[M+H]^+$.

Intermediate AO. 2-(4-(1-allylcyclopropyl)piperazin-1-yl)-4-chlorobenzoic acid



Step 1. methyl 2-(4-(1-allylcyclopropyl)piperazin-1-yl)-4-chlorobenzoate

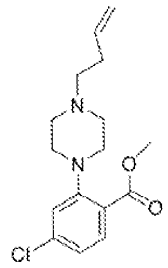
[000465] K_2CO_3 (661 mg, 4.79 mmol) was added to a mixture of methyl 4-chloro-2-fluorobenzoate (300 mg, 1.60 mmol) and 1-(1-allylcyclopropyl)piperazine (264 mg, 1.60 mmol) in DMSO (5 mL). The resulting mixture was heated to 140 °C and stirred for 2 hours.

After cooling to room temperature, the reaction mixture was diluted with water (5 mL) and extracted with EA (2 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with PE / EA 4 : 1 to afford methyl 2-(4-(1-allylcyclopropyl)piperazin-1-yl)-4-chlorobenzoate (310 mg, 58.3% yield), LCMS (ESI-MS) m/z = 335.1 $[M+H]^+$.

Step 2. 2-(4-(1-allylcyclopropyl)piperazin-1-yl)-4-chlorobenzoic acid

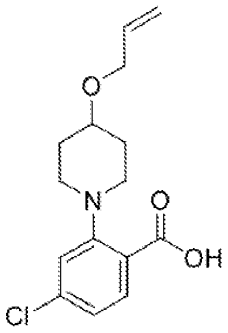
[000466] LiOH (215 mg, 8.90 mmol) was added to a mixture of methyl 2-(4-(1-allylcyclopropyl)piperazin-1-yl)-4-chlorobenzoate (300 mg, 0.89 mmol) in THF (5 mL). The resulting mixture was heated to 60 °C and stirred for 16 hours. Then, the reaction mixture was filtered and concentrated under vacuum to afford the crude product 2-(4-(1-allylcyclopropyl)piperazin-1-yl)-4-chlorobenzoic acid (270 mg, crude), LCMS (ESI-MS) m/z = 321.1 $[M+H]^+$.

Intermediate AP. Methyl 2-(4-(but-3-en-1-yl)piperazin-1-yl)-4-chlorobenzoate



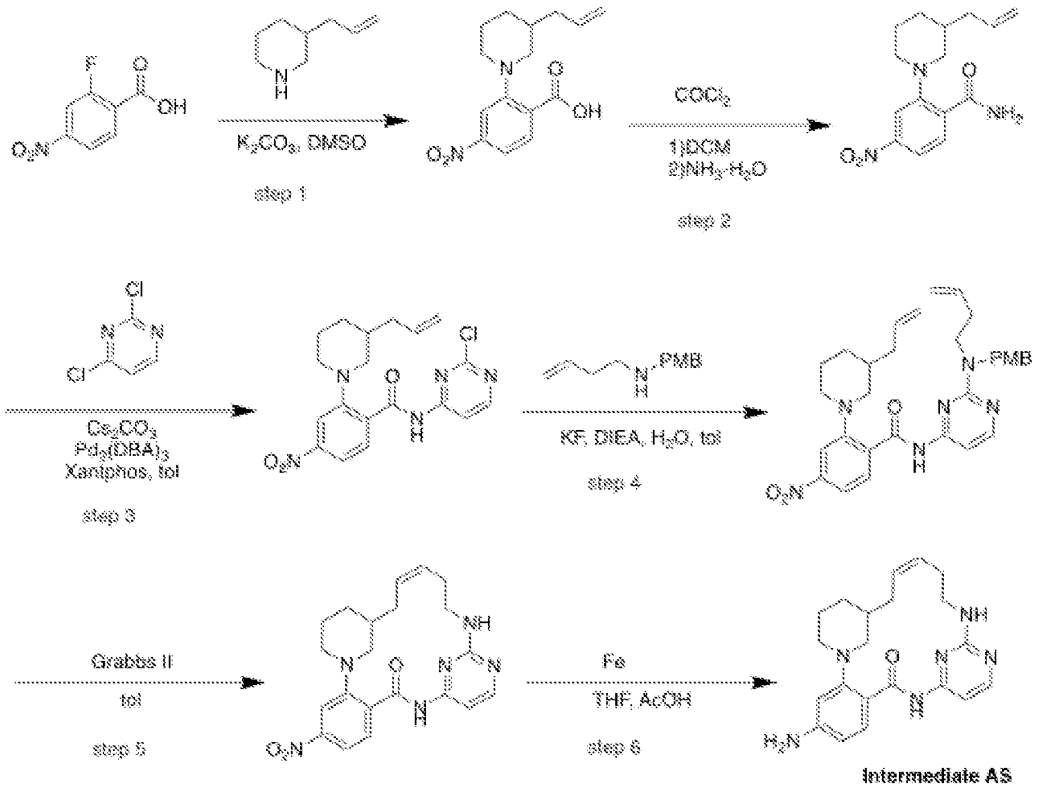
[000467] Intermediate AP was synthesized from 4-chloro-2-fluorobenzoic acid and 1-(but-3-en-1-yl)piperazine using the procedure described in step 4 of preparation of Intermediate AB.

Intermediate AR. 2-(4-(allyloxy)piperidin-1-yl)-4-chlorobenzoic acid



[000468] Intermediate AR was synthesized from *tert*-butyl 4-hydroxy-piperidine-1-carboxylate following the same route and procedure as for intermediate AW-1.

Intermediate AS. (*Z*)-25-amino-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one.



Step 1. 2-(3-allylpiperidin-1-yl)-4-nitrobenzoic acid.

[000469] 2-fluoro-4-nitrobenzoic acid (2.74 g, 14.79 mol, 1.0 eq), K_2CO_3 (5.111 g, 36.978 mmol, 2.5 eq) and DMSO (12V) were charged into a reactor with stirring. 3-allylpiperidine (2.778 g, 22.187 mmol, 1.5 eq) was dropped into the mixture. The reaction mixture was warmed up to 110~130 °C and stirred for 2~4 h. The reaction was monitored by HPLC. After the reaction was completed, the reactor was cooled to 20-30 °C and the mixture was poured into the water (15 V). After adjusting the pH to 1-2 with 6M HCl, the mixture was filtered and the filter cake was rinsed with H_2O (2 V). The filter cake was collected and dried under reduced pressure at < 60 °C to produce 2-(3-allylpiperidin-1-yl)-4-nitrobenzoic acid (3.70 g, 86% yield)

Step 2. 2-(3-allylpiperidin-1-yl)-4-nitrobenzamide.

[000470] DCM(10V) and 2-(3-allylpiperidin-1-yl)-4-nitrobenzoic acid (17.65 g, 60.796 mmol, 1.0 eq) were charged into a reactor with stirring. $(COCl)_2$ (19.292 g, 151.991 mmol, 2.5 eq) was dropped into the mixture. The reaction mixture was stirred at 20~30 °C for 1~2 h. The reaction was monitored by HPLC. After the reaction was completed, the solvent was removed under reduced pressure at < 40 °C until no significant distillate observed. The residue was dissolved with 10V DCM and added dropwise to the 10V ammonia water. The mixture was

filtered and the filter cake was rinsed with 2V DCM. The filter cake was collected and dried under reduced pressure at < 50 °C. 2-(3-allylpiperidin-1-yl)-4-nitrobenzamide (17.00 g, 97% yield) was obtained.

Step 3. 2-(3-allylpiperidin-1-yl)-*N*-(2-chloropyrimidin-4-yl)-4-nitrobenzamide.

[000471] 2-(3-allylpiperidin-1-yl)-4-nitrobenzamide (5.000g, 17.28mmol, 1.0 eq), PB125249 (2.832g, 19.01mmol, 1.1eq), Cs_2CO_3 (6.194g, 19.01mmol ,1.1 eq), $PD_2(DBA)_3$ (158.2 mg,172.8 μmol, 0.01 eq), Xantphos(300.0mg, 518.4 μmol, 0.03 eq) and toluene (100ml) were charged to a reactor under nitrogen. The reaction mixture was stirred at 70-90 °C for 2 h. The reaction was monitored by HPLC. After the reaction was completed, it was cooled to 20-30°C and filtered. The filter cake was washed with 3V toluene, the filtrate was concentrated under reduced pressure, and 2-(3-allylpiperidin-1-yl)-*N*-(2-chloropyrimidin-4-yl)-4-nitrobenzamide (7.5g > 100% yield) was obtained.

Step 4. 2-(3-allylpiperidin-1-yl)-*N*-(2-(but-3-en-1-yl(4-methoxybenzyl)amino)pyrimidin-4-yl)-4-nitrobenzamide.

[000472] 2-(3-allylpiperidin-1-yl)-*N*-(2-chloropyrimidin-4-yl)-4-nitrobenzamide (5.000 g, 12.411 mmol, 1 eq), H_2O (5V) and toluene (5V) were charged to a reactor, followed by KF (2.884 g, 49.646 mmol, 4.0 eq) and DIPEA (4.812 g, 37.234 mmol, 3.0 eq). N-(4-methoxybenzyl)but-3-en-1-amine (2.849 g, 14.894 mmol, 1.2 eq) was added, and the mixture was stirred at 100°C for 60 h. The reaction was monitored by HPLC. After the reaction was completed, the mixture was concentrated under reduced pressure. The aqueous phase was extracted with 10V MTBE, and the organic phase was concentrated under reduced pressure. Column chromatography was performed and 2-(3-allylpiperidin-1-yl)-*N*-(2-(but-3-en-1-yl(4-methoxybenzyl)amino)pyrimidin-4-yl)-4-nitrobenzamide (4.5g, 65.1% yield) was obtained

Step 5. (*Z*)-5^6-methyl-25-nitro-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one .

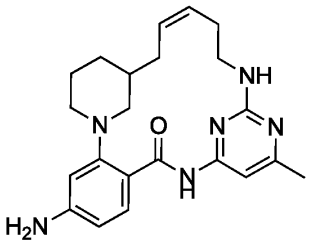
[000473] 2-(3-allylpiperidin-1-yl)-*N*-(2-(but-3-en-1-yl(4-methoxybenzyl)amino)pyrimidin-4-yl)-4-nitrobenzamide (3.000 g, 5.389 mmol, 1 eq) and toluene (100V) were charged to a reactor, and the solution was heated to 80-90 °C. Toluene (100V) solution of Grubbs II (686.317 mg, 808.402 μmol, 0.15 eq) was added, the mixture was stirred at 80-90°C for 2h. 2-(3-allylpiperidin-1-yl)-*N*-(2-(but-3-en-1-yl(4-methoxybenzyl)amino)pyrimidin-4-yl)-4-nitrobenzamide (1.500 g, 2.695 mmol, 1 eq) and toluene (100V) were charged to a reactor and the solution was heated to 80-90 °C. Toluene (100V) solution of Grubbs II (343.158 mg,404.201 μmol, 0.15 eq) was added, the mixture was stirred at 80-90°C for 2h.

[000474] The reaction was monitored by HPLC. After the reaction was completed, the mixture of 015# and 016# experiments were combined and concentrated under reduced pressure. Column chromatography purification was performed, and (*Z*)-5^{6}-methyl-25-nitro-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (2.5 g, 58.5% yield) was obtained.

Step 6. ((*Z*)-25-amino-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one.

[000475] (*Z*)-5^{6}-methyl-25-nitro-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (1.5000 g, 2.838 mmol, 1eq), CH_3COOH (1.363 g, 22.701 mmol, 8 eq), Fe (3.169 g, 56.754 mmol, 20 eq) and THF (20V) were charged to a reactor, and the reaction mixture was stirred at 10-20°C for 3hr. The reaction was monitored by HPLC. After the reaction was completed, the mixture was concentrated under reduced pressure. To the residue was added 20V DCM and 20V H_2O, and the mixture was filtered. The organic phase was separated and concentrated under reduced pressure. Column chromatography purification was performed and (*Z*)-2^{5}-amino-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (860mg) was obtained.

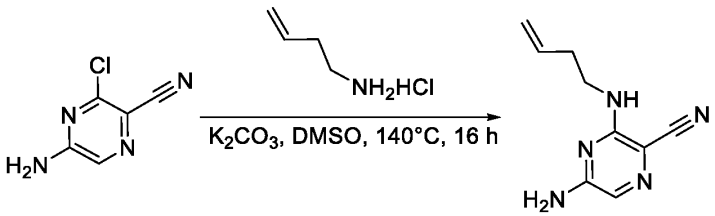
Intermediate AT. (*Z*)-2^{5}-amino-56-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one.



Intermediate AT

[000476] Intermediate AT was obtained following the same procedure as Intermediate AS, 2,4-dichloro-6-methylpyrimidine was used in step 3.

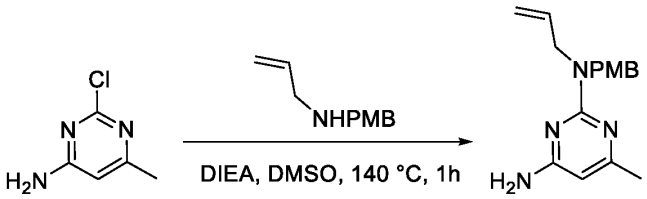
Intermediate AU. 5-amino-3-(but-3-en-1-ylamino)pyrazine-2-carbonitrile



[000477] K_2CO_3 (5 g, 0.04 mol) was added to the mixture of 5-amino-3-chloropyrazine-2-carbonitrile (2 g, 0.01 mol) and but-3-en-1-amine hydrochloride (3 g, 4 Eq, 0.03 mol) in DMSO

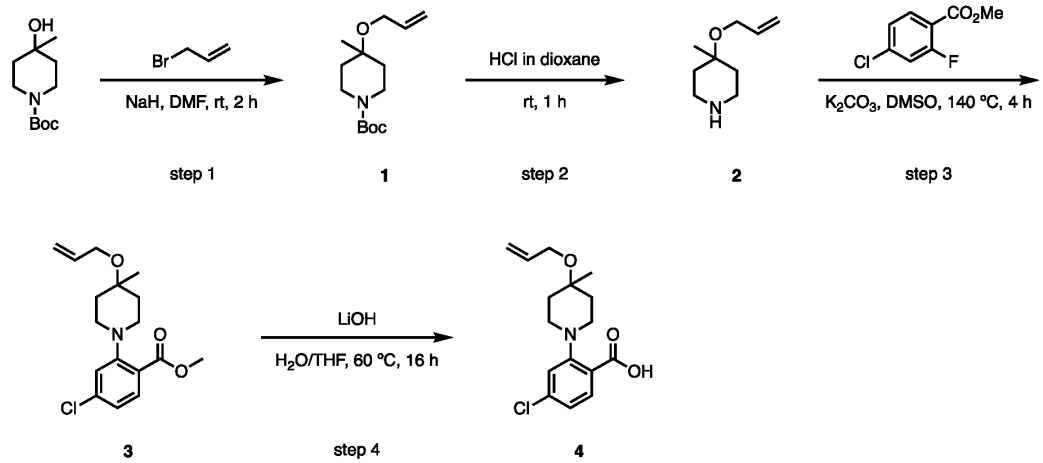
(50 mL). The mixture was stirred at 140 °C for 16 hours. The reaction mixture was diluted with water (100 mL). The resulting mixture was extracted with EA (3 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA / PE 1:2 to afford 5-amino-3-(but-3-en-1-ylamino)pyrazine-2-carbonitrile (2 g, 80 % yield), LCMS (ESI-MS) m/z =190.2$[M+H]^+$.

Intermediate AV. N2-allyl-N2-(4-methoxybenzyl)-6-methylpyrimidine-2,4-diamine



[000478] DIEA (8 g, 0.06 mol) was added to the mixture of 2-chloro-6-methylpyrimidin-4-amine (3 g, 0.02 mol) and N-(4-methoxybenzyl)prop-2-en-1-amine (4 g, 0.03 mol) in DMSO (60 mL). The mixture was stirred at 140 °C for 1 hour. The reaction mixture was diluted with water (600 mL). The resulting mixture was extracted with EA (3 x 30 mL). The combined organic layers were washed with brine (3 x 1.2 L), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA / PE (1:5) to afford N^2-allyl-N^2-(4-methoxybenzyl)-6-methylpyrimidine-2,4-diamine (2.2 g, 40 % yield), LCMS (ESI-MS) m/z =285.2 $[M+H]^+$.

Intermediate AW. 2-(4-(allyloxy)-4-methylpiperidin-1-yl)-4-chlorobenzoic acid



Step 1. tert-butyl 4-(allyloxy)-4-methylpiperidine-1-carboxylate

[000479] To a stirred solution of *tert*-butyl 4-hydroxy-4-methylpiperidine-1-carboxylate (3 g, 13.93 mmol) in anhydrous DMF (30 mL) was added NaH (1 g, 41.80 mmol) at 0 °C and stirred for 1 hour. Then add dropwise 3-bromoprop-1-ene (2.53 g, 20.92 mmol) dissolved in DMF. The resulting mixture was stirred. After 2 hours, the reaction was quenched with water (10 mL) and the aqueous layer was extracted with EA (2 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with PE : EA = 4 : 1 to afford tert-butyl 4-(allyloxy)-4-methylpiperidine-1-carboxylate (2.6 g, 73% yield). LCMS (ESI-MS) m/z = 256.2 $[M+H]^+$.

Step 2. 4-(allyloxy)-4-methylpiperidine

[000480] 4M HCl in 1,4-dioxane (10 mL) was added to a stirred mixture of tert-butyl 4-(allyloxy)-4-methylpiperidine-1-carboxylate (2.6 g, 10.18 mmol) in 1,4-dioxane (10 mL). The resulting mixture was stirred at room temperature for 1 hour and concentrated to afford the crude product 4-(allyloxy)-4-methylpiperidine (1.5 g), which was used for the next step without further purification. LCMS (ESI-MS) m/z = 156.1 $[M+H]^+$.

Step 3. Methyl 2-(4-(allyloxy)-4-methylpiperidin-1-yl)-4-chlorobenzoate (intermediate AW)

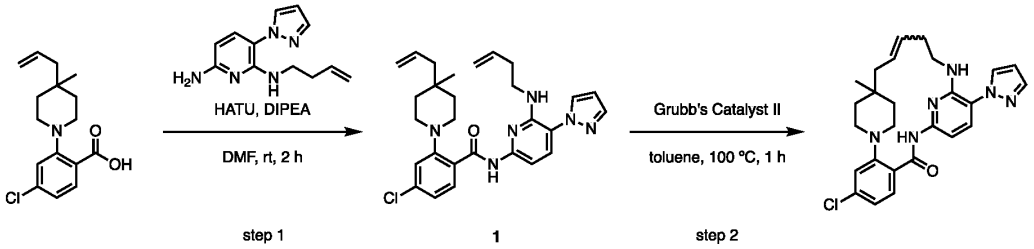
[000481] K_2CO_3 (3.7 g, 27.05 mmol) was added to a mixture of 4-(allyloxy)-4-methylpiperidine (1.4 g, 9.02 mmol) and methyl 4-chloro-2-fluorobenzoate (1.7 g, 9.02 mmol) in DMSO (10 mL). The resulting mixture was heated to 140 °C and stirred for 4 hours. After cooling to room temperature, the reaction mixture was diluted with water (20 mL) and extracted with EA (2 x 20 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with PE : EA = 4 : 1 to afford methyl 2-(4-(allyloxy)-4-methylpiperidin-1-yl)-4-chlorobenzoate (2 g, 68% yield). LCMS (ESI-MS) m/z = 324.1 $[M+H]^+$.

Step 4. 2-(4-(allyloxy)-4-methylpiperidin-1-yl)-4-chlorobenzoic acid (Intermediate AW-1)

[000482] LiOH (1.4 g, 58.6 mmol) was added to a mixture of methyl 2-(4-(allyloxy)-4-methylpiperidin-1-yl)-4-chlorobenzoate (1.9 g, 5.87 mmol) in THF (15 mL) and H_2O (5 mL). The resulting mixture was heated to 50 °C and stirred for 16 hours. After cooling to room temperature, the reaction mixture was diluted with water (20 mL) and extracted with EA (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous

Na_2SO_4, filtered and concentrated under vacuum to afford 2-(4-(allyloxy)-4-methylpiperidin-1-yl)-4-chlorobenzoic acid (1.8 g, 99% yield). LCMS (ESI-MS) m/z = 310.1 $[M+H]^+$.

Intermediate AX. 2^5-chloro-1^4-methyl-5^5-(1H-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one



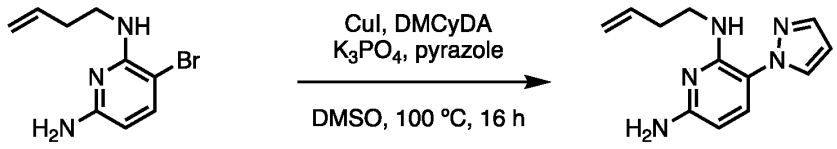
Step 1. 2-(4-allyl-4-methylpiperidin-1-yl)-N-(6-(but-3-en-1-ylamino)-5-(1H-pyrazol-1-yl)pyridin-2-yl)-4-chlorobenzamide

[000483] Intermediate AN (6.5 g, 0.022 mol) was added to a stirred mixture of HATU (12.6 g, 0.033 mol), Intermediate AY (5.1 g, 0.022 mol) and DIPEA (8.5 g, 0.066 mol) in DMF (50 mL) .The resulting mixture was stirred at room temperature. After 2 hour, the reaction mixture was diluted with H_2O (50 mL) and extracted with EA (2 x 2 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified with silica gel column, eluted with PE : DCM = 2 : 1 to afford methyl 2-(4-allyl-4-methylpiperidin-1-yl)-4-chlorobenzoate (10 g, 89.6% yield). LCMS (ESI-MS) m/z = 505.2 $[M+H]^+$.

Step 2. 25-chloro-14-methyl-55-(1H-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one

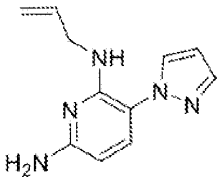
[000484] 2-(4-allyl-4-methylpiperidin-1-yl)-*N*-(6-(but-3-en-1-ylamino)-5-(1*H*-pyrazol-1-yl)pyridin-2-yl)-4-chlorobenzamide (10 g, 0.020 mol) was added to a stirred mixture of Dichloro(1,3-dimesityl-2-imidazolidinylidene)(2-isopropoxybenzylidene)ruthenium (1.25 g, 0.002 mol) in Toluene (400 mL). The resulting mixture was stirred for 1 hours at 100 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE : EA =6:1 to afford 2^5-chloro-1^4-methyl-5^5-(1*H*-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (6 g, 63.6% yield). LCMS (ESI-MS) m/z = 477.2 $[M+H]^+$.

Intermediate AY. N2-(but-3-en-1-yl)-3-(1H-pyrazol-1-yl)pyridine-2,6-diamine



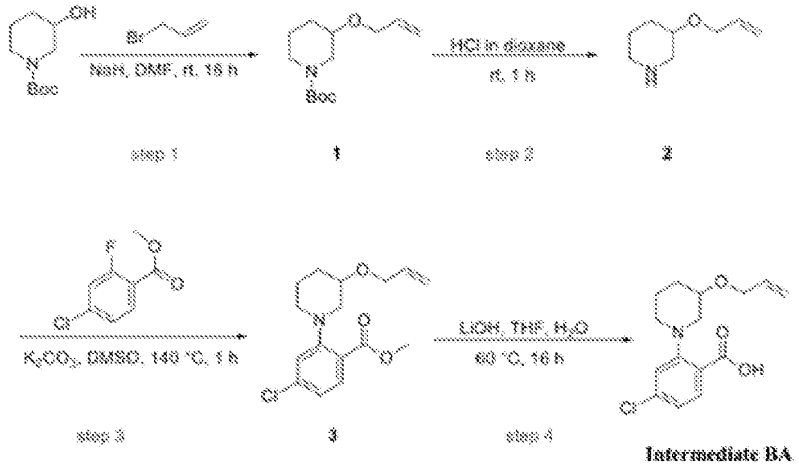
[000485] CuI (47 g, 0.25 mol) was added to the mixture of 3-bromo-*N*²-(but-3-en-1-yl)pyridine-2,6-diamine (40 g, 0.17 mol), K_3PO_4 (110 g, 0.51 mol), 1H-pyrazole (34 g, 0.50 mol) and (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (35 g, 0.25 mol) in DMSO (400 mL) under N_2 atmosphere. The mixture was stirred at 100°C overnight. The reaction mixture was diluted with water (2 L). The resulting mixture was extracted with EA (3 x 2 L). The combined organic layers were washed with brine (3 L), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography, eluted with EA : PE = 1:4 to afford *N*²-(but-3-en-1-yl)-3-(1H-pyrazol-1-yl)pyridine-2,6-diamine (20.1 g, 53% yield). LCMS (ESI-MS) m/z = 230.1 $[M+H]^+$.

Intermediate AZ. N2-allyl-3-(1H-pyrazol-1-yl)pyridine-2,6-diamine



[000486] Intermediate AZ was synthesized using the same procedure as Intermediate AY with *N*²-allyl-3-bromopyridine-2,6-diamine (synthesized from allyl amine in similar manner as described in Step 1 of Intermediate AG) being used in place of 3-bromo-*N*²-(but-3-en-1-yl)pyridine-2,6-diamine.

Intermediate BA. 2-(3-(allyloxy)piperidin-1-yl)-4-chlorobenzoic acid



Step 1. tert-butyl 3-(allyloxy)piperidine-1-carboxylate

[000487] NaH (0.9 g, 0.04 mol) was added to the mixture of 3-bromoprop-1-ene (3 g, 0.02 mol) and tert-butyl 3-hydroxypiperidine-1-carboxylate (5 g, 0.02 mol) in DMF (25 mL). The

mixture was stirred at room temperature for 16 hours. The resulting mixture was diluted with aq. NH_4Cl (200 mL). The resulting mixture was extracted with EA (3 x 200 mL). The combined organic layers were washed with brine (600 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford the crude product *tert*-butyl 3-(allyloxy)piperidine-1-carboxylate (4.2 g, crude), LCMS (ESI-MS) m/z =242.2 $[M+H]^+$.

Step 2.3-(allyloxy)piperidine hydrochloride

[000488] 2 M HCl in dioxane (10 mL) was added to *tert*-butyl 3-(allyloxy)piperidine-1-carboxylate (4 g, 0.02 mol) in EA (10 mL). The mixture was stirred at room temperature for 1 hour. The resulting mixture was concentrated under vacuum to afford the crude product 3-(allyloxy)piperidine hydrochloride (3.7 g, crude), LCMS (ESI-MS) m/z =142.2 $[M+H]^+$.

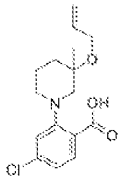
Step 3. methyl 2-(3-(allyloxy)piperidin-1-yl)-4-chlorobenzoate.

[000489] K_2CO_3 (10 g, 74 mmol) was added to the mixture of 3-(allyloxy)piperidine (3.5 g, 25 mmol) and methyl 4-chloro-2-fluorobenzoate (4.7 g, 25 mmol) in DMSO (30 mL). The mixture was stirred at 140°C for 1 hour. The reaction mixture was diluted with water (500 mL). The resulting mixture was extracted with EA (3 x 500 mL). The combined organic layers were washed with brine (1.5 L), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA / PE 1:5 to afford methyl 2-(3-(allyloxy)piperidin-1-yl)-4-chlorobenzoate (2 g, 30 % yield), LCMS (ESI-MS) m/z =142.2 $[M+H]^+$.

Step 4.2-(3-(allyloxy)piperidin-1-yl)-4-chlorobenzoic acid

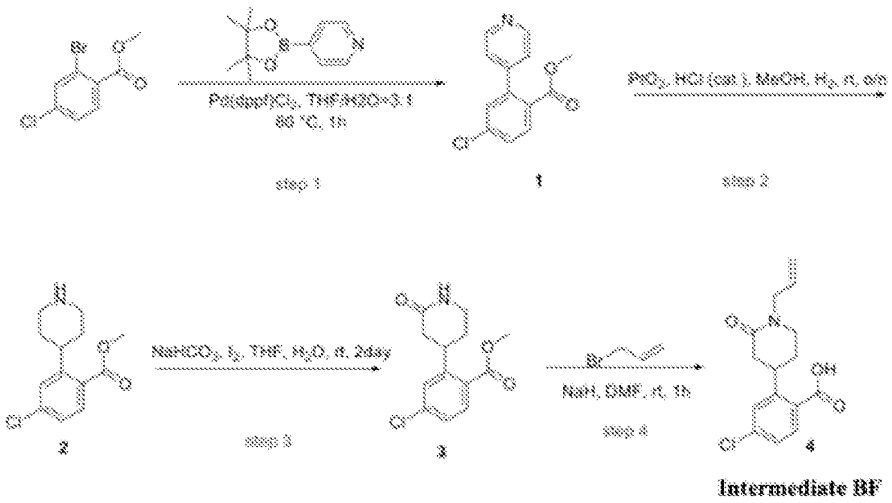
[000490] LiOH (0.9 g, 0.04 mol) was added to the mixture of methyl 2-(3-(allyloxy)piperidin-1-yl)-4-chlorobenzoate (2 g, 6 mmol) in THF (60 mL) and water (20 mL). The mixture was stirred at 60°C for 16 hours. The mixture was acidified to pH 2 with conc. HCl. The resulting mixture was extracted with EA (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford the crude product 2-(3-(allyloxy)piperidin-1-yl)-4-chlorobenzoic acid (1.3 g, crude), LCMS (ESI-MS) m/z =296.1$[M+H]^+$.

Intermediate BE. 2-(3-(allyloxy)-3-methylpiperidin-1-yl)-4-chlorobenzoic acid



[000491] Intermediate BE was synthesized from *tert*-butyl 3-hydroxy-3-methylpiperidine-1-carboxylate using the same 4-step sequence as in synthesis of Intermediate BA. LCMS (ESI-MS) m/z = 324.1 $[M+H]^+$.

Intermediate BF. 2-(1-allyl-2-oxopiperidin-4-yl)-4-chlorobenzoic acid



Step 1. methyl 4-chloro-2-(pyridin-4-yl)benzoate

[000492] $PdCl_2(dppf)$ (1.6 g, 2.20 mmol) was added to the mixture of methyl 2-bromo-4-chlorobenzoate (5.5 g, 22 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (5.4 g, 26 mmol) and K_2CO_3 (9.1 g, 66 mmol) in THF (30 mL) and water (10 mL) under nitrogen atmosphere. The mixture was stirred at 80 °C for 1 hour. The reaction mixture was diluted with water (60 mL). The resulting mixture was extracted with EA (3 x 60 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA / PE (1:10) to afford methyl 4-chloro-2-(pyridin-4-yl)benzoate (4.4 g, 18 mmol, 81 %), LCMS (ESI-MS) m/z = 248.0 $[M+H]^+$.

Step 2. methyl 4-chloro-2-(piperidin-4-yl)benzoate

[000493] Platinic oxide (4.0 g, 18 mmol) was added the mixture of methyl 4-chloro-2-(pyridin-4-yl)benzoate (4.4 g, 18 mmol) and con. HCl (0.15 mL) in MeOH (60 mL) under nitrogen atmosphere. The mixture was stirred at room temperature overnight under hydrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with MeOH (3 x 30 mL). The filtrate was concentrated under reduced pressure to afford the crude product methyl 4-chloro-2-(piperidin-4-yl)benzoate (3.2 g, crude), LCMS (ESI-MS) m/z = 254.1 $[M+H]^+$.

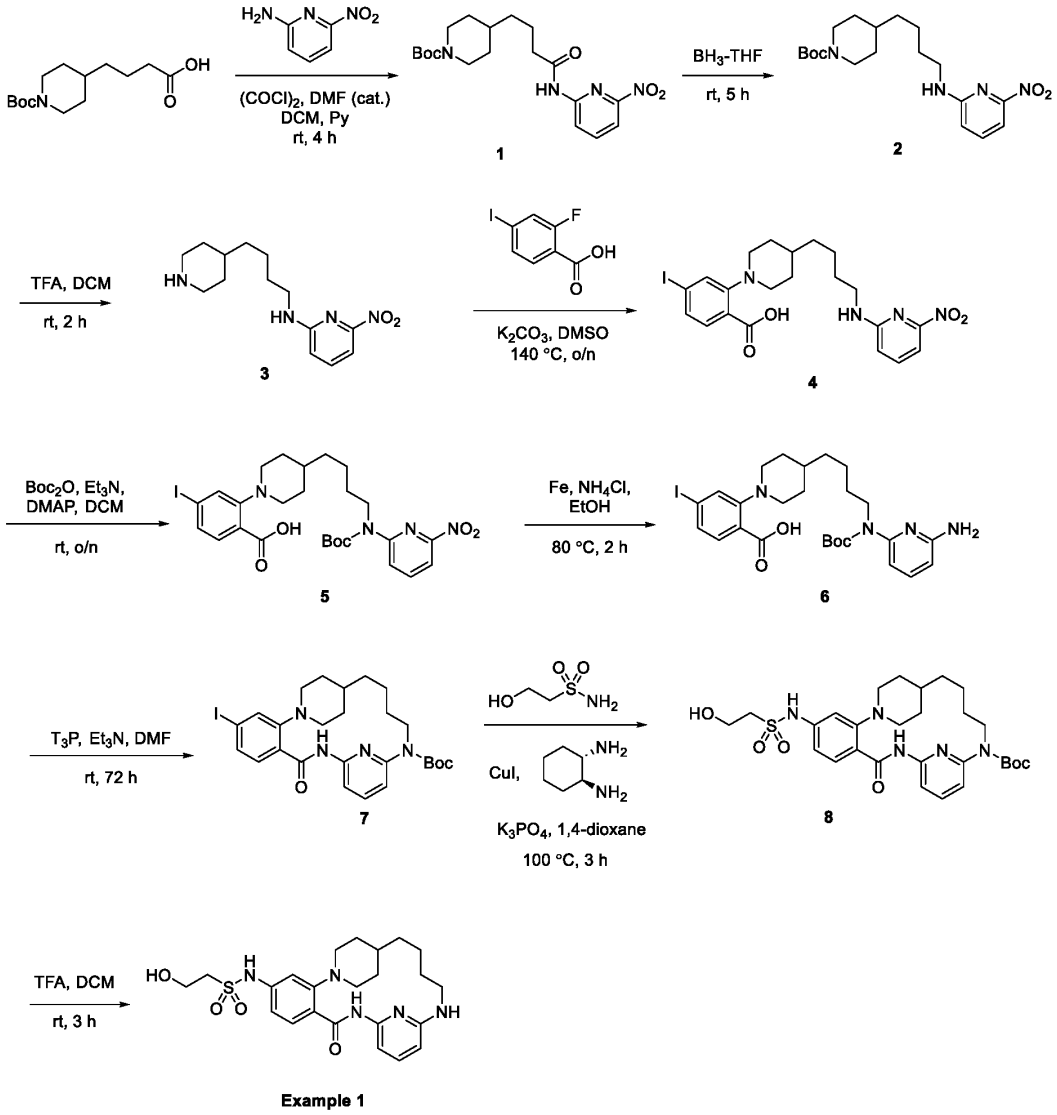
Step 3. methyl 4-chloro-2-(2-oxopiperidin-4-yl)benzoate

[000494] I_2 (13 g, 4 Eq, 50 mmol) was added to the mixture of methyl 4-chloro-2-(piperidin-4-yl)benzoate (3.2 g, 13 mmol) and Sodium bicarbonate (11 g, 0.13 mol) in THF (25 mL) and water (10 mL). The mixture was stirred at room temperature for 48 hours. The reaction mixture was diluted with aq. $Na_2S_2O_3$(30 mL). The resulting mixture was extracted with EA (3 x 50 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA / PE (1:10) to afford methyl 4-chloro-2-(2-oxopiperidin-4-yl)benzoate (1.2 g, 36.0 % yield), LCMS (ESI-MS) m/z = 248.0 $[M+H]^+$.

Step 4. 2-(1-allyl-2-oxopiperidin-4-yl)-4-chlorobenzoic acid

[000495] NaH (0.16 g, 6.7 mmol) was added to the mixture of methyl 4-chloro-2-(2-oxopiperidin-4-yl)benzoate (1.2 g, 4.5 mmol), 3-bromoprop-1-ene (0.65 g, 5.4 mmol) in DMF (30 mL). The mixture was stirred at room temperature for 1 hour. The resulting mixture was diluted with aq. NH_4Cl (200 mL). The resulting mixture was extracted with EA (3 x 100 mL). The combined organic layers were washed with brine (3 x 300 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford the crude product 2-(1-allyl-2-oxopiperidin-4-yl)-4-chlorobenzoic acid (40 mg, crude), LCMS (ESI-MS) m/z = 294.1$[M+H]^+$.

Example 1. 2-hydroxy-N-(3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide was prepared starting from 4-(1-(tert-butoxycarbonyl)piperidin-4-yl)butanoic acid following General synthetic route 1A as outlined in the procedure below.



Step 1. tert-butyl 4-(4-((6-nitropyridin-2-yl)amino)-4-oxobutyl)piperidine-1-carboxylate

[000496] $(COCl)_2$ (3.04 g, 23.9 mmol) was added into a stirred mixture of 4-(1-(tert-butoxycarbonyl)piperidin-4-yl)butanoic acid (5 g, 18.4 mmol) in DCM (60 mL) at 0 °C, followed by addition a drop of DMF. The resulting mixture was stirred for 2 hours at room temperature. A mixture of 6-nitropyridin-2-amine (2.56 g, 18.4 mmol) in pyridine (40 mL) was added to the reaction mixture above dropwise at room temperature. The resulting mixture was

stirred for additional 2 hours at room temperature, diluted with saturated aqueous NH_4Cl (500 mL) and extracted with EA (3 x 500 mL). The combined organic layers were concentrated under vacuum. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 10% to 80% gradient in 50 min to afford the desired product tert-butyl 4-(4-((6-nitropyridin-2-yl)amino)-4-oxobutyl)piperidine-1-carboxylate (4.5 g, 62.2% yield). LCMS (ESI-MS) m/z = 393.2 $[M+H]^+$.

Step 2. tert-butyl 4-(4-((6-nitropyridin-2-yl)amino)butyl)piperidine-1-carboxylate

[000497] BH_3-THF complex (1 M in THF, 14.9 mL, 14.9 mmol) was added into a stirred mixture of tert-butyl 4-(4-((6-nitropyridin-2-yl)amino)-4-oxobutyl)piperidine-1-carboxylate (4.5 g, 11.5 mmol) in THF (60 mL) at 0 °C. The resulting mixture was stirred for 5 hours at room temperature, quenched by addition of MeOH dropwise at 0 °C. The resulting mixture was diluted with saturated aqueous NH_4Cl (500 mL) and extracted with EA (3 x 500 mL). The combined organic layers were washed with water (2 x 500 mL) and brine (500 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE:EA = 5:1 to afford the desired product tert-butyl 4-(4-((6-nitropyridin-2-yl)amino)butyl)piperidine-1-carboxylate (3.3 g, 76.0% yield). LCMS (ESI-MS) m/z = 379.2 $[M+H]^+$.

Step 3. 6-nitro-N-(4-(piperidin-4-yl)butyl)pyridin-2-amine

[000498] TFA (4 mL) was added to a stirred mixture of tert-butyl 4-(4-((6-nitropyridin-2-yl)amino)butyl)piperidine-1-carboxylate (3.3 g, 8.71 mmol) in DCM (12 mL). The resulting mixture was stirred for 2 hours at room temperature and concentrated under vacuum to afford the crude product (2.5 g crude) as yellow gum. The crude product was used for next step without further purification. LCMS (ESI-MS) m/z = 279.2 $[M+H]^+$.

Step 4. 4-iodo-2-(4-(4-((6-nitropyridin-2-yl)amino)butyl)piperidin-1-yl)benzoic acid

[000499] K_2CO_3 (4.97 g, 35.9 mmol) was added to a mixture of 6-nitro-N-(4-(piperidin-4-yl)butyl)pyridin-2-amine (2.5 g, 8.98 mmol) and 2-fluoro-4-iodobenzoic acid (2.39 g, 8.98 mmol) in DMSO (30 mL). The resulting mixture was stirred overnight at 140 °C. After cooling to room temperature, the resulting mixture was diluted with water (300 mL) and extracted with EA (3 x 400 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford the crude product. The residue was purified by silica gel

column chromatography, eluted with EA:PE = 1:1 to afford the desired product 4-iodo-2-(4-(4-((6-nitropyridin-2-yl)amino)butyl)piperidin-1-yl)benzoic acid (2 g, 42.4% yield). LCMS (ESI-MS) m/z = 525.1 $[M+H]^+$.

Step 5. 2-(4-(4-((tert-butoxycarbonyl)(6-nitropyridin-2-yl)amino)butyl)piperidin-1-yl)-4-iodobenzoic acid

[000500] DMAP (0.02 g, 0.19 mmol) and TEA (0.39 g, 3.81mmol) were added to a mixture of 4-iodo-2-(4-(4-((6-nitropyridin-2-yl)amino)butyl)piperidin-1-yl)benzoic acid (1 g, 1.90 mmol) and Boc_2O (0.83 g, 3.81 mmol) in THF (10 mL). The resulting mixture was stirred overnight at room temperature. The reaction mixture was purified directly without any workup by silica gel column, eluted with PE:EA = 1:1 to afford the desired product 2-(4-(4-((tert-butoxycarbonyl)(6-nitropyridin-2-yl)amino)butyl)piperidin-1-yl)-4-iodobenzoic acid (500 mg, 41.9% yield). LCMS (ESI-MS) m/z = 625.1 $[M+H]^+$.

Step 6. 2-(4-(4-((6-aminopyridin-2-yl)(tert-butoxycarbonyl)amino)butyl)piperidin-1-yl)-4-iodobenzoic acid

[000501] Iron powder (393 mg, 7.05 mmol) and NH_4Cl (150 mg, 2.82 mmol) was added to a stirred mixture of 2-(4-(4-((tert-butoxycarbonyl)(6-nitropyridin-2-yl)amino)butyl)piperidin-1-yl)-4-iodobenzoic acid (440 mg, 0.70 mmol) in EtOH (9 mL) and H_2O (3 mL). The resulting mixture was heated to 80 °C and stirred for 2 hours. After cooled to room temperature, the reaction mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified with silica gel column, eluted with PE:EA = 3:1 to afford the desired product 2-(4-(4-((6-aminopyridin-2-yl)(tert-butoxycarbonyl)amino)butyl)piperidin-1-yl)-4-iodobenzoic acid (200 g, 47.7% yield). LCMS (ESI-MS) m/z = 595.2 $[M+H]^+$.

Step 7. tert-butyl 2^5-iodo-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphane-6-carboxylate

[000502] Et_3N (170 mg, 1.68 mmol) were added to a stirred mixture of 2-(4-(4-((6-aminopyridin-2-yl)(tert-butoxycarbonyl)amino)butyl)piperidin-1-yl)-4-iodobenzoic acid (200 mg, 0.33 mmol) and T_3P (321 mg, 1.00 mmol) in DMF (6 mL). The resulting mixture was stirred at room temperature for 72 hours, diluted with water (50 mL) and extracted with EA (3 x 60 mL). The combined organic layers were washed with brine (50 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified with silica gel column, eluted with PE:EA = 5:1 to afford the desired product tert-butyl

2^5-iodo-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphane-6-carboxylate (6.7 mg, 3.45% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.30 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.85-7.76 (m, 2H), 7.74-7.65 (m, 2H), 7.39 (d, J = 8.1 Hz, 1H), 3.98-3.88 (m, 2H), 3.20-3.09 (m, 2H), 2.89-2.77 (m, 2H), 1.83-1.72 (m, 2H), 1.62 (s, 2H), 1.50 (s, 2H), 1.44 (s, 8H), 1.32 (s, 6H). LCMS (ESI-MS) m/z = 577.2 $[M+H]^+$.

Step 8. tert-butyl 2^5-((2-hydroxyethyl)sulfonamido)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphane-6-carboxylate

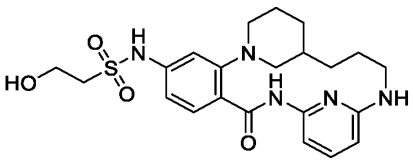
[000503] Into a mixture of tert-butyl 25-iodo-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphane-6-carboxylate (70 mg, 0.130 mmol) in 1,4-dioxane (3 mL) was added 2-hydroxyethanesulfonamide (17.9 mg, 0.143 mmol), trans-1,2-diaminocyclohexane (2.97 mg, 0.026 mmol) , CuI (2.48 mg, 0.013 mmol) and K_3PO_4 (82.8 mg, 0.390 mmol). The resulting solution was heated to 100 °C and stirred for 3 hours. After cooling to room temperature, the reaction mixture was concentrated under vacuum to afford the crude product. The residue was and purified by silica gel column chromatography, eluted with PE:EA = 1:1 to afford the desired product tert-butyl 2^5-((2-hydroxyethyl)sulfonamido)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphane-6-carboxylate (50 mg, 42.3% yield). LCMS (ESI-MS) m/z =574.9 $[M+H]^+$.

Step 9. 2-hydroxy-N-(3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide

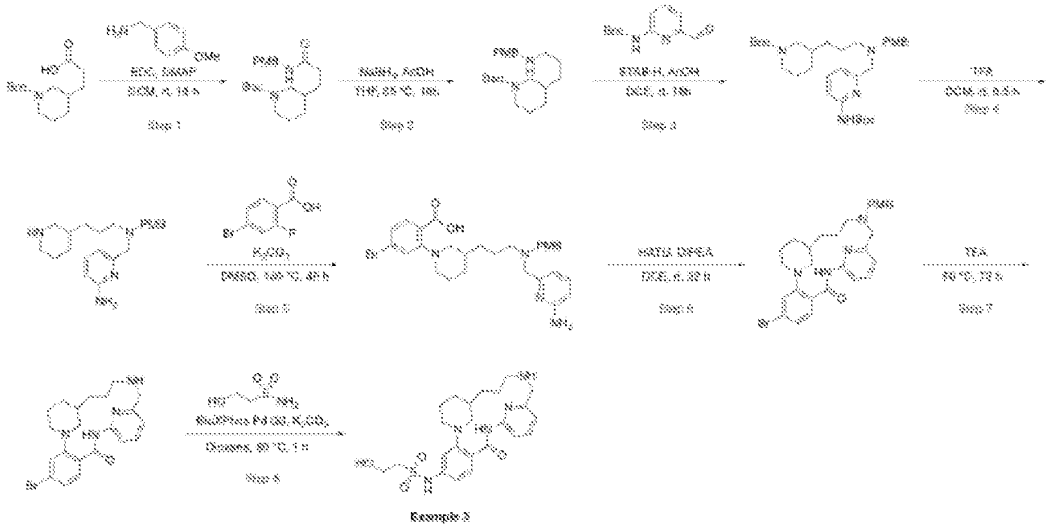
[000504] TFA (1 mL) was added to a stirred mixture of tert-butyl 2^5-((2-hydroxyethyl)sulfonamido)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphane-6-carboxylate (45 mg, 0.078 mmol) in DCM (3 mL). The resulting mixture was stirred at room temperature for 3 hours and concentrated under vacuum to afford the crude product. The residue was purified by Prep-HPLC with the following conditions (Column: ACN; Mobile Phase A: 60 mL/min, Mobile Phase B: 18% B to 48% B in 8 min; Flow rate: 7.4 mL/min; Gradient: isocratic 2; Wave Length: Water(10mmol/L NH_4HCO_3) nm; RT1(min): 24) to afford the desired product 2-hydroxy-N-(3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphane-25-yl)ethane-1-sulfonamide (2.6 mg, 6.9% yield). (Compound 1)

Example 2. 2-hydroxy-N-(3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphane-2^5-yl)ethane-1-sulfonamide was prepared starting from 3-(1-

(tert-butoxycarbonyl)piperidin-3-yl)propanoic acid following General synthetic route 1A as outlined in Example 1 procedure Steps 1 through 9. (Compound 2)



Example 3. 2-hydroxy-*N*-(3-oxo-4,7-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide 2,2,2-trifluoroacetate and 2-hydroxy-*N*-(3-oxo-4,7-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide (Compound 3) were prepared following the synthetic route outlined below.



Step 1.*tert*-butyl 3-(3-((4-methoxybenzyl)amino)-3-oxopropyl)piperidine-1-carboxylate

[000505] To a flask was added 3-(1-(Tert-butoxycarbonyl)piperidin-3-yl)propanoic acid (1.00 g, 1 Eq, 3.89 mmol), 3-(((ethylimino)methylene)amino)-N,N-dimethylpropan-1-amine hydrochloride (1.12 g, 1.5 Eq, 5.83 mmol), DMAP (237 mg, 0.5 Eq, 1.94 mmol), DCM (40 mL), and Benzenemethanamine, 4-methoxy (640 mg, 609 µL, 1.2 Eq, 4.66 mmol). The reaction mixture was then stirred at rt. After 18 h, the reaction mixture was washed with sat. aq. $NaHCO_3$ and water, then the aq. layer was extracted with DCM (3 x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-50% EtOAc in heptane) provided tert-butyl 3-(3-((4-methoxybenzyl)amino)-3-oxopropyl)piperidine-1-carboxylate (1.45 g, 3.85 mmol, 99.1 %). LCMS M+1/Z = 377.2. ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.17-7.22 (m, 2 H) 6.82-6.88 (m, 2 H)

5.56-5.93 (m, 1 H) 4.35 (d, *J* = 5.5 Hz, 2 H) 3.73-3.97 (m, 5 H) 2.82 (br s, 1 H) 2.53 (br dd, *J* = 12.7, 10.0 Hz, 1 H) 2.22 (br t, *J* = 7.7 Hz, 2 H) 1.76-1.86 (m, 1 H) 1.03-1.69 (m, 15 H).

Step 2.*tert*-butyl 3-(3-((4-methoxybenzyl)amino)propyl)piperidine-1-carboxylate

[000506] To a vial was added tert-butyl 3-(3-((4-methoxybenzyl)amino)-3-oxopropyl)piperidine-1-carboxylate (100 mg, 1 Eq, 266 µmol), $NaBH_4$ (32.2 mg, 3.2 Eq, 850 µmol), and THF (1.0 mL). The reaction mixture was stirred 5 min then acetic acid (51.0 mg, 48.6 µL, 3.2 Eq, 850 µmol) was added slowly. The reaction mixture was then heated to 65 °C. After 18 h, the reaction mixture was cooled to rt and slowly quenched with MeOH. The reaction mixture was diluted with aq. $NaHCO_3$ and extracted with EtOAc (3 x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-10% MeOH in DCM) provided tert-butyl 3-(3-((4-methoxybenzyl)amino)propyl)piperidine-1-carboxylate (68.9 mg, 190 µmol, 71.6 %). LCMS M+1/Z = 363.2

Step 3.*tert*-butyl 3-(3-(((6-((*tert*-butoxycarbonyl)amino)pyridin-2-yl)methyl)(4-methoxybenzyl)amino)propyl)piperidine-1-carboxylate

[000507] To a vial with stir bar was added tert-butyl (6-formylpyridin-2-yl)carbamate (338 mg, 1.05 Eq, 1.52 mmol), tert-butyl 3-(3-((4-methoxybenzyl)amino)propyl)piperidine-1-carboxylate (525 mg, 1 Eq, 1.45 mmol), and DCE (13.0 mL), and Acetic acid (261 mg, 250 µL, 3 Eq, 4.34 mmol). The reaction mixture was then stirred at rt for 30 min, then Sodium triacetoxyborohydride (767 mg, 537 µL, 2.5 Eq, 3.62 mmol) was added. After 18 h, the reaction was washed with aq. $NaHCO_3$. The aq. layer was extracted with DCM (3 x) and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-100% EtOAc in heptane) provided tert-butyl 3-(3-(((6-((tert-butoxycarbonyl)amino)pyridin-2-yl)methyl)(4-methoxybenzyl)amino)propyl)piperidine-1-carboxylate (690.2 mg, 1.214 mmol, 83.8 %). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.73 (br d, *J* = 8.2 Hz, 1 H) 7.61 (t, *J* = 7.9 Hz, 1 H) 7.24 (d, *J* = 8.5 Hz, 2 H) 7.14 (d, *J* = 7.7 Hz, 2 H) 6.84 (d, *J* = 8.5 Hz, 2 H) 3.89 (br d, *J* = 12.9 Hz, 1 H) 3.79 (s, 3 H) 3.54 (br d, *J* = 6.0 Hz, 4 H) 2.71 (br s, 1 H) 2.40 (br t, *J* = 7.0 Hz, 2 H) 1.71 - 1.83 (m, 1 H) 1.65 (br s, 2 H) 1.51 (s, 9 H) 1.44 (s, 9 H) 1.41 - 1.42 (m, 1 H) 1.22 - 1.40 (m, 4 H) 1.06 - 1.22 (m, 2 H) 0.99 (br d, *J* = 7.1 Hz, 1 H). LCMS M+1/Z = 569.3

Step 4. 6-(((4-methoxybenzyl)(3-(piperidin-3-yl)propyl)amino)methyl)pyridin-2-amine

[000508] To a vial was added tert-butyl 3-(3-(((6-((tert-butoxycarbonyl)amino)pyridin-2-yl)methyl)(4-methoxybenzyl)amino)propyl)piperidine-1-carboxylate (685 mg, 1 Eq, 1.20 mmol), DCM (5.0 mL), and TFA (1.37 g, 928 µL, 10 Eq, 12.0 mmol). The reaction mixture was then stirred at rt for 30 min, then the volatiles were removed in vacuo. The crude material was used for the next step without further purification. LCMS M+1/Z = 369.2

Step 5. 2-(3-(3-(((6-aminopyridin-2-yl)methyl)(4-methoxybenzyl)amino)propyl)piperidin-1-yl)-4-bromobenzoic acid

[000509] To the crude material from the previous step was added 4-Bromo-2-fluorobenzoicacid (317 mg, 1.2 Eq, 1.45 mmol), K_2CO_3 (999 mg, 6 Eq, 7.23 mmol), and DMSO (8.0 mL). The reaction mixture was then heated to 140 °C. After 48 h, the reaction was diluted with EtOAc and washed with aq. $NaHCO_3$. The aq. layer was extracted with EtOAc (3 x) and the combined organic layers were washed with brine (5 x), dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-15% MeOH in DCM) provided 2-(3-(3-(((6-aminopyridin-2-yl)methyl)(4-methoxybenzyl)amino)propyl)piperidin-1-yl)-4-bromobenzoic acid (192.9 mg, 339.9 µmol, 28.2 % over 2 steps). LCMS M+1/Z = 567.2

Step 6. 2^5-bromo-7-(4-methoxybenzyl)-4,7-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one

[000510] To a flask was added 2-(3-(3-(((6-aminopyridin-2-yl)methyl)(4-methoxybenzyl)amino)propyl)piperidin-1-yl)-4-bromobenzoic acid (180 mg, 1 Eq, 317 µmol), DIPEA (205 mg, 276 µL, 5 Eq, 1.59 mmol), 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (241 mg, 2 Eq, 634 µmol), and DCE (18.0 mL). The reaction mixture was then stirred at rt. After 22 h, the reaction mixture was washed with aq. $NaHCO_3$ and the aq. layer was extracted with DCM (3 x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-50% EtOAc in heptane) provided 25-bromo-7-(4-methoxybenzyl)-4,7-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (109.0 mg, 0.17 mmol, 53 %). LCMS M+1/Z = 549.1

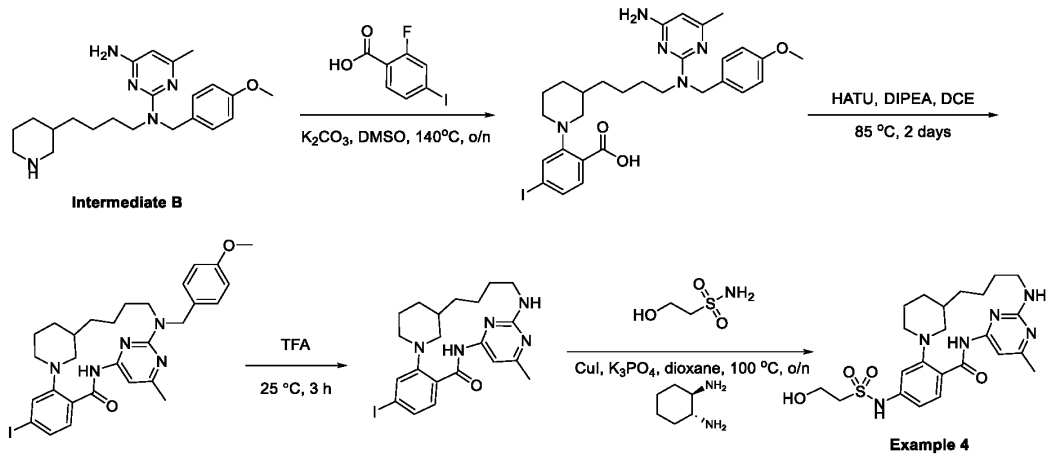
Step 7.2^5-bromo-4,7-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one

[000511] To a flask was added 25-bromo-7-(4-methoxybenzyl)-4,7-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (100 mg, 1 Eq, 182 μmol), DCM (1.0 mL), and TFA (415 mg, 280 μL, 20 Eq, 3.64 mmol). The reaction mixture was then heated to 60 °C. After 72 h, reaction mixture was diluted with sat. aq. NaHCO3 and washed with DCM (4 x). The combined organic layers were washed with brine, dried over MgSO4, and concentrated. Purification via Isco column chromatography provided 25-bromo-4,7-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (29.1 mg, 67.8 μmol, 37.2 %). LCMS M+1/Z = 429.0

Step 8.2-hydroxy-*N*-(3-oxo-4,7-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide, Example 3 (Compound 3)

[000512] To a vial was added 25-bromo-4,7-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (29 mg, 1 Eq, 68 μmol), 2-hydroxyethane-1-sulfonamide (51 mg, 6 Eq, 0.41 mmol), 2-hydroxyethane-1-sulfonamide (51 mg, 6 Eq, 0.41 mmol), tBuXPhos Pd G3 (5.4 mg, 0.1 Eq, 6.8 μmol), and K_2CO_3 (28 mg, 3 Eq, 0.20 mmol). The vial was capped and evacuated and refilled with N_2 (3 x). N_2 sparged Dioxane (0.50 mL) was added via syringe, and the reaction mixture was heated to 80 °C. After 1 h, the reaction mixture was cooled to rt, diluted with EtOAc, then washed with aq. $NaHCO_3$. The aqueous layer was extracted with DCM (3 x), and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification via prepHPLC (10-100% MeCN in H_2O with 0.1% TFA), followed by lyophilization provided 2-hydroxy-N-(3-oxo-4,7-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-25-yl)ethane-1-sulfonamide 2,2,2-trifluoroacetate, (10.32 mg, 17 μmol, 25 %). LCMS M+1/Z = 475.2

Example 4. 2-hydroxy-*N*-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide was prepared via General synthetic route 3A using Intermediate B and following the procedure described below (Compound 4).



1. 2-(3-(4-((4-amino-6-methylpyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)piperidin-1-yl)-4-iodobenzoic acid

[000513] K_2CO_3 (540 mg, 3.91 mmol) was added to a mixture of 2-fluoro-4-iodobenzoic acid (173 mg, 0.65 mmol,) and N^2-(4-methoxybenzyl)-6-methyl-N^2-(4-(piperidin-3-yl)butyl)pyrimidine-2,4-diamine (500 mg, 1.30 mmol) in DMSO (8 mL). The resulting mixture was heated to 140°C and stirred overnight. After cooling to room temperature, the reaction was quenched by addition of water (40 mL) and extracted with EA (3 x 40 mL). The combined organic layers were washed with brine (3x 80 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE : EA = 1 : 1 to afford the desired product 2-(3-(4-((4-amino-6-methylpyrimidin-2-yl)(4-methoxybenzyl)amino) butyl)piperidin-1-yl)-4-iodobenzoic acid (220 mg, 21.4% yield). LCMS (ESI-MS) m/z = 630.2 $[M+H]^+$.

2. 2^5-iodo-6-(4-methoxybenzyl)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one

[000514] DIEA (54 mg, 0.41 mmol) was added to a mixture of 2-(3-(4-((4-amino-6-methylpyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)piperidin-1-yl)-4-iodobenzoic acid (220 mg, 0.34 mmol) and HATU (199 mg, 0.52 mmol) in DCE (5 mL). The reaction mixture was heated to 85°C and stirred at for 2 days. The reaction mixture was diluted with water (20 mL) and extracted with EA (3 x 20 mL). The combined organic layers were washed with brine

(50 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA: PE = 10 : 1 to afford the desired product 2^5-iodo-6-(4-methoxybenzyl)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclo-decaphan-3-one (110 mg, 51.4% yield). LCMS (ESI-MS) m/z = 612.2 $[M+H]^+$.

3. 2^5-iodo-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one

[000515] A mixture of 2^5-iodo-6-(4-methoxybenzyl)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (110 mg, 0.18 mmol) in TFA (2 mL) was stirred at room temperature for 3 hours and concentrated under vacuum to afford the crude product 2^5-iodo-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (70 mg crude). LCMS (ESI-MS) m/z = 492.1 $[M+H]^+$.

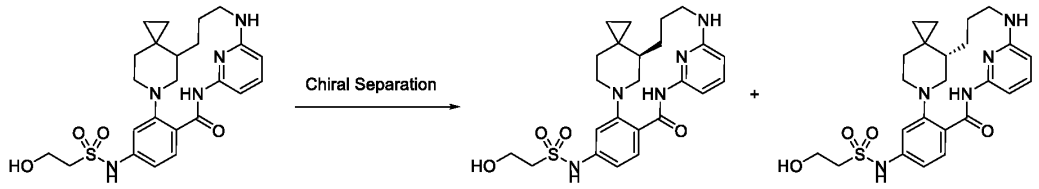
4. 2-hydroxy-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide (Compound 4)

[000516] CuI (40 mg, 0.21 mmol) was added to a mixture of 2^5-iodo-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (70 mg, 0.14 mmol), 2-hydroxyethane-sulfonamide (26 mg, 0.21 mmol), (1R,2R)-cyclohexane-1,2-diamine (19.5 mg, 0.17 mmol) and K_3PO_4 (39 mg, 0.28 mmol) in DMSO (1 mL) under nitrogen atmosphere. The mixture was heated to 100 °C and stirred overnight. After cooling to room temperature, the reaction was concentrated under vacuum directly and the residue was purified by silica gel column chromatography, eluted with PE : EA = 1:1 to afford the desired product 2-hydroxy-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide (25 mg, 32.3% yield). LCMS (ESI-MS) m/z = 489.3 $[M+H]^+$. (Compound 4)

Example 5. 2-hydroxy-N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphan]-5'-yl)ethane-1-sulfonamide was prepared starting from Intermediate A, following General synthetic route 1A as outlined in Steps 1 through 9 procedure for Example 1 (Compound 5).

Examples 6 and 7. 2-hydroxy-N-((3'R)-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphan]-5'-yl)ethane-1-sulfonamide and 2-hydroxy-N-((3'S)-3'-oxospiro [cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphan]-5'-yl)ethane-1-sulfonamide were prepared

using the Chiral HPLC separation as outlined below (Compound 6 and Compound 7, respectively)



[000517] The racemic mixture of 2-hydroxy-N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzena-cyclononaphan]-5'-yl)ethane-1-sulfonamide (10 mg, 0.02 mmol) was dissolved with MeOH and separated by Prep-Chiral-HPLC with the following conditions : Column: CHIRAL ART Cellulose-SZ, 3*25 cm, 5 μm; Mobile Phase A: Hex--HPLC, Mobile Phase B: MEOH: ETOH=1: 1--HPLC; Flow rate: 30ML/MIN mL/min; Gradient: isocratic 20; Wave Length: 254/220nm nm; RT1(min): 24.619; RT2(min): 28.718; Sample Solvent: EtOH--HPLC; Injection Volume: 0.8 mL; Number Of Runs: 2 to afford the two products:

first eluting isomer:

[000518] Enantiopure 2-hydroxy-N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphan]-5'-yl)ethane-1-sulfonamide (1.7 mg, 13.0% yield). LCMS (ESI-MS) m/z = 486.2 $[M+H]^+$. 100% e.e.

Second eluting isomer:

[000519] Enantiopure 2-hydroxy-N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphan]-5'-yl)ethane-1-sulfonamide (1.3 mg, 19.1% yield). LCMS (ESI-MS) m/z = 486.2 $[M+H]^+$. 99.7% e.e.

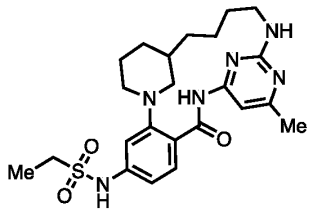
Table 2. 2-hour KIF18A Biochemical data for Examples 6 and 7

Compound	KIF18A ADP-Glo IC50, nM (2h)
First eluting isomer	+
Second eluting isomer	+++

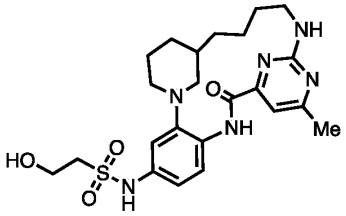
IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 8. *N*-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethanesulfonamide was prepared via General synthetic

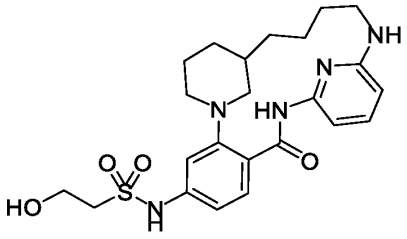
route 3A using intermediate C and ethanesulfonamide in Step 4 following the same Pd-catalyzed coupling procedure as in Step 4 of Example 15. (Compound 8)



Example 9. 2-hydroxy-*N*-(5^{6}-methyl-4-oxo-3,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^{5}-yl)ethane-1-sulfonamide was prepared via General synthetic route 2A using procedure Step 1 through 8 for Example 14 except methyl 2-amino-6-methylpyrimidine-4-carboxylate was used in step 1 in place of methyl 6-aminopicolinate. (Compound 9)

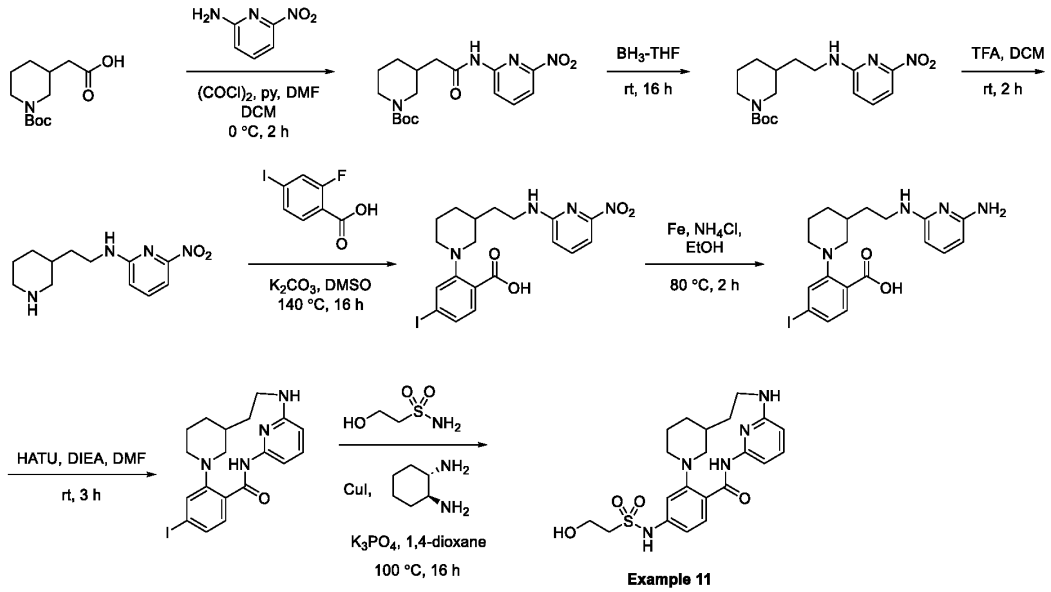


Example 10. 2-hydroxy-N-(3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^{5}-yl)ethane-1-sulfonamide was prepared starting from 4-(1-(tert-butoxycarbonyl)piperidin-3-yl)butanoic acid following General synthetic route 1A as outlined in Steps 1 through 9 procedure for Example 1 with exception for Step 7 where HATU and DIEA in DMF were used at room temperature in place of T3P and Et_3N to afford the intramolecular amide bond formation. (Compound 10)



Example 11. 2-hydroxy-N-(3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclooctaphane-2^{5}-yl)ethane-1-sulfonamide was prepared starting from 4-(1-

(tert-butoxycarbonyl)piperidin-4-yl)butanoic acid following General synthetic route 1B as outlined in the procedure below. (Compound 11)



1. tert-butyl 3-(2-((6-nitropyridin-2-yl)amino)-2-oxoethyl)piperidine-1-carboxylate

[000520] $(COCl)_2$ (6.78 g, 53.4 mmol) was added to a stirred mixture of [1-(tert-butoxycarbonyl)piperidin-3-yl]acetic acid (10 g, 41.1 mmol) in DCM (150 mL) at 0 °C, followed by addition of a drop of DMF. The resulting mixture was stirred for 1 hour and a mixture of 6-nitropyridin-2-amine (5.72 g, 41.1 mmol) in Pyridine (50 mL) was added to the reaction mixture above dropwise. The resulting mixture was stirred at 0 °C for 2 hours and concentrated under vacuum to afford the crude product. The residue was purified with silica gel column, eluted with EA:PE = 1:1 to afford the desired product tert-butyl 3-(2-((6-nitropyridin-2-yl)amino)-2-oxoethyl)piperidine-1-carboxylate (8 g, 53.4% yield). LCMS (ESI-MS) m/z =365.2 $[M+H]^+$.

2. tert-butyl 3-(2-((6-nitropyridin-2-yl)amino)ethyl)piperidine-1-carboxylate

[000521] BH_3-THF (1 M in THF, 43.9 mL, 43.9 mmol) was added to a stirred mixture of tert-butyl 3-(2-((6-nitropyridin-2-yl)amino)-2-oxoethyl)piperidine-1-carboxylate (8 g, 21.9 mmol) in THF (160 mL) dropwise at 0 °C. The resulting solution was stirred at room temperature for 16 hours, quenched by addition of MeOH (2 mL) and then extracted with EA (2 x 50 mL). The combined organic layers were washed with brine (100 mL), dried with anhydrous Na_2SO_4, filtered and concentrated to afford the crude product tert-butyl 3-(2-((6-nitropyridin-2-yl)amino)ethyl)piperidine-1-carboxylate (7 g crude). The crude product was used for next step without further purification. LCMS (ESI-MS) m/z = 351.3 $[M+H]^+$.

3. 6-nitro-N-(2-(piperidin-3-yl)ethyl)pyridin-2-amine

[000522] TFA (40 mL) was added to a stirred mixture of tert-butyl 3-(2-((6-nitropyridin-2-yl)amino)ethyl)piperidine-1-carboxylate (7 g, 20.0 mmol) in DCM (140 mL). The resulting mixture was stirred at room temperature for 2 hours and concentrated to afford the crude product 6-nitro-N-(2-(piperidin-3-yl)ethyl)pyridin-2-amine (4.8 g crude). LCMS (ESI-MS) m/z = 251.2 $[M+H]^+$.

4. 4-iodo-2-(3-(2-((6-nitropyridin-2-yl)amino)ethyl)piperidin-1-yl)benzoic acid

[000523] K_2CO_3 (7.12 g, 51.5 mmol) was added to a mixture of 2-fluoro-4-iodobenzoic acid (4.57 g, 17.2 mmol) and 6-nitro-N-(2-(piperidin-3-yl)ethyl)pyridin-2-amine (4.3 g, 17.2 mmol) in DMSO (80 mL). The resulting mixture was heated to 140 °C and stirred for 16 hours. After cooling to room temperature, the reaction mixture was diluted with water (100 mL) and extracted with EA (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified with silica gel column, eluted with EA:PE = 1:1 to afford the desired product 4-iodo-2-(3-(2-((6-nitropyridin-2-yl)amino)ethyl)piperidin-1-yl)benzoic acid (2.6 g, 30.5% yield). LCMS (ESI-MS) m/z = 497.1 $[M+H]^+$.

5. 2-(3-(2-((6-aminopyridin-2-yl)amino)ethyl)piperidin-1-yl)-4-iodobenzoic acid

[000524] Iron powder (980 mg, 17.6 mmol) was added to a mixture of 4-iodo-2-(3-(2-((6-nitropyridin-2-yl)amino)ethyl)piperidin-1-yl)benzoic acid (650 mg, 1.76 mmol) and NH_4Cl (375 mg, 7.02 mmol) in EtOH (10 mL) and H_2O (3 mL). The resulting mixture was heated to 80 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated under vacuum to afford the crude product. The residue was purified with silica gel column, eluted with DCM:MeOH = 10:1 to afford the desired product 2-(3-(2-((6-aminopyridin-2-yl)amino)ethyl)piperidin-1-yl)-4-iodobenzoic acid (400 mg, 37.1% yield). LCMS (ESI-MS) m/z = 467.1 $[M+H]^+$.

6. 2^5-iodo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclooctaphan-3-one

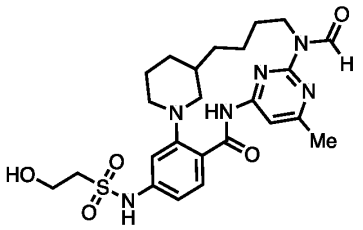
[000525] DIEA (291 mg, 2.25 mmol) was added to a stirred mixture of 2-(3-(2-((6-aminopyridin-2-yl)amino)ethyl)piperidin-1-yl)-4-iodobenzoic acid (350 mg, 0.751 mmol) and HATU (428 mg, 1.13 mmol) in DMF (5 mL). The resulting mixture was stirred at room temperature for 3 hours, diluted with water (10 mL), and extracted with EA (3 x 10 mL). The combined organic layers were washed with brine (10 mL x 2), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified with silica gel column, eluted with EA:PE = 1:1 to afford the desired product 2^5-iodo-4,6-diaza-5(2,6)-pyridina-1(1,3)-

piperidina-2(1,2)-benzenacyclooctaphan-3-one (300 mg, 79.1% yield). LCMS (ESI-MS) m/z = 449.1 $[M+H]^+$.

7. **2-hydroxy-N-(3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclooctaphane-2^5-yl)ethane-1-sulfonamide**

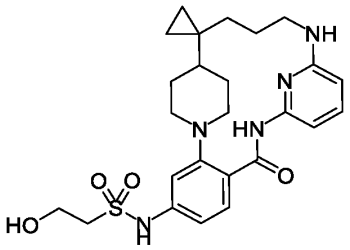
[000526] Into a solution of 2^5-iodo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclooctaphan-3-one (30 mg, 0.067 mmol) in dioxane (5 mL) was added 2-hydroxyethanesulfonamide (16.75 mg, 0.134 mmol) , (1R,2R)-cyclohexane-1,2-diamine (22.92 mg, 0.201 mmol) , CuI (38.23 mg, 0.201 mmol) and K_3PO_4 (56.82 mg, 0.268 mmol). The resulting mixture was heated to 100 °C and stirred for 16 hours. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by prep-HPLC with the following conditions: Column: Xselect CSH Prep C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 8% B to33 % B in 10 min; Wave Length: 254nm/220nm nm; RT1(min): 8.68 to afford the desired product 2-hydroxy-N-(3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclooctaphane-2^5-yl)ethane-1-sulfonamide (2.7 mg, 8.62% yield). LCMS (ESI-MS) m/z = 446.4 $[M+H]^+$.

Example 12. *N*-(6-formyl-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide was prepared using General synthetic route 5 following the same procedure as for Example 42 except for using formic acid and place of acetic acid. (Compound 12)

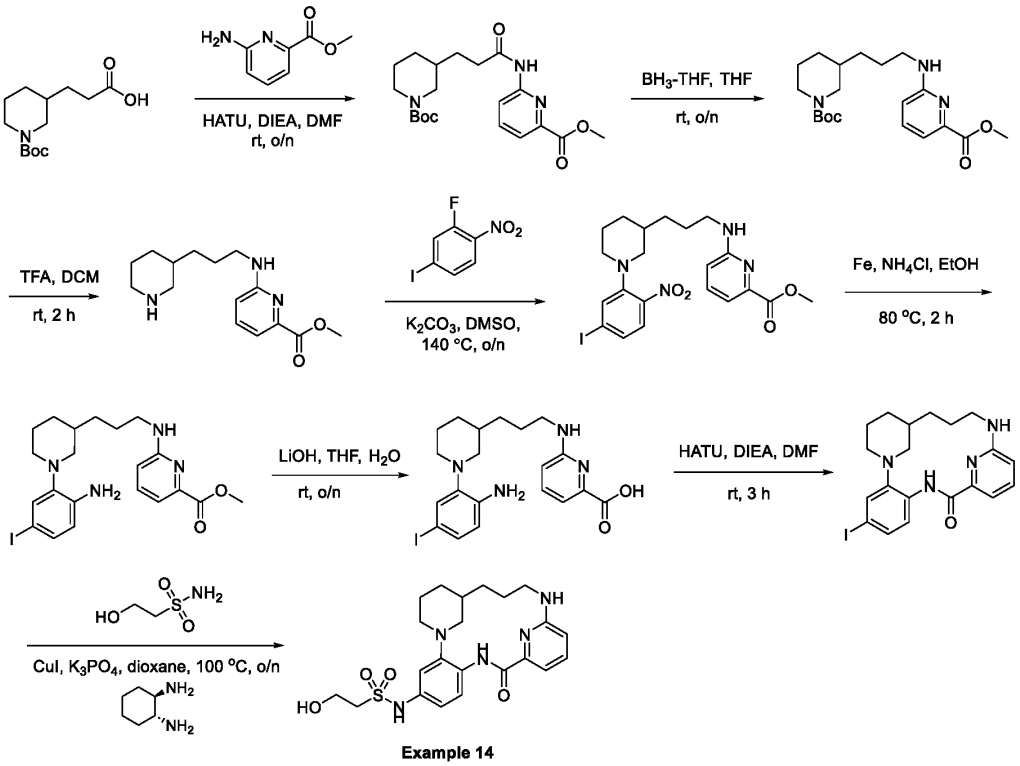


Example 13. 2-hydroxy-N-(3'-oxospiro[cyclopropane-1,10'-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide was prepared starting from 3-(1-(1-(tert-butoxycarbonyl)piperidin-4-yl)cyclopropyl)propanoic acid, Intermediate D, following General synthetic route 1A as outlined in Steps 1 through 9 procedure for Example 1 with exception for Step 7 where

HATU and DIEA in DMF were used at room temperature in place of T3P and Et_3N to afford the intramolecular amide bond formation. (Compound 13)



Example 14. 2-hydroxy-N-(4-oxo-3,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphane-2^5-yl)ethane-1-sulfonamide was prepared starting from 3-(1-(tert-butoxycarbonyl)piperidin-3-yl)propanoic acid following General synthetic route 2A as outlined in the procedure below. (Compound 14)



Example 14

1. methyl 6-(3-(1-(tert-butoxycarbonyl)piperidin-3-yl)propanamido)picolinate

[000527] DIEA (2.01 g, 15.5 mmol) was added to a stirred mixture of 3-(1-(tert-butoxycarbonyl)piperidin-3-yl)propanoic acid (1 g, 3.88 mmol), methyl 6-aminopicolinate (0.59 g, 3.88 mmol) and HATU (2.22 g, 5.82 mmol) in DMF (10 mL). The resulting mixture was stirred overnight at room temperature, diluted with water (200 mL) and extracted with EA

(3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified with silica gel column, eluted with EA:PE = 1:1 to afford the desired product methyl 6-(3-(1-(tert-butoxycarbonyl)piperidin-3-yl)propanamido)picolinate (630 mg, 41.4% yield). LCMS (ESI-MS) m/z = 392.2 $[M+H]^+$.

2. methyl 6-((3-(1-(tert-butoxycarbonyl)piperidin-3-yl)propyl)amino)picolinate

[000528] BH_3-THF complex (1 M in THF, 3.1 mL, 3.1 mmol) was added to a stirred mixture of methyl 6-(3-(1-(tert-butoxycarbonyl)piperidin-3-yl)propanamido)picolinate (600 mg, 1.53 mmol) in THF (8 mL) dropwise at 0 °C. The resulting mixture was stirred overnight at room temperature, quenched by addition of MeOH (2 mL) dropwise and then diluted with EA (100 mL). The resulting mixture was washed with brine (100 mL), dried with anhydrous Na_2SO_4, filtered and concentrated to afford the crude product methyl 6-((3-(1-(tert-butoxycarbonyl)piperidin-3-yl)propyl)amino)picolinate (450 mg crude). The crude product was used for next step directly without further purification. LCMS (ESI-MS) m/z = 378.2 $[M+H]^+$.

3. methyl 6-((3-(piperidin-3-yl)propyl)amino)picolinate

[000529] TFA (2 mL) was added to a stirred mixture of methyl 6-((3-(1-(tert-butoxycarbonyl)piperidin-3-yl)propyl)amino)picolinate (400 mg, 1.06 mmol) in DCM (6 mL). The resulting mixture was stirred for 2 hours at room temperature and concentrated under vacuum to afford the crude product (350 mg crude). The crude product was used for next step directly without further purification. LCMS (ESI-MS) m/z = 278.2 $[M+H]^+$.

4. methyl 6-((3-(1-(5-iodo-2-nitrophenyl)piperidin-3-yl)propyl)amino)picolinate

[000530] K_2CO_3 (986 mg, 7.14 mmol) was added to a mixture of methyl 6-((3-(piperidin-3-yl)propyl)amino)picolinate (330 mg, 1.19 mmol) and 2-fluoro-4-iodo-1-nitrobenzene (317 mg, 1.19 mmol) in DMSO (6 mL) and resulting mixture was heated to 140 °C and stirred overnight. After cooling to room temperature, the reaction mixture was diluted with brine (100 mL) and extracted with EA (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with EA: PE = 1:1 to afford the desired product methyl 6-((3-(1-(5-iodo-2-nitrophenyl)piperidin-3-yl)propyl)amino)picolinate (280 mg, 44.8% yield). LCMS (ESI-MS) m/z = 525.1 $[M+H]^+$.

5. methyl 6-((3-(1-(2-amino-5-iodophenyl)piperidin-3-yl)propyl)amino)picolinate

[000531] Iron powder (266 mg, 4.77 mmol) and NH_4Cl (102 mg, 1.90 mmol) was added to a stirred mixture of methyl 6-((3-(1-(5-iodo-2-nitrophenyl)piperidin-3-yl)propyl)amino)picolinate (250 mg, 0.47 mmol) in EtOH (6 mL) and H_2O (2 mL). The resulting mixture was heated to 80 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified with silica gel column, eluted with PE:EA = 1:1 to afford the desired product methyl 6-((3-(1-(2-amino-5-iodophenyl)piperidin-3-yl)propyl)amino)picolinate (200 mg, 84.8% yield). LCMS (ESI-MS) m/z = 495.1 $[M+H]^+$.

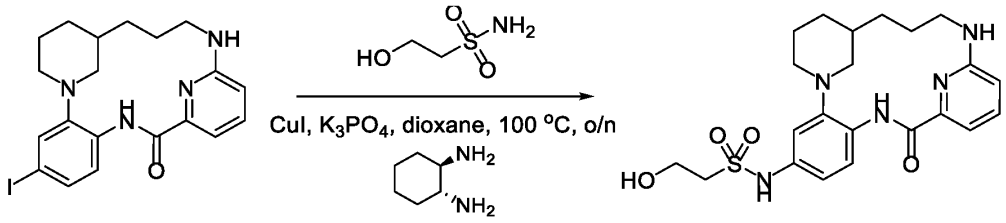
6. 6-((3-(1-(2-amino-5-iodophenyl)piperidin-3-yl)propyl)amino)picolinic acid

[000532] A solution of LiOH (26.2 mg, 1.09 mmol) in water (2 mL) was added to a stirred mixture of methyl 6-((3-(1-(2-amino-5-iodophenyl)piperidin-3-yl)propyl)amino)picolinate (180 mg, 0.36 mmol) in THF (6 mL). The resulting mixture was stirred overnight at room temperature and diluted with water (10 mL). Then THF was evaporated off under vacuum and the remained aqueous phase was neutralized to pH 6~7 by addition of aqueous HCl (1 M). The resulting mixture was extracted with EA (3 x 50 mL). The combined organic layers were washed with brine (2 x 10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product (150 mg crude). The crude product was used for next step directly without further purification.

7. 2^5-iodo-3,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphan-4-one

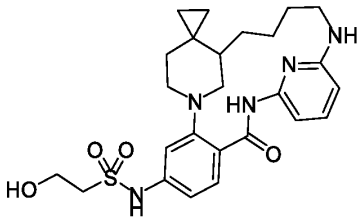
[000533] DIEA (118 mg, 0.91 mmol) was added to a stirred mixture of 6-((3-(1-(2-amino-5-iodophenyl)piperidin-3-yl)propyl)amino)picolinic acid (110 mg, 0.22 mmol) and HATU ((130 mg, 0.34 mmol) in DMF (2mL). The resulting mixture was stirred at room temperature for 3 hours, diluted with water (10 mL) and extracted with EA (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford crude product. The residue was purified with silica gel column, eluted with EA:PE=1:1 to afford the desired product 2^5-iodo-3,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphan-4-one (20 mg, 18.8% yield). LCMS (ESI-MS) m/z = 463.1 $[M+H]^+$.

8. 2-hydroxy-N-(4-oxo-3,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphane-2^5-yl)ethane-1-sulfonamide

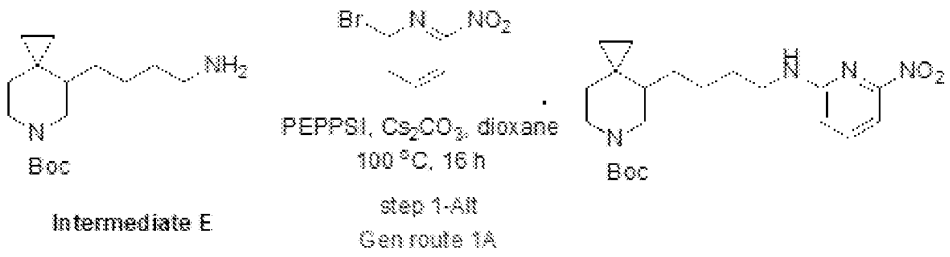


[000534] Into a solution of 2^5-iodo-3,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphan-4-one (20 mg, 0.043 mmol) in dioxane (2 mL) was added 2-hydroxyethane-1-sulfonamide (5.95 mg, 0.047 mmol) , (1R,2R)-cyclohexane-1,2-diamine (5.43 mg, 0.047 mmol) , CuI (9.06 mg, 0.047 mmol) and K_3PO_4 (27.5 mg, 0.12 mmol). The resulting mixture was heated to 100 °C and stirred for overnight. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified with silica gel column, eluted with EA:PE=1:1 to afford the desired product 2-hydroxy-N-(4-oxo-3,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphane-2^5-yl)ethane-1-sulfonamide, Example 14 (7.1 mg, 34.75% yield). LCMS (ESI-MS) m/z = 460.2 $[M+H]^+$. (Compound 14)

Example 15. 2-hydroxy-N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide was prepared starting from *tert*-butyl 4-(4-aminobutyl)-6-azaspiro[2.5]octane-6-carboxylate, Intermediate E, following General synthetic route 1A as outlined in Step 1-Alt shown below to produce intermediate tert-butyl 4-(4-((6-nitropyridin-2-yl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate and then following Steps 3 through 9 of procedure for Example 1 with exception for Step 7 where HATU and DIEA in DMF were used at room temperature in place of T3P and Et_3N to afford the intramolecular amide bond formation. (Compound 15)

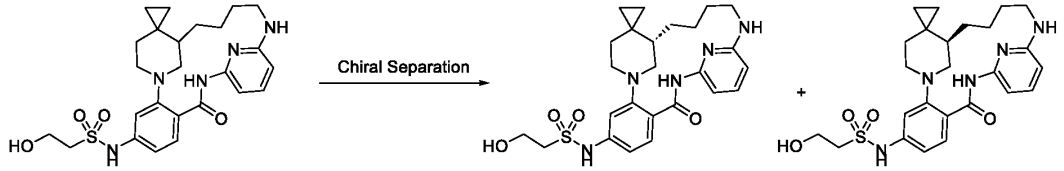


1-Alt. tert-butyl 4-(4-((6-nitropyridin-2-yl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate



[000535] Pd-PEPPSI-IHeptCl 3-chloropyridine (310. mg, 0.32 mmol) and Cs_2CO_3 (2.07 g, 6.37 mmol) was added to a stirred mixture of tert-butyl 4-(4-aminobutyl)-6-azaspiro[2.5]octane-6-carboxylate (900 mg, 3.19 mmol) and 2-bromo-6-nitropyridine (646.8 mg, 3.19 mmol) in 1,4-dioxane (10 mL). The resulting solution was heated to 100 °C and stirred at for 16 hours. After cooling to room temperature, the reaction mixture was concentrated under high vacuum to afford the crude product. The residue was purified with silica gel column, eluted with PE : EA = 1 : 1 to afford the desired product tert-butyl 4-(4-((6-nitropyridin-2-yl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate (580 mg, 27.9% yield). LCMS (ESI-MS) m/z = 405.3 $[M+H]^+$.

Examples 16 and 17. 2-hydroxy-N-((3'S)-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide & 2-hydroxy-N-((3'R)-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide were prepared via separation of Example 15 using chiral HPLC. (Compound 16 and 17, respectively)



Example 15 Example 16 Example 17

[000536] The racemic mixture of 2-hydroxy-N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (16.7 mg, 0.033 mmol) was dissolved with MeOH (2 mL) and separated by Chiral-prep-HPLC with the following conditions: Column: CHIRALPAKID3; Mobile Phase A: Hex(0.1%FA): (EtOH: DCM=1: 1)=80: 20; Flow rate: 1mL/min; Gradient: isocratic ; Injection Volume: 1μl mL to afford:

First eluting isomer:

[000537] Enantiopure 2-hydroxy-N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (1 mg, 5.72%). LCMS (ESI-MS) m/z = 500.3 $[M+H]^+$. 100% ee.

Second eluting isomer:

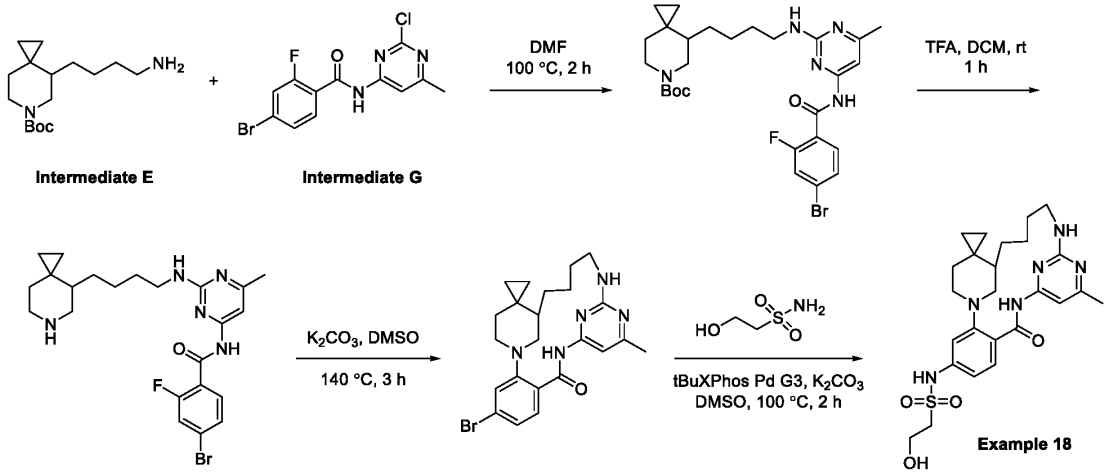
[000538] Enantiopure 2-hydroxy-N-((3'S)-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (1 mg, 5.72%). LCMS (ESI-MS) m/z = 500.3 $[M+H]^+$. 100% e.e.

Table 3 2 hour KIF18A Biochemical data for Examples 16 and 17

Compound	**KIF18A ADP-Glo IC50, nM (2h)**
First eluting isomer	+++++
Second eluting isomer	++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 18. 2-hydroxy-N-(6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide was prepared starting from Intermediate E and Intermediate G, following General synthetic route 4A as outlined in the procedure below (Compound 18).



1. **tert-butyl 4-(4-((4-(4-bromo-2-fluorobenzamido)-6-methylpyrimidin-2-yl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate**

[000539] 4-bromo-N-(2-chloro-6-methylpyrimidin-4-yl)-2-fluorobenzamide (939 mg, 2.72 mmol) was added to a stirred mixture of tert-butyl 4-(4-aminobutyl)-6-azaspiro[2.5]octane-6-

carboxylate (700 mg, 2.48 mmol) in DMF (10 mL) at rt. The resulting mixture was heated to 100 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was quenched by addition of saturated aqueous brine (20 mL) and extracted with EA (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford tert-butyl 4-(4-((4-(4-bromo-2-fluorobenzamido)-6-methylpyrimidin-2-yl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate (300 mg, 20.5 % yield). LCMS (ESI-MS) m/z = 378.2 $[M+H]^+$.

2. N-(2-((4-(6-azaspiro[2.5]octan-4-yl)butyl)amino)-6-methylpyrimidin-4-yl)-4-bromo-2-fluorobenzamide

[000540] TFA (1 mL) was added to a stirred mixture of Tert-butyl 4-(4-((4-(4-bromo-2-fluorobenzamido)-6-methylpyrimidin-2-yl)amino)butyl)-6-azaspiro[2.5]oct-ane-6-carboxylate (300 mg, 0.508 mmol) in DCM (3 mL). The resulting solution was stirred at room temperature for 1 hour and concentrated under vacuum to afford the crude product N-(2-((4-(6-azaspiro[2.5]octan-4-yl)butyl)amino)-6-methylpyrimidin-4-yl)-4-bromo-2-fluorobenzamide (130 mg crude). LCMS (ESI-MS) m/z = 490.2 $[M+H]^+$.

3. 5'-bromo-6'-methylspiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one

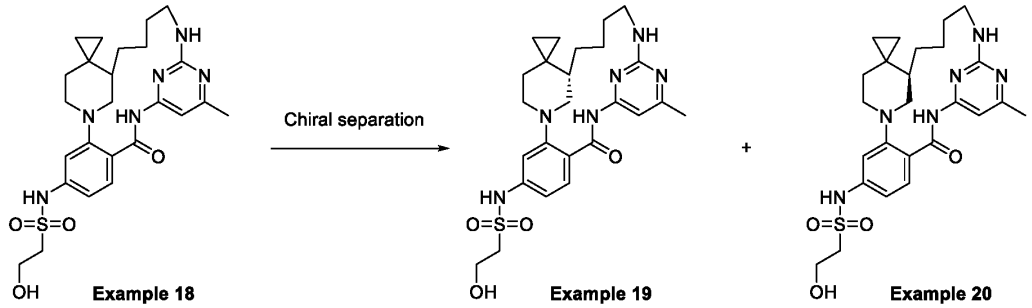
[000541] K_2CO_3 (110 mg, 0.795 mmol) was added to a mixture of N-(2-((4-(6-azaspiro[2.5]octan-4-yl)butyl)amino)-6-methylpyrimidin-4-yl)-4-bromo-2-fluorobenzamide (130 mg, 0.265 mmol) in DMSO (3 mL). The resulting mixture was heated to 140 °C and stirred for 3 hours. After cooling to room temperature, the reaction mixture was diluted with water (15 mL) and extracted with EA (3 x 15 mL). The combined organic layers were washed with brine (15 mL x 2), dried with anhydrous Na_2SO_4, filtered and concentration under vacuum to afford the crude product. The residue was purified with silica gel column, eluted with EA:PE=1:1 to afford the desired product 5'-bromo-6'-methylspiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one (100 mg, 72.5% yield). LCMS (ESI-MS) m/z = 470.2 $[M+H]^+$.

4. 2-hydroxy-N-(6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide

[000542] Into a solution of 5'-bromo-6'-methylspiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one (100 mg, 0.213 mmol) in DMSO (5 mL) was added 2-hydroxyethanesulfonamide (26.6 mg, 0.213 mmol), tBuXPhos Pd

G3 (16.89 mg, 0.021 mmol) and K_2CO_3 (88.1 mg, 0.639 mmol). The resulting solution was heated to 100 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was diluted with water (20 mL) and extracted with EA (3 x 30 mL). The combined organic layers were washed with brine (30 mL x 2), dried with anhydrous Na_2SO_4, filtered and concentration under vacuum to afford the crude product. The residue was purified with silica gel column, eluted with EA:PE=1:1 to afford the desired product 2-hydroxy-N-(6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (25 mg, 21.7% yield). LCMS (ESI-MS) m/z = 515.3 $[M+H]^+$. (Compound 18)

Examples 19 and 20. 2-hydroxy-N-((3'S)-6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide & 2-hydroxy-N-((3'R)-6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide were prepared using the Chiral HPLC separation as outlined below. (Compound 19 and 20, respectively)



[000543] 2-hydroxy-N-(6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (23 mg, 0.045 mmol) was dissolved with MeOH and purified by Chiral-prep-HPLC with the following conditions: Column: CHIRALPAKIE3; Mobile Phase A: Hex(0.1%DEA): EtOH=65: 35; Flow rate: 1 mL/min; Gradient: isocratic ; Injection Volume: 1μl mL to afford the two products:

First eluting isomer:

[000544] Enantiopure 2-hydroxy-N-(6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (6.3 mg, 26.98%). LCMS (ESI-MS) m/z = 515.4 $[M+H]^+$. 99.9% ee.

Second eluting isomer:

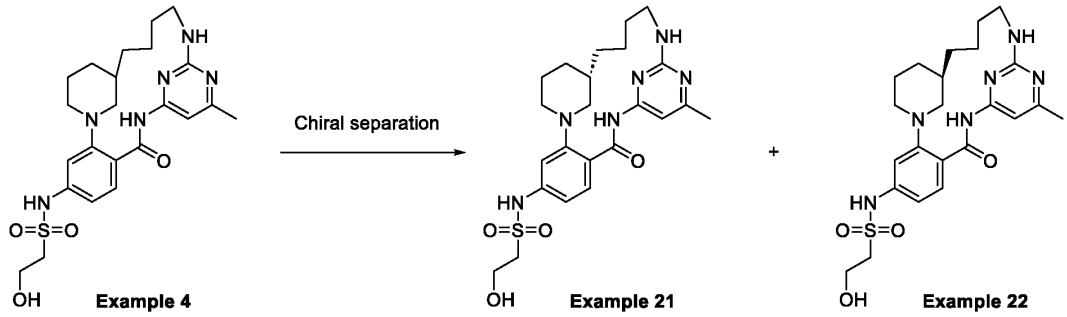
[000545] Enantiopure 2-hydroxy-N-(6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (7.3 mg, 31.04%). LCMS (ESI-MS) m/z = 515.4 $[M+H]^+$. 99.3% ee.

Table 4 2 hour KIF18A Biochemical data for Examples 19 and 20

Compound	**KIF18A ADP-Glo IC50, nM (2h)**
First eluting isomer	+++++
Second eluting isomer	++++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Examples 21 and 22. 2-hydroxy-N-((1^{3}S)-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide and 2-hydroxy-N-((1^{3}R)-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide were prepared using the Chiral HPLC separation as outlined below. (Compound 21 and 22)



[000546] The racemic mixture of 2-hydroxy-*N*-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide (25 mg, 0.051 mmol) was separated by Prep-Chiral-HPLC with the following conditions: Column: CHIRALPAK AD-H, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)-HPLC, Mobile Phase B: EtOH: IPA=1: 1-HPLC; Flow rate: 20mL/MIN mL/min; Gradient: isocratic 40; Wave Length: 254/220nm nm; RT1(min): 7.472; RT2(min): 13.005; Sample Solvent: EtOH-HPLC; Injection Volume: 1.1 mL; Number Of Runs: 3 to afford the two products:

First eluting isomer

[000547] Enantiopure 2-hydroxy-*N*-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide (2.9 mg, 11.1% yield). LCMS (ESI-MS) m/z = 489.3 $[M+H]^+$. 100% ee.

Second eluting isomer

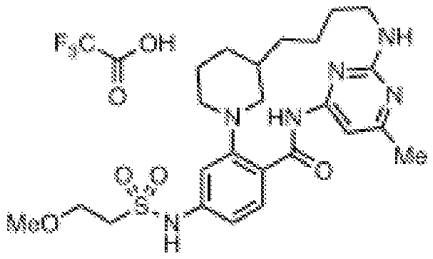
[000548] Enantiopure 2-hydroxy-*N*-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide (2.5 mg, 9.8% yield). LCMS (ESI-MS) m/z = 489.3 $[M+H]^+$. 96.6% ee.

Table 5. 2 hour KIF18A Biochemical data for Examples 21 and 22

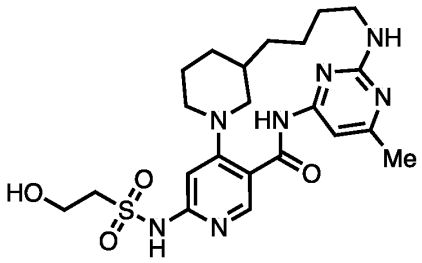
Compound	**KIF18A ADP-Glo IC50, nM (2h)**
First eluting isomer	+++++
Second eluting isomer	++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

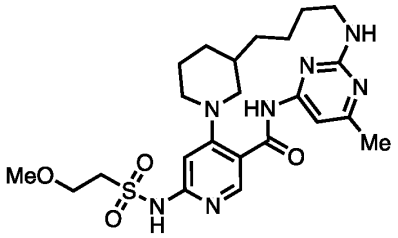
Example 23. 2-methoxy-*N*-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide 2,2,2-trifluoroacetate was prepared via General synthetic route 3A using intermediate C and 2-methoxyethane-1-sulfonamide in Step 4. For the last step Pd-catalyzed coupling procedure as in Step 4 of Example 18 was used.



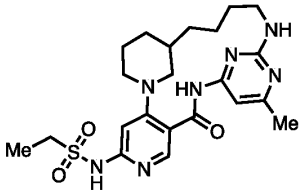
Example 24. 2-hydroxy-*N*-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-2(4,3)-pyridina-1(1,3)-piperidinacyclodecaphane-2^6-yl)ethane-1-sulfonamide was prepared via General synthetic route 3A using intermediate B and 6-bromo-4-chloronicotinic acid in Step 1. For the last step Pd-catalyzed coupling procedure with 2-hydroxyethane-1-sulfonamide as in Step 4 of Example 18 was used. (Compound 24).



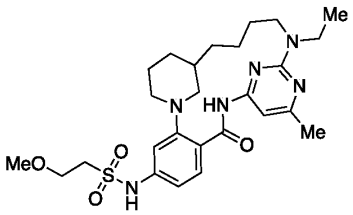
Example 25. 2-methoxy-*N*-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-2(4,3)-pyridina-1(1,3)-piperidinacyclodecaphane-2^6-yl)ethane-1-sulfonamide was prepared via General synthetic route 3A using intermediate B and 6-bromo-4-chloronicotinic acid in Step 1. For the last step Pd-catalyzed coupling procedure with 2-methoxyethane-1-sulfonamide as in Step 4 of Example 18 was used. (Compound 25)



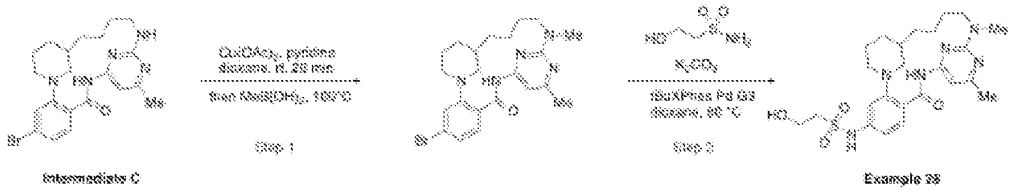
Example 26. *N*-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-2(4,3)-pyridina-1(1,3)-piperidinacyclodecaphane-2^6-yl)ethanesulfonamide was prepared via General synthetic route 3A using intermediate B and 6-bromo-4-chloronicotinic acid in Step 1. For the last step Pd-catalyzed coupling procedure with ethanesulfonamide as in Step 4 of Example 18 was used. (Compound 26)



Example 27. *N*-(6-ethyl-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)-2-methoxyethane-1-sulfonamide was prepared using General synthetic route 5 from 2-methoxy-*N*-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide, Example 23, following the same procedure as for Example 42 (Compound 27).



Example 28. *N*-(5^6,6-dimethyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide was prepared following the synthetic route outlined below. (Compound 28)



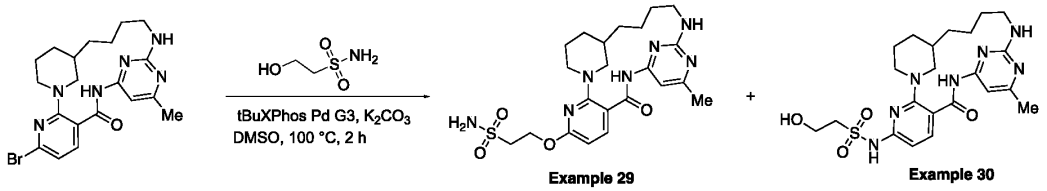
1. 2^5-bromo-5^6,6-dimethyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one

[000549] Intermediate C (15.0 mg, 1 Eq, 33.8 μmol), Copper diacetate (15.3 mg, 3.5 μL, 2.5 Eq, 84.4 μmol), pyridine (13.4 mg, 13.7 μL, 5 Eq, 169 μmol), and 1,4-Dioxane (0.30 mL) was added to a vial and stirred at rt for 15 min, then Boronic acid, methyl- (20.2 mg, 10 Eq, 338 μmol) was added and the reaction mixture was heated to 100 °C. After 2 h, an extra portion of Boronic acid, methyl- (20.2 mg, 10 Eq, 338 μmol) was added. After 18 h, an extra portion of Boronic acid, methyl- (20.2 mg, 10 Eq, 338 μmol) was added. After 3 h, the reaction mixture was diluted with aq. NaHCO3 and extracted with EtOAc (3 x). The combined organic layers were washed with brine, dried over MgSO4, and concentrated. The crude material was used for the next step without further purification. LCMS M+1/Z = 458.1

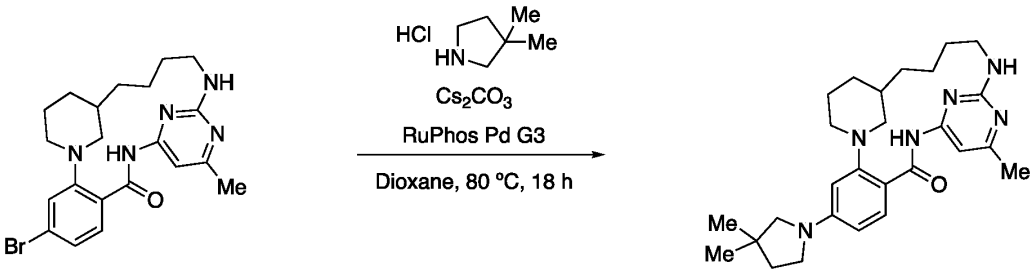
2. *N*-(5^6,6-dimethyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide 2,2,2-trifluoroacetate

[000550] To a vial was added the crude material from the previous reaction, 2-hydroxyethane-1-sulfonamide (27.3 mg, 10 Eq, 218 µmol), tBuXPhos Pd G3 (3.47 mg, .2 Eq, 4.36 µmol), and K2CO3 (9.04 mg, 3 Eq, 65.4 µmol). The vial was capped and evacuated and refilled with N2 (3 x). N2 sparged 1,4-Dioxane (0.25 mL) was added via syringe, and the reaction mixture was heated to 80 °C. After 18 h, the reaction mixture was cooled to rt, diluted with EtOAc, filtered through celite, and concentrated. Purification via prepHPLC (10-100% MeCN in H2O with 0.1% TFA), followed by lyophilization provided N-(5^6,6-dimethyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide 2,2,2-trifluoroacetate(1.12 mg, 1.7 µmol, 7.9 %). LCMS M+1/Z = 503.2

Examples 29 and 30. 2-((5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,3)-piperidinacyclodecaphane-2^6-yl)oxy)ethane-1-sulfonamide and 2-hydroxy-*N*-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,3)-piperidinacyclodecaphane-2^6-yl)ethane-1-sulfonamide were prepared via General synthetic route 3A using intermediate B and 6-bromo-2-chloronicotinic acid in Step 1. For the last step Pd-catalyzed coupling procedure as in Step 4 of Example 18 was used, the reaction yielded a mixture of Example 29 and Example 30 which were separated by HPLC chromatography. (Compound 29 and 30, respectively)



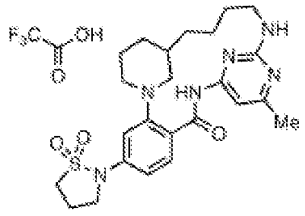
Example 31. 2^5-(3,3-dimethylpyrrolidin-1-yl)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one 2,2,2-trifluoroacetate was prepared following the synthetic procedure outlined below. (Compound 31)



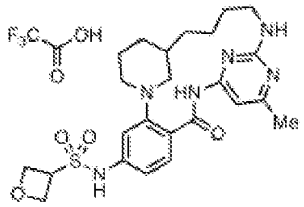
Intermediate C **Example 31**

[000551] To a vial was added 25-bromo-56-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (10.0 mg, 1 Eq, 22.5 µmol), RuPhos Pd G3 (3.76 mg, .2 Eq, 4.50 µmol), 3,3-dimethylpyrrolidine hydrochloride (9.16 mg, 3 Eq, 67.5 µmol), and cesium carbonate (22.0 mg, 3 Eq, 67.5 µmol). The vial was capped and evacuated and refilled with N2 (3 x). N2 sparged 1,4-Dioxane (0.40 mL) was added via syringe, and the reaction mixture was heated to 80 °C. After 18 h, the reaction mixture was cooled to rt, diluted with EtOAc, filtered through celite, and concentrated. Purification via prepHPLC (10-100% MeCN in H2O with 0.1% TFA), followed by lyophilization provided 25-(3,3-dimethylpyrrolidin-1-yl)-56-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one 2,2,2-trifluoroacetate (1.59 mg, 2.5 µmol, 11 %). Compound 31 LCMS M+1/Z = 463.2

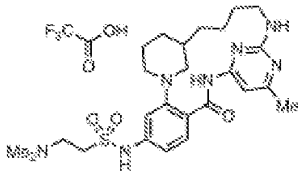
Example 32. 2^5-(1,1-dioxidoisothiazolidin-2-yl)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one 2,2,2-trifluoroacetate was prepared via General synthetic route 3A using intermediate C and isothiazolidine 1,1-dioxide in Step 4. For the last step Pd-catalyzed coupling procedure as in Step 4 of Example 18 was used.



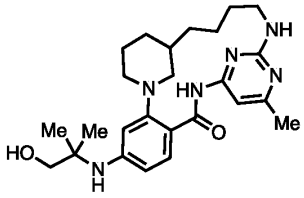
Example 33. ***N*****-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)oxetane-3-sulfonamide 2,2,2-trifluoroacetate was prepared via General synthetic route 3A using intermediate C and oxetane-3-sulfonamide in Step 4. For the last step Pd-catalyzed coupling procedure as in Step 4 of Example 18 was used.**



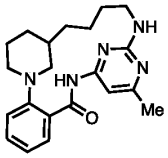
Example 34. 2-(dimethylamino)-*N*-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide 2,2,2-trifluoroacetate was prepared via General synthetic route 3A using intermediate C and 2-(dimethylamino)ethane-1-sulfonamide in Step 4. For the last step Pd-catalyzed coupling procedure as in Step 4 of Example 18 was used.



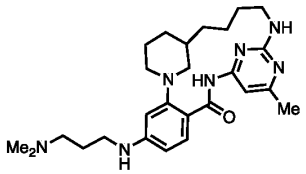
Example 35. 2^5-((1-hydroxy-2-methylpropan-2-yl)amino)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one was prepared via General synthetic route 3A using intermediate C and 2-amino-2-methylpropan-1-ol in Step 4 that engage in a Pd-catalyzed coupling procedure described in Step 4 of Example 18. (Compound 35)



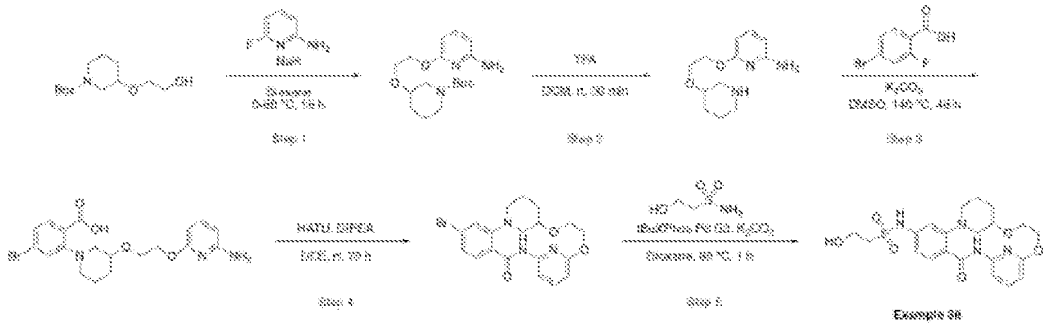
Example 36. 5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one was prepared via General synthetic route 3A using intermediate C and 2-amino-2-methylpropan-1-ol in Step 4 that engage in a Pd-catalyzed coupling procedure described in Step 4 of Example 18. Example 36 was a protodehalogentaion by-product in this reaction. (Compound 36)



Example 37. 2^5-((3-(dimethylamino)propyl)amino)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one was prepared via General synthetic route 3A using intermediate C and N1,N1-dimethylpropane-1,3-diamine in Step 4 that engage in a Pd-catalyzed coupling procedure described in Step 4 of Example 18. (Compound 37)



Example 38. 2-hydroxy-*N*-(3-oxo-6,9-dioxa-4-aza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphane-2^5-yl)ethane-1-sulfonamide 2,2,2-trifluoroacetate was prepared following the synthetic route outlined below. (Compound 38)



1. *tert*-butyl 3-(2-((6-aminopyridin-2-yl)oxy)ethoxy)piperidine-1-carboxylate

[000552] To a vial added tert-butyl 3-(2-hydroxyethoxy)piperidine-1-carboxylate (650 mg, 1 Eq, 2.65 mmol), 6-Fluoropyridin-2-amine (356 mg, 1.2 Eq, 3.18 mmol), DMF (14.0 mL) and NaH (286 mg, 60% Wt, 2.7 Eq, 7.15 mmol). The reaction mixture was then stirred at 0 °C for

30 min then heated to 80 °C. After 18 h, the reaction mixture was diluted with EtOAc and washed with brine (3 x), dried over MgSO4, and concentrated. Purification via Isco column chromatography (0-100% EtOAc in heptane) provided tert-butyl 3-(2-((6-aminopyridin-2-yl)oxy)ethoxy)piperidine-1-carboxylate (425.2 mg, 1.260 mmol, 47.6 %). M+1/Z = 338.2

2. 6-(2-(piperidin-3-yloxy)ethoxy)pyridin-2-amine

[000553] To vial was added tert-butyl 3-(2-((6-aminopyridin-2-yl)oxy)ethoxy)piperidine-1-carboxylate (230 mg, 1 Eq, 682 µmol), DCM (5 mL), and TFA (1.55 g, 1.05 mL, 20 Eq, 13.6 mmol). The reaction mixture was stirred at rt. After 30 min, the reaction mixture was concentrated and the crude material was used for the next step without further purification. M+1/Z = 238.2

3. 2-(3-(2-((6-aminopyridin-2-yl)oxy)ethoxy)piperidin-1-yl)-4-bromobenzoic acid

[000554] To the crude residue from the previous step was added 4-bromo-2-fluorobenzoic acid (179 mg, 1.2 Eq, 818 µmol), K2CO3 (565 mg, 6 Eq, 4.09 mmol), and DMSO (4 mL). The vial was capped and heated to 140 °C. After 48 h, the reaction was cooled to rt, diluted with EtOAc, and pH was adjusted to ~7 with 1 M aq. HCl. The aq. layer was washed with EtOAc (3x), then the combined organic layers were washed with brine (5 x), dried over MgSO4, and concentrated. Purification via Isco column chromatography (0-100% EtOAc in heptane) provided 2-(3-(2-((6-aminopyridin-2-yl)oxy)ethoxy)piperidin-1-yl)-4-bromobenzoic acid (140.7 mg, 322.5 µmol, 47.3 % over 2 steps). M+1/Z = 436.0

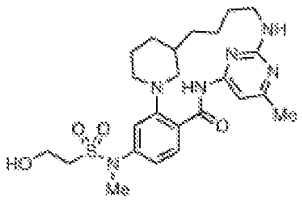
4. 2^5-bromo-6,9-dioxa-4-aza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphan-3-one

[000555] To a vial with stir bar was added 2-(3-(2-((6-aminopyridin-2-yl)oxy)ethoxy)piperidin-1-yl)-4-bromobenzoic acid (50.0 mg, 1 Eq, 115 µmol), triethylamine (34.8 mg, 47.9 µL, 3 Eq, 344 µmol), and DCM (2.0 mL), and SOCl2 (15.0 mg, 9.20 µL, 1.1 Eq, 126 µmol). The reaction mixture was then stirred at rt. After 70 h, the reaction mixture was washed with aq. NaHCO3. The aq. layer was extracted with DCM (3 x). The combined organic layers were washed with brine, dried over MgSO4, and concentrated. Purification via Isco column chromatography (0-50% EtOAc in heptane) provided 25-bromo-6,9-dioxa-4-aza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphan-3-one (9.4 mg, 22 µmol, 20 %). M+1/Z = 418.0

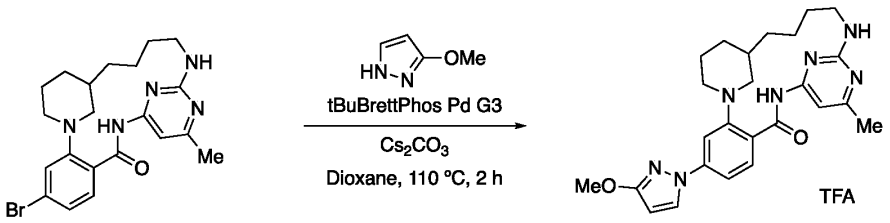
2. 2-hydroxy-*N*-(3-oxo-6,9-dioxa-4-aza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphane-2^5-yl)ethane-1-sulfonamide 2,2,2-trifluoroacetate

[000556] To a 1-dram vial with stir bar was added 25-bromo-6,9-dioxa-4-aza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphan-3-one (29 mg, 1 Eq, 69 μmol), 2-hydroxyethane-1-sulfonamide (35 mg, 4 Eq, 0.28 mmol), 2-hydroxyethane-1-sulfonamide (35 mg, 4 Eq, 0.28 mmol), tBuXPhos Pd G3 (5.5 mg, 0.1 Eq, 6.9 μmol), and K2CO3 (29 mg, 3 Eq, 0.21 mmol). The vial was capped and evacuated and refilled with N2 (3 x). Sparged 1,4-dioxane (0.50 mL) was added through the septum via syringe, and the reaction mixture was heated to 80 °C. After 1 h, the reaction mixture was cooled to rt, diluted with EtOAc, then washed with aq. NaHCO3. The aqueous layer was extracted with EtOAc (3 x), and the combined organic layers were washed with brine, dried over MgSO4, and concentrated. Purification via prep HPLC (10-100% MeCN in H2O with 0.1% TFA), followed by lyophilization provided 2-hydroxy-N-(3-oxo-6,9-dioxa-4-aza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphane-25-yl)ethane-1-sulfonamide 2,2,2-trifluoroacetate, Example 38 (6.76 mg, 11.7 μmol, 17 %). LCMS M+1/Z = 463.1 (Compound 38)

Example 39. 2-hydroxy-*N*-methyl-*N*-(56-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-25-yl)ethane-1-sulfonamide 2,2,2-trifluoroacetate was prepared via General synthetic route 3A using intermediate C and 2-hydroxy-N-methylethane-1-sulfonamide in Step 4. For this step Pd-catalyzed coupling procedure as described in Step 4 of Example 18 was used. (Compound 39)



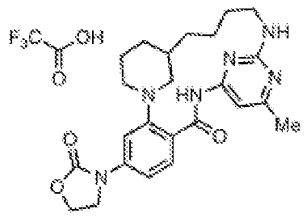
Example 40. 2[5]-(3-methoxy-1*H*-pyrazol-1-yl)-5[6]-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one 2,2,2-trifluoroacetate was prepared following the synthetic route outlined below.



Intermediate C **Example 40**

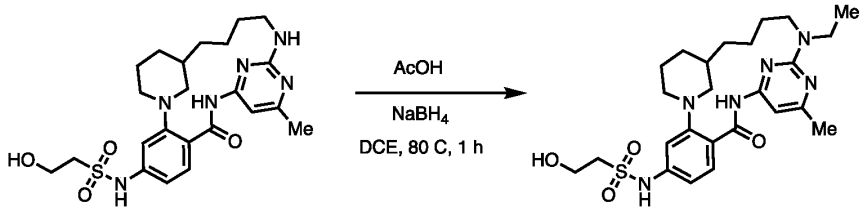
[000557] To a vial was added Intermediate C (5.0 mg, 1 Eq, 11 µmol), tBuBrettPhos Pd G3 (1.9 mg, .2 Eq, 2.3 µmol), K2CO3 (4.7 mg, 3 Eq, 34 µmol), K2CO3 (4.7 mg, 3 Eq, 34 µmol), and 3-methoxy-1H-pyrazole (11 mg, 10 Eq, 0.11 mmol). The vial was capped and evacuated and refilled with N2 (3 x), then 1,4-Dioxane (0.20 mL) was added through the septum. The reaction mixture was heated to 110 °C. After 2 h, the reaction mixture was diluted with DCM and washed with aq. NaHCO3. The aq. layer was extracted with DCM (3 x), and the combined organic layers were washed with brine, dried over MgSO4, and concentrated. Purification via prepHPLC (10-100% MeCN in H2O with 0.1% TFA) provided 25-(3-methoxy-1H-pyrazol-1-yl)-56-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one 2,2,2-trifluoroacetate, Compound 207 (3.01 mg, 5.0 µmol, 44 %). Compound 40 LCMS M+1/Z = 462.2

Example 41. 3-(5[6]-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2[5]-yl)oxazolidin-2-one 2,2,2-trifluoroacetate was prepared via General synthetic route 3A using intermediate C and oxazolidin-2-one in Step 4 that engage in a Pd-catalyzed coupling procedure described in Step 4 of Example 18.



Example 42. *N*-(6-ethyl-5[6]-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2[5]-yl)-2-hydroxyethane-1-sulfonamide was prepared using General synthetic route 5 from 2-hydroxy-*N*-(5[6]-methyl-3-oxo-4,6-diaza-5(4,2)-

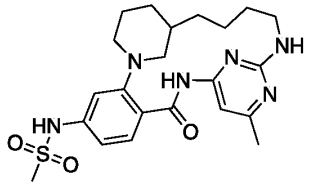
pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide, Example 4, following the procedure outlined below. (Compound 42)



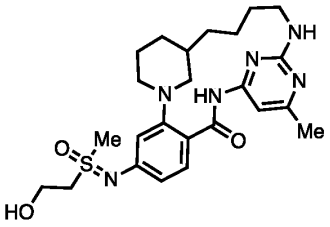
Example 4 Example 42

[000558] A dram vial equipped with a stir bar was sequentially charged with 2-hydroxy-*N*-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide (10 mg, 0.02 mmol) and a mixture of AcOH and DCE (1.0 mL, 5:1 ratio, respectively). The solution was stirred at RT while NaBH4 (38 mg, 0.1 mmol, 5.0 equiv) was carefully added portion wise. The vial was sealed with a screw-top cap equipped with a Teflon septum, and the vessel was transferred to a heating block. After heating at 80 °C for 1 h, the reaction vial was removed from the block, cooled to RT, and quenched with NaOH (aq, 1.0 M, 2.0 mL). The solution was extracted with DCM (3 x 5 mL), the organic layers combined, dried over MgSO4, and concentrated under reduced pressure via the aid of a rotary evaporator. The resulting crude product was purified via automated, HPLC (ACN in TFA modified water) to afford the desired product, N-(6-ethyl-56-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-25-yl)-2-hydroxyethane-1-sulfonamide (4.1 mg, 39%). LCMS (M+1)/Z = 516.2

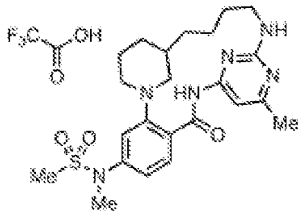
Example 43. *N*-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)methanesulfonamide was prepared via General synthetic route 3A using intermediate C and methanesulfonamide in Step 4. For this step Pd-catalyzed coupling procedure as described in Step 4 of Example 18 was used. (Compound 43)



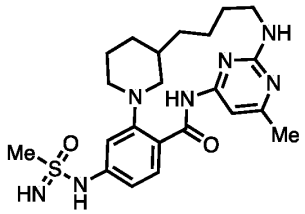
Example 44. 2^5-(((2-hydroxyethyl)(methyl)(oxo)-λ^6-sulfaneylidene)amino)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one was prepared via General synthetic route 3A using intermediate C and (2-hydroxyethyl)(imino)(methyl)-λ6-sulfanone in Step 4. For this step Pd-catalyzed coupling procedure as described in Step 4 of Example 18 was used. (Compound 44)



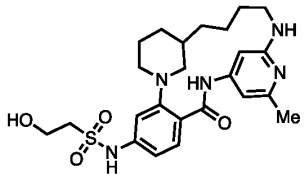
Example 45. *N*-methyl-*N*-(56-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-25-yl)methanesulfonamide 2,2,2-trifluoroacetate was prepared via General synthetic route 3A using intermediate C and N-methylmethanesulfonamide in Step 4. For this step the Pd-catalyzed coupling procedure as described in Step 4 of Example 18 was used.



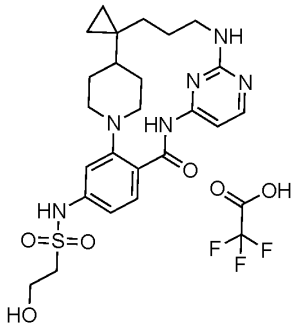
Example 46. *N*-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)methanesulfonimidamide was prepared via General synthetic route 3A using intermediate C and methanesulfonimidamide in Step 4. For this step Pd-catalyzed coupling procedure as described in Step 4 of Example 18 was used. (Compound 46)



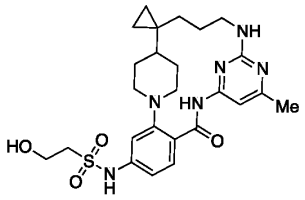
Example 47. 2-hydroxy-*N*-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide was prepared via General synthetic route 3A from intermediate I in Step 1 and 2-hydroxyethane-1-sulfonamide in Step 4. For the latter, Pd-catalyzed coupling procedure as described in Step 4 of Example 18 was used. (Compound 47)



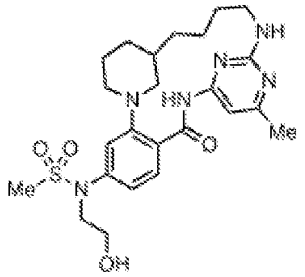
Example 48. 2-hydroxy-N-(3'-oxospiro[cyclopropane-1,10'-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide 2,2,2-trifluoroacetate was prepared via General synthetic route 3A from intermediate K in Step 1 and 2-hydroxyethane-1-sulfonamide in Step 4. For the latter, Pd-catalyzed coupling procedure as described in Step 4 of Example 18 was used. Alternatively Example 48 can be synthesized via General synthetic route 4B using Intermediate J and Intermediate H in Step 1.



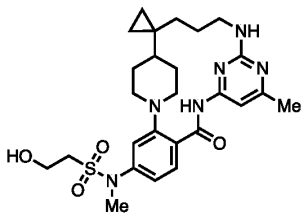
Example 49. 2-hydroxy-*N*-(6'-methyl-3'-oxospiro[cyclopropane-1,10'-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide was prepared via General synthetic route 3A from intermediate L in Step 1 and 2-hydroxyethane-1-sulfonamide in Step 4. For the latter, Pd-catalyzed coupling procedure as described in Step 4 of Example 18 was used. Alternatively Example 49 can be synthesized via General synthetic route 4B using Intermediate J and Intermediate G in Step 1 (Compound 49).



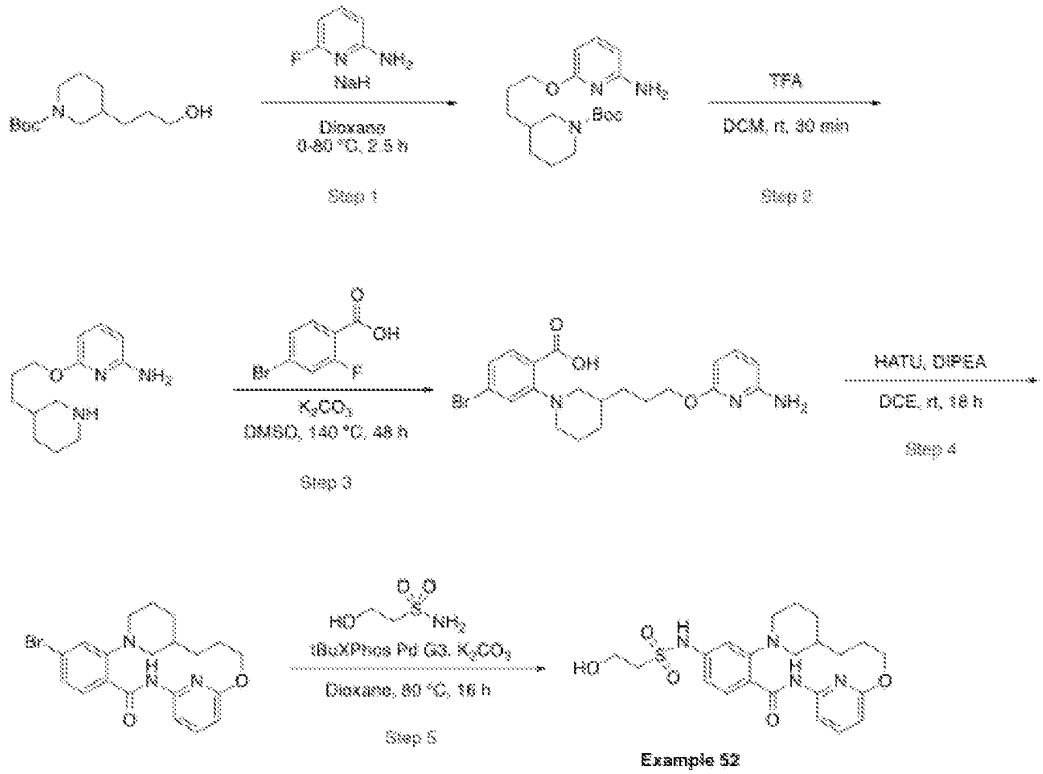
Example 50. *N*-(2-hydroxyethyl)-*N*-(56-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-25-yl)methanesulfonamide was prepared via General synthetic route 3A using intermediate C and N-(2-hydroxyethyl)methanesulfonamide in Step 4. For this step Pd-catalyzed coupling procedure as described in Step 4 of Example 18 was used. (Compound 50)



Example 51. 2-hydroxy-*N*-methyl-*N*-(6'-methyl-3'-oxospiro[cyclopropane-1,10'-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide was prepared in a fashion similar to Example 49 via General synthetic route 3A from intermediate L in Step 1 and 2-hydroxy-N-methylethane-1-sulfonamide in Step 4. For the latter, Pd-catalyzed coupling procedure as described in Step 4 of Example 18 was used. (Compound 51)



Example 52. 2-hydroxy-*N*-(3-oxo-6-oxa-4-aza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphane-2^5-yl)ethane-1-sulfonamide 2,2,2-trifluoroacetate was prepared following the synthetic route outlined below. (Compound 52)



1. *tert*-butyl 3-(3-((6-aminopyridin-2-yl)oxy)propyl)piperidine-1-carboxylate

[000559] To a vial was added tert-butyl 3-(3-hydroxypropyl)piperidine-1-carboxylate (448 mg, 1.2 Eq, 1.84 mmol) and Dioxane (7.67 mL). The reaction mixture was cooled to 0 °C and sodium hydride (153 mg, 60% Wt, 2.5 Eq, 3.84 mmol) was added. After stirring for 20 minutes, 6-fluoropyridin-2-amine (172 mg, 1 Eq, 1.53 mmol) slowly via syringe. The reaction mixture was then stirred at 80 °C . After 2 hour, the reaction mixture was diluted with water and sat. aq. $NaHCO_3$, then extracted with EtOAc (3 x). The combined organic layers were washed with brine, dried over MgSO4, and concentrated. Purification via Isco column chromatography provided tert-butyl 3-(3-((6-aminopyridin-2-yl)oxy)propyl)piperidine-1-carboxylate (241.4 mg, 719.6 µmol, 46.7%). M+1/Z = 336.2

2. 6-(3-(piperidin-3-yl)propoxy)pyridin-2-amine

[000560] To a vial with stir bar was added tert-butyl 3-(3-((6-aminopyridin-2-yl)oxy)propyl)piperidine-1-carboxylate (240 mg, 1 Eq, 715 µmol), DCM (5.0 mL), and TFA

(1.63 g, 1.10 mL, 20 Eq, 14.3 mmol). The reaction mixture was stirred at rt. After 30 min, the volatiles were removed in vacuo and the crude material was used for the next step without further purification. M+1/Z = 236.2

3. 2-(3-(3-((6-aminopyridin-2-yl)oxy)propyl)piperidin-1-yl)-4-bromobenzoic acid

[000561] To the crude residue from the previous step was added 4-bromo-2-fluorobenzoic acid (188 mg, 1.2 Eq, 859 µmol), K2CO3 (593 mg, 6 Eq, 4.29 mmol), and DMSO (4.0 mL). The reaction mixture was then heated to 140 °C. After 48 h, the reaction mixture was diluted with EtOAc and washed with brine (5 x), dried over MgSO4, and concentrated. Purification via Isco column chromatography (0-100% EtOAc in heptane) provided 2-(3-(3-((6-aminopyridin-2-yl)oxy)propyl)piperidin-1-yl)-4-bromobenzoic acid (206.7 mg, 475.9 µmol, 66.5 % over 2 steps). M+1/Z = 434.0

4. 2^5-bromo-6-oxa-4-aza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphan-3-one

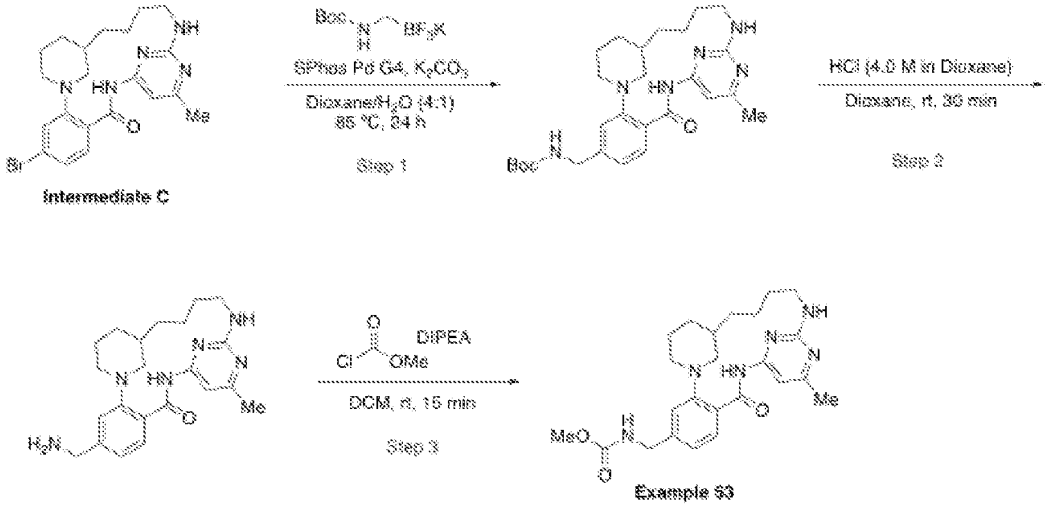
[000562] To a flask was added 2-(3-(3-((6-aminopyridin-2-yl)oxy)propyl)piperidin-1-yl)-4-bromobenzoic acid (50 mg, 1 Eq, 0.12 mmol), Diisopropylethylamine (74 mg, 99 µL, 5 Eq, 0.58 mmol), DCE (100 mL), and HATU (88 mg, 2 Eq, 0.23 mmol). The reaction mixture was then stirred at rt. After 18 h, the reaction mixture was washed with sat. aq. NaHCO3 and brine, then dried over MgSO4, and concentrated. Purification via Isco column chromatography (0-100% EtOAc in heptane) provided 25-bromo-6-oxa-4-aza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphan-3-one (24.7 mg, 59.3 µmol, 52 %). M+1/Z = 416.0

5. 2-hydroxy-*N*-(3-oxo-6-oxa-4-aza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphane-2^5-yl)ethane-1-sulfonamide 2,2,2-trifluoroacetate.

[000563] To a vial was added 25-bromo-6-oxa-4-aza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphan-3-one (24 mg, 1 Eq, 58 µmol), 2-hydroxyethane-1-sulfonamide (18 mg, 2.5 Eq, 0.14 mmol), 2-hydroxyethane-1-sulfonamide (18 mg, 2.5 Eq, 0.14 mmol), tBuXPhos Pd G3 (4.6 mg, 0.1 Eq, 5.8 µmol), and K2CO3 (24 mg, 3 Eq, 0.17 mmol). The vial was capped and evacuated and refilled with N2 (3 x). Sparged 1,4-dioxane (0.50 mL) was added through the septum via syringe, and the reaction mixture was heated to 80 °C. After 16 h, the reaction mixture was diluted with EtOAc and washed with sat. aq. NaHCO3 and brine. The organic layer was dried over MgSO4 and concentrated. Purification via prep-HPLC (0-100% MeCN in H2O with 0.1% TFA) followed by lyophilization provided 2-hydroxy-N-(3-oxo-6-oxa-4-aza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphane-25-

yl)ethane-1-sulfonamide 2,2,2-trifluoroacetate, Example 52 (4.00 mg, 6.6 µmol, 11 %). M+1/Z = 461.1 (Compound 52)

Example 53. Methyl ((5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)methyl)carbamate 2,2,2-trifluoroacetate



1. 2-(3-(4-((4-amino-6-methylpyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)piperidin-1-yl)-4-bromobenzoic acid

[000564] To a vial was added 25-bromo-56-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (10.0 mg, 1 Eq, 22.5 µmol), Potassium (aminomethyl)trifluoroborate, N-BOC protected (21.3 mg, 4 Eq, 90.0 µmol), SPhos Pd G4 (1.79 mg, 0.1 Eq, 2.25 µmol), and K2CO3 (9.33 mg, 3 Eq, 67.5 µmol). The vial was capped and evacuated and refilled with N2 (3 x). N2 sparged 1,4-Dioxane (1.2 mL) and Water (0.30 mL) were added via syringe, and the reaction mixture was heated to 85 °C. After 24 h, the reaction mixture was diluted with water and extracted with DCM (3 x). The combined organic layers were washed with brine, dried over MgSO4, and concentrated. Purification via Isco column chromatography (0-60% EtOAc in heptane) provided tert-butyl ((56-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-25-yl)methyl)carbamate (3.6 mg, 7.3 µmol, 32 %). LCMS M+1/Z = 495.3

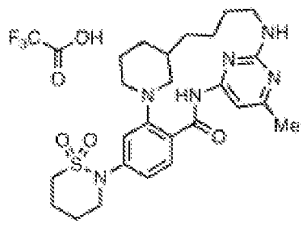
2. 2^5-(aminomethyl)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one

[000565] To tert-butyl ((56-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-25-yl)methyl)carbamate (5.2 mg, 1 Eq, 11 μmol) in 1,4-Dioxane (0.25 mL) was added HCl (in 1,4-dioxane) (38 mg, 0.26 mL, 4.0 molar, 100 Eq, 1.1 mmol). The reaction mixture was stirred for 30 minutes then concentrated in vacuo. The crude material was used for the next step without further purification. LCMS M+1/Z = 395.2

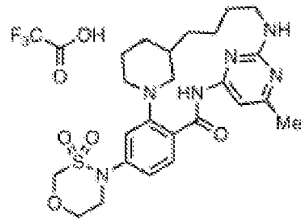
3. methyl ((5^{6}-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^{5}-yl)methyl)carbamate

[000566] To the crude material from the previous step was added DIPEA (5.4 mg, 7.3 μL, 4 Eq, 42 μmol) and Methyl chlorocarbonate (5.0 mg, 4.1 μL, 5 Eq, 53 μmol). The reaction mixture was stirred for 15 min, then quenched with MeOH and concentrated in vacuo. Purification via prepHPLC (10-100% MeCN in water with 0.1% TFA) provided methyl ((56-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-25-yl)methyl)carbamate 2,2,2-trifluoroacetate, Compound 211 (4.11 mg, 6.9 μmol, 66% over 2 steps). Compound 53 LCMS M+1/Z = 453.2

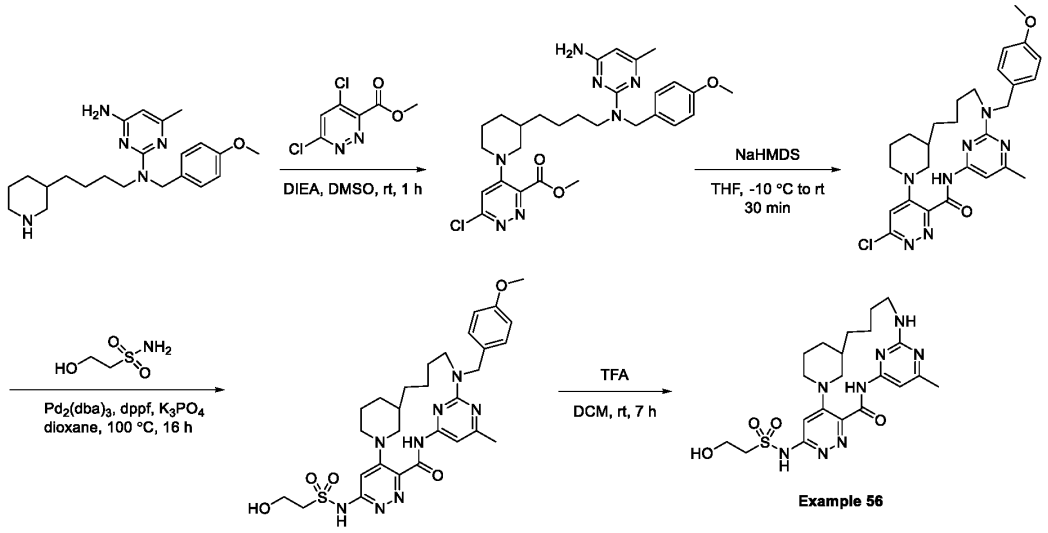
Example 54. 2^{5}-(1,1-dioxido-1,2-thiazinan-2-yl)-5^{6}-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one 2,2,2-trifluoroacetate was prepared via General synthetic route 3A using intermediate C and 1,2-thiazinane 1,1-dioxide in Step 4. For this step Pd-catalyzed coupling procedure as described in Step 4 of Example 18 was used.



Example 55. 2^5-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one 2,2,2-trifluoroacetate was prepared via General synthetic route 3A using intermediate C and 1,4,3-oxathiazinane 4,4-dioxide in Step 4. For this step Pd-catalyzed coupling procedure as described in Step 4 of Example 18 was used



Example 56. 2-hydroxy-*N*-(5^6-methyl-3-oxo-4,6-diaza-2(4,3),5(4,2)-dipyridazina-1(1,3)-piperidinacyclodecaphane-2^6-yl)ethane-1-sulfonamide was prepared from Intermediate B via modified General synthetic route 3B following the procedure outlined below. (Compound 56)



1. methyl 4-(3-(4-((4-amino-6-methylpyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)piperidin-1-yl)-6-chloropyridazine-3-carboxylate

[000567] DIEA (506 mg, 3.91 mmol) was added to a stirred mixture of *N*^{2}-(4-methoxybenzyl)-6-methyl-*N*^{2}-(4-(piperidin-3-yl)butyl)pyrimidine-2,4-diamine (500 mg, 1.30 mmol) and methyl 4,6-dichloropyridazine-3-carboxylate (270 mg, 1.30 mmol) in DMSO (5 mL). The resulting mixture was stirred at room temperature for 1 hour. The resulting mixture was diluted with EA (50 ml) and washed with brine (3 x 50 ml). The organic layer was dried

over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with EA in PE (0~60%) to afford the desired product methyl 4-(3-(4-((4-amino-6-methylpyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)piperidin-1-yl)-6-chloropyridazine-3-carboxylate (130 mg, 18.9% yield). LCMS (ESI-MS) m/z = 554.3 $[M+H]^+$.

2. 2^6-chloro-6-(4-methoxybenzyl)-5^6-methyl-4,6-diaza-2(4,3),5(4,2)-dipyridazina-1(1,3)-piperidinacyclodecaphan-3-one

[000568] NaHMDS (0.5 mL, 0.4 M in THF) was added to a stirred solution of methyl 4-(3-(4-((4-amino-6-methylpyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)piperidin-1-yl)-6-chloropyridazine-3-carboxylate (110 mg, 0.19 mmol) in THF (2 mL) at -10 °C. The resulting mixture was stirred at -10 °C for 5 minutes and warmed to room temperature for 30 minutes. The resulting mixture was diluted with water (20 ml) and extracted with EA (3 x 20 ml). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford a crude product. The residue was purified by Prep-TLC (EA:PE=1:1) to afford 2^6-chloro-6-(4-methoxybenzyl)-5^6-methyl-4,6-diaza-2(4,3),5(4,2)-dipyridazina-1(1,3)-piperidina-cyclodecaphan-3-one (25 mg, 24.1% yield). LCMS (ESI-MS) m/z = 522.2 $[M+H]^+$.

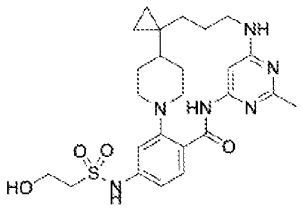
3. 2-hydroxy-*N*-(6-(4-methoxybenzyl)-5^6-methyl-3-oxo-4,6-diaza-2(4,3),5(4,2)-dipyridazina-1(1,3)-piperidinacyclodecaphane-2^6-yl)ethane-1-sulfonamide

[000569] Into a stirred mixture of 2^6-chloro-6-(4-methoxybenzyl)-5^6-methyl-4,6-diaza-2(4,3),5(4,2)-dipyridazina-1(1,3)-piperidinacyclodecaphan-3-one (20 mg, 0.038 mmol), 2-hydroxyethane-1-sulfonamide (9.59 mg, 0.076 mmol) and K_3PO_4 (16.3 mg, 0.076 mmol) in 1,4-dioxane (1 mL) were added $Pd_2(dba)_3$ (3.51 mg, 0.004 mmol) and dppf (4.23 mg, 0.008 mmol) under nitrogen atmosphere. The resulting mixture was heated to 100 °C and stirred for 16 hours. After cooling to room temperature, the resulting mixture was diluted with water (20 ml) and extracted with EA (3 x 20 ml). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford a crude product. The residue was purified by Prep-TLC (EA) to afford 2-hydroxy-*N*-(6-(4-methoxybenzyl)-5^6-methyl-3-oxo-4,6-diaza-2(4,3),5(4,2)-dipyridazina-1(1,3)-piperidinacyclodecaphane-2^6-yl)ethane-1-sulfonamide (15 mg, crude). The crude product was used for next step without purification. LCMS (ESI-MS) m/z = 611.2 $[M+H]^+$.

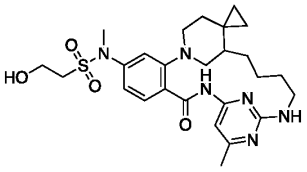
4. 2-hydroxy-*N*-(5^6-methyl-3-oxo-4,6-diaza-2(4,3),5(4,2)-dipyridazina-1(1,3)-piperidinacyclodecaphane-2^6-yl)ethane-1-sulfonamide (Compound 56)

[000570] TFA (2 mL) was added to a stirred mixture of 2-hydroxy-*N*-(6-(4-methoxybenzyl)-5^6-methyl-3-oxo-4,6-diaza-2(4,3),5(4,2)-dipyridazina-1(1,3)-piperidinacyclodecaphane-2^6-yl)ethane-1-sulfonamide (15 mg, 0.025 mmol) in DCM (2 mL) at room temperature. The reaction mixture was stirred at room temperature for 7 hours and concentrated under vacuum to afford the crude product. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, water in ACN, 36% to 43% gradient in 5 min; detector, UV 254 nm. The target solution is lyophilized to afford 2-hydroxy-*N*-(5^6-methyl-3-oxo-4,6-diaza-2(4,3),5(4,2)-dipyridazina-1(1,3)-piperidinacyclodecaphane-2^6-yl)ethane-1-sulfonamide (1.0 mg, 4.2% yield). LCMS (ESI-MS) m/z = 491.2 $[M+H]^+$. (Compound 56)

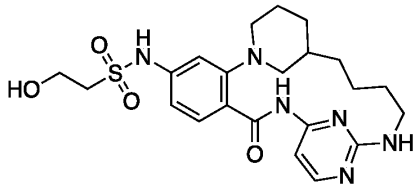
Example 57. 2-hydroxy-*N*-(5^2-methyl-3-oxo-4,6-diaza-5(4,6)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide was prepared via General synthetic route 3A using *tert*-butyl 3-(4-((6-amino-2-methylpyrimidin-4-yl)(4-methoxybenzyl)amino)butyl)piperidine-1-carboxylate and 4-bromo-2-fluorobenzoic acid in Step 1. For the last step Pd-catalyzed coupling procedure with 2-hydroxyethane-1-sulfonamide as in Step 4 of Example 18 was used (Compound 57).



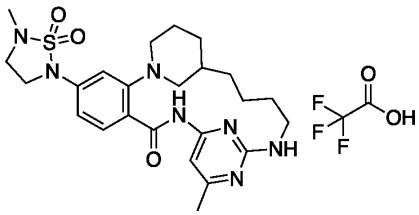
Example 58. 2-hydroxy-N-methyl-N-(6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide was prepared starting from Intermediate E and Intermediate G, following General synthetic route 4A as described in procedure from Example 18. In Step 4 - hydroxy-N-methylethanesulfonamide was used in place of 2-hydroxyethanesulfonamide to produce the product (Compound 58).



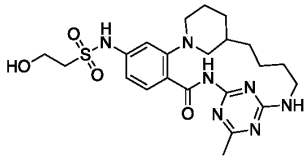
Example 59. 2-hydroxy-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide was prepared starting from tert-butyl 3-(4-aminobutyl)piperidine-1-carboxylate and Intermediate H, following General synthetic route 4A as described in procedure of Example 62 (Compound 59).



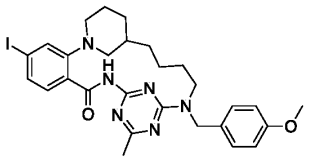
Example 60. 5^6-methyl-2^5-(5-methyl-1,1-dioxido-1,2,5-thiadiazolidin-2-yl)-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one trifloroacetate was prepared via General synthetic route 3A using intermediate C and 2-methyl-1,2,5-thiadiazolidine 1,1-dioxide in Step 4 following the same Pd-catalyzed coupling procedure as in Step 4 of Example 15. (Compound 60).



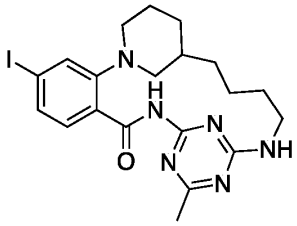
Example 61. 2-hydroxy-*N*-(5^6-methyl-3-oxo-4,6-diaza-5(2,4)-triazina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide was prepared following the synthetic route outlined below. (Compound 61).



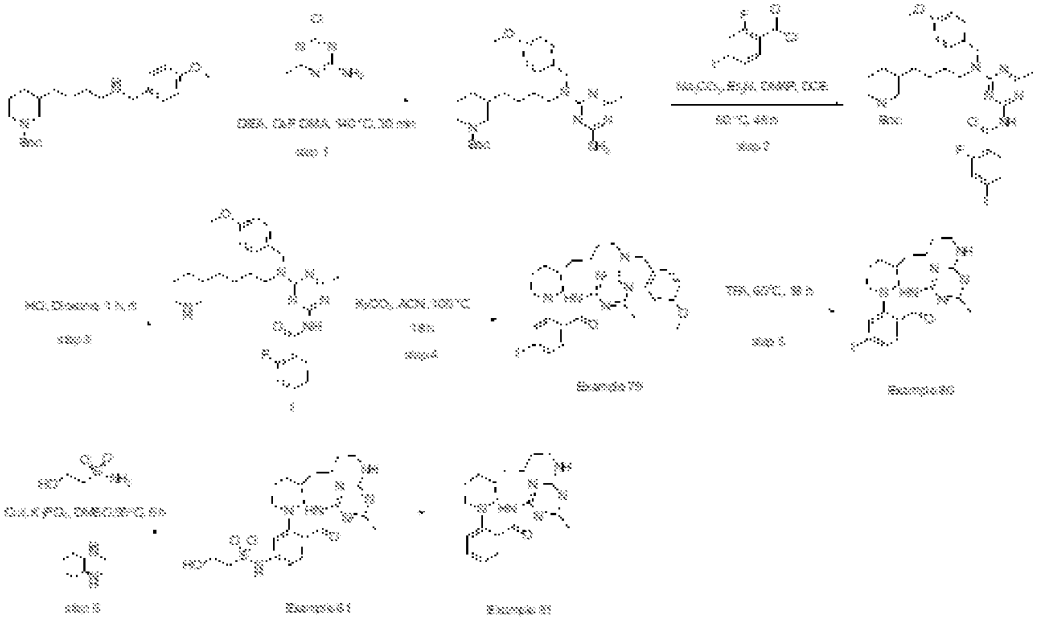
Example 79. 2^5-iodo-6-(4-methoxybenzyl)-5^6-methyl-4,6-diaza-5(2,4)-triazina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one was isolated in step 4 of the sequence below (Compound 79).



Example 80. 2^5-iodo-5^6-methyl-4,6-diaza-5(2,4)-triazina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one was isolated in step 5 of the sequence below (Compound 80).



Example 81. 5[6]-methyl-4,6-diaza-5(2,4)-triazina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one was isolated as a by-product in step 6 of the sequence below (Compound 81).



1. *tert*-butyl 3-(4-((4-amino-6-methyl-1,3,5-triazin-2-yl)(4-methoxybenzyl)amino)butyl)piperidine-1-carboxylate

[000571] To a vial was added intermediate B (250 mg, 664 µmol), 4-chloro-6-methyl- 1,3,5-triazin-2-amine (115 mg, 797 µmol), CsF (151 mg, 996 µmol) , and DIEA (172 mg, 231 µL, 1.33 mmol) in DMA (2.5 mL). The reaction mixture was heated to 140 °C. After 30 min, the reaction mixture was diluted with EtOAc, washed with brine, dried over MgSO4, and concentrated. Purification via Isco column chromatography (0-100% EA- Heptane) provided *tert*-butyl 3-(4-((4-amino-6-methyl-1,3,5-triazin-2-yl)(4-methoxybenzyl)amino)butyl)piperidine-1-carboxylate (245 mg, 77.4 %). LCMS M+1/Z = 485.3.

2. tert-butyl 3-(4-((4-(2-fluoro-4-iodobenzamido)-6-methyl-1,3,5-triazin-2-yl)(4-methoxybenzyl)amino)butyl)piperidine-1-carboxylate

[000572] 2-fluoro-4-iodobenzoyl chloride (123 mg, 433 µmol) was added to a mixture of *tert*-butyl 3-(4-((4-amino-6-methyl-1,3,5-triazin-2-yl)(4-methoxybenzyl)amino)butyl)piperidine-1-carboxylate (175 mg, 361 µmol), DMAP (44.1 mg, 361 µmol), and Na2CO3 (76.5 mg, 722 µmol) in DCE (2 mL). The reaction mixture was heated at 60 °C for 48h. The reaction mixture was diluted with EtOAc, washed with brine, dried over MgSO4, and concentrated. Purification via Isco column chromatography (0-100% EA: Heptane) provided tert-butyl 3-(4-((4-(2-

fluoro-4-iodobenzamido)-6-methyl-1,3,5-triazin-2-yl)(4-methoxybenzyl)amino)butyl)piperidine-1-carboxylate (180 mg, 68 %). LCMS M+1/Z = 733.2.

3. 2-fluoro-4-iodo-N-(4-((4-methoxybenzyl)(4-(piperidin-3-yl)butyl)amino)-6-methyl-1,3,5-triazin-2-yl)benzamide

[000573] HCl in dioxane (2.03 mL, 4 molar, 8.11 mmol)was added to a solution of tert-butyl 3-(4-((4-(2-fluoro-4-iodobenzamido)-6-methyl-1,3,5-triazin-2-yl)(4-methoxybenzyl)amino)butyl)piperidine-1-carboxylate (180 mg, 246 μmol)in dioxane (2 mL). The reaction mixture was stirred at room temperature for an hour. The reaction mixture was concentrated, and the residue was dissolved in DCM and washed with saturated NaHCO3 and brine. Organics were dried over MgSO4 and concentrated under vacuum to provide 2-fluoro-4-iodo-N-(4-((4-methoxybenzyl)(4-(piperidin-3-yl)butyl)amino)-6-methyl-1,3,5-triazin-2-yl)benzamide (122 mg, 74.2 %). The crude material was used for the next step without further purification. LCMS M+1/Z = 633.2.

4. 2^5-iodo-6-(4-methoxybenzyl)-5^6-methyl-4,6-diaza-5(2,4)-triazina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (Compound 79)

[000574] A mixture of 2-fluoro-4-iodo-N-(4-((4-methoxybenzyl)(4-(piperidin-3-yl)butyl)amino)-6-methyl-1,3,5-triazin-2-yl)benzamide (122 mg, 193 μmol), K2CO3 (53.3 mg, 386 μmol), and Acetonitrile (4 mL) was heated to 100 °C for 18h. The reaction mixture was diluted with water and extracted with DCM. Organics were dried over MgSO4, and concentrated under vacuum. The crude was purified by Isco column chromatography, eluting with 0-100% EA: heptane to afford 2^5-iodo-6-(4-methoxybenzyl)-5^6-methyl-4,6-diaza-5(2,4)-triazina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one, Compound 79 (31 mg, 51 μmol, 26 %). LCMS M+1/Z = 613.2. ^{1}H NMR (499 MHz, DMSO-d_6) δ = 12.74 - 12.47 (m, 1H), 7.70 - 7.66 (m, 1H), 7.66 - 7.56 (m, 2H), 7.24 (d, J = 8.8 Hz, 2H), 6.93 - 6.86 (m, 2H), 4.87 - 4.63 (m, 3H), 3.73 (s, 3H), 3.47 - 3.34 (m, 2H), 3.12 (br d, J = 8.2 Hz, 1H), 3.02 - 2.93 (m, 1H), 2.93 - 2.84 (m, 1H), 2.63 - 2.54 (m, 1H), 2.36 (s, 3H), 1.82 - 1.69 (m, 2H), 1.60 - 1.50 (m, 1H), 1.49 - 1.32 (m, 2H), 1.31 - 1.11 (m, 5H)

5. 2^5-iodo-5^6-methyl-4,6-diaza-5(2,4)-triazina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (Compound 80)

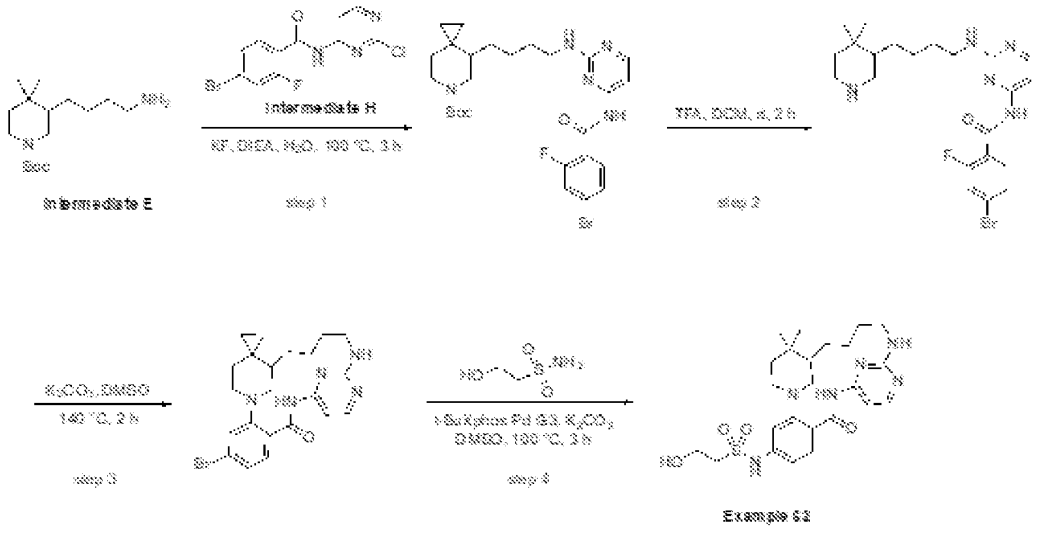
[000575] In a vial, TFA (2 mL) was added to 2^5-iodo-6-(4-methoxybenzyl)-5^6-methyl-4,6-diaza-5(2,4)-triazina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (28 mg, 1 Eq, 46 μmol). The reaction mixture was heated at 65 °C overnight. The reaction mixture was concentrated. The residue was purified via prepHPLC (10-100% MeCN in H_2O with 0.1% TFA). Fractions were combined, diluted with EA, and neutralized with saturated aqueous

NaHCO3 and brine. organics were dried over MgSO4 and concentrated under vacuum to afford 2^5-iodo-5^6-methyl-4,6-diaza-5(2,4)-triazina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (Compound 80) (9.7 mg, 20 µmol, 43 %). LCMS M+1/Z = 493.1.

6. 2-hydroxy-*N*-(5^6-methyl-3-oxo-4,6-diaza-5(2,4)-triazina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide (Compound 61) and 5^6-methyl-4,6-diaza-5(2,4)-triazina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (Compound 81)

[000576] In a vial, DMSO (2 mL) was added to a mixture of 2^5-iodo-5^6-methyl-4,6-diaza-5(2,4)-triazina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (9.7 mg, 1 Eq, 20 µmol), 2-hydroxyethane-1-sulfonamide (15 mg, 6 Eq, 0.12 mmol), K_3PO_4 (21 mg, 5 Eq, 99 µmol), Trans- (1r,2r)-n,n\'-bismethyl-1,2-cyclohexanediamine (9.0 mg, 9.9 µL, 1.6 Eq, 32 µmol), and copper(I) iodide (3.0 mg, 0.8 Eq, 16 µmol). The reaction mixture was heated at 95 °C for 6 hours. After cooling to room temperature, the crude was purified via prep-HPLC (10-100% MeCN in H_2O with 0.1% TFA) followed by lyophilization to afford the desired product 2-hydroxy-*N*-(5^6-methyl-3-oxo-4,6-diaza-5(2,4)-triazina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide (Compound 61) (1 mg, 2 µmol, 10 %) LCMS M+1/Z = 490.2 and the protodehalogenation by-product 5^6-methyl-4,6-diaza-5(2,4)-triazina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (Compound 81) (1 mg, 2 µmol, 10 %) LCMS M+1/Z = 367.2.

Example 62. 5'-bromospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one was prepared starting from Intermediate E and Intermediate H, following General synthetic route 4A as described in procedure outlined below (Compound 62).



1. **tert-butyl 4-(4-((4-(4-bromo-2-fluorobenzamido)pyrimidin-2-yl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate**

[000577] KF (411 mg, 7.08 mmol) and DIEA (915 mg, 7.08 mmol) were added to a mixture of 4-bromo-N-(2-chloropyrimidin-4-yl)-2-fluorobenzamide (1.17 mg, 3.54 mmol) and tert-butyl 4-(4-aminobutyl)-6-azaspiro[2.5]octane-6-carboxylate (1 g, 3.54 mmol) in H_2O (15 mL). The resulting mixture was heated to 100 °C and stirred for 3 hours. After cooling to room temperature, the reaction mixture was extracted with EA (20 mL x 2). The combined organic layers were washed with brine (20 mL x 2), dried with anhydrous Na2SO4, filtered and concentrated under vacuum to afford the crude product. The residue was purified via silica gel chromatography, eluted with EA/PE 1:1 to afford desired product tert-butyl 4-(4-((4-(4-bromo-2-fluorobenzamido)pyrimidin-2-yl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate (1.1 g, 49.3% yield). LCMS (ESI-MS) m/z = 576.3 $[M+H]^+$.

2. **N-(2-((4-(6-azaspiro[2.5]octan-4-yl)butyl)amino)pyrimidin-4-yl)-4-bromo-2-fluorobenzamide**

[000578] TFA (3 mL) was added to a stirred solution of 4-(4-((4-(4-bromo-2-fluorobenzamido)pyrimidin-2-yl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate (1.1 g, 1.91 mmol) in DCM (9 mL). The resulting mixture was stirred at room temperature for 2 hour and concentrated under vacuum to afford crude product N-(2-((4-(6-azaspiro[2.5]octan-4-yl)butyl)amino)pyrimidin-4-yl)-4-bromo-2-fluorobenzamide (900 mg crude). LCMS (ESI-MS) m/z = 476.1 $[M+H]^+$.

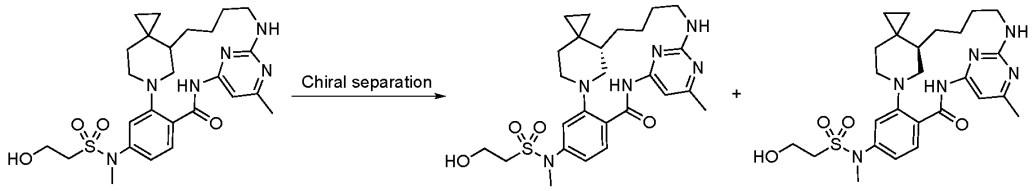
3. **5'-bromospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one**

[000579] K_2CO_3 (740 mg, 5.35 mmol) was added to a solution of N-(2-((4-(6-azaspiro[2.5]octan-4-yl)butyl)amino)pyrimidin-4-yl)-4-bromo-2-fluorobenzamide (850 mg, 1.78 mmol) in DMSO (10 mL). The resulting mixture was heated to140 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was diluted with water (20 mL) and extracted with EA (3 x 20 mL). The combined organic layers were washed with brine (20 mL x 2), dried with anhydrous Na_2SO_4, filtered and concentration under vacuum to afford the crude product. The residue was purified via silica gel chromatography, eluted with EA/PE 1:1 to afford desired product 5'-bromospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one (420 mg, 50.6% yield). LCMS (ESI-MS) m/z = 456.1 $[M+H]^+$.

4. **2-hydroxy-N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide**

[000580] Into a solution of 5'-bromospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one (400 mg, 0.88 mmol) in DMSO (10 mL) was added 2-hydroxyethanesulfonamide (110 mg, 0.88 mmol), G3 t-BuXPhos Pd precatalyst (69.7 mg, 0.088 mmol) and K_2CO_3 (363 mg, 2.63 mmol) . The resulting mixture was heated to 100 °C and stirred for 3 hours. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.05% TFA), 10% to 50% gradient in 10 min; detector, UV 254 nm to give the desired product 2-hydroxy-N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide, Example 62 (75 mg, 17.0 yield). LCMS (ESI-MS) m/z = 501.3 [M+H]+.

Examples 63 and 64.2-hydroxy-N-methyl-N-((3'S)-6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide & 2-hydroxy-N-methyl-N-((3'R)-6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide were prepared using the Chiral HPLC separation as outlined below. (Compound 63 and 64 respectively)



Example 58 Example 63 Example 64

[000581] The racemic mixture of 2-hydroxy-N-methyl-N-(6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (16 mg, 0.034 mmol) was dissolved with MeOH and purified by Chiral-prep-HPLC with the following conditions: Column: Column: CHIRAL ART Cellulose-SC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 40; Wave Length: 254/220nm nm; RT1(min): 6.881; RT2(min): 8.399; Sample Solvent: EtOH--HPLC; Injection Volume: 1.0 mL; Number Of Runs: 2 to afford the two products:

First eluting isomer:

[000582] Enantiopure 2-hydroxy-N-methyl-N-(6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (2.0 mg, 12.0%). LCMS (ESI-MS) m/z = 529.4 $[M+H]^+$. 100% ee.

Second eluting isomer:

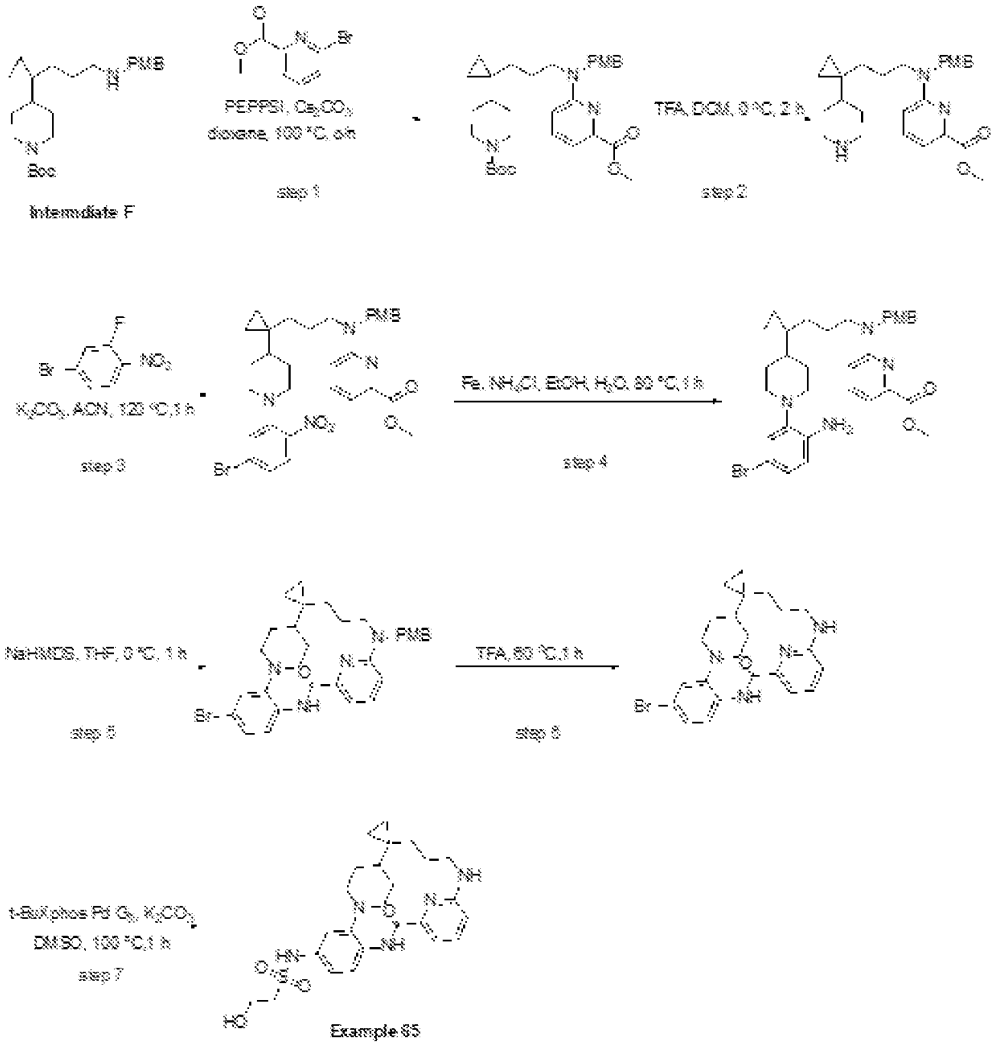
[000583] 2 Enantiopure 2-hydroxy-N-methyl-N-(6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (2.0 mg, 12.4%). LCMS (ESI-MS) m/z = 529.4 $[M+H]^+$. 99.8% ee.

Table 6. 2 hour KIF18A Biochemical data for Examples 63 and 64

Compound	**KIF18A ADP-Glo IC50, nM (2h)**
First eluting isomer	+++++
Second eluting isomer	+++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 65. 2-hydroxy-*N*-(4'-oxospiro[cyclopropane-1,10'-3,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide was prepared starting from methyl 6-bromopicolinate and Intermediate F following General synthetic route 2B as outlined in the procedure below. (Compound 65).



Step 1. methyl 6-((3-(1-(1-(tert-butoxycarbonyl)piperidin-4-yl)cyclopropyl)propyl)(4-methoxybenzyl)-amino)picolinate

[000584] Pd-PEPPSI-IPentCl (0.21 g, 0.25 mmol) was added to a mixture of Intermediate F (1 g, 2.48 mmol), methyl 6-bromopicolinate (0.54 g, 2.45 mmol) and K_2CO_3 (0.69 g, 4.97 mmol) in 1,4-dioxane (10 mL) under nitrogen atmosphere. The mixture was stirred at 100 °C overnight. The reaction mixture was concentrated under vacuum to afford the residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (3:1) to afford

methyl 6-((3-(1-(1-(tert-butoxycarbonyl)piperidin-4-yl)cyclopropyl)propyl)(4-methoxybenzyl)amino)picolinate (600 mg, 35% yield). LCMS (ESI-MS) m/z =552.3 $[M+H]^+$.

Step 2. methyl 6-((4-methoxybenzyl)(3-(1-(piperidin-4-yl)cyclopropyl)propyl)amino)picolinate

[000585] Methyl 6-((3-(1-(1-(tert-butoxycarbonyl)piperidin-4-yl)cyclopropyl)propyl)(4-methoxybenzyl)amino)picolinate (600 mg, 1.08 mmol) was added to a solution of TFA (1 mL) in DCM (6 mL). The mixture was stirred at 0 °C for 2 hours. The reaction was quenched with $NaHCO_3$ (aq.) (7 mL) at room temperature. The resulting mixture was extracted with EA (3 x 30 mL), the combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford methyl 6-((4-methoxybenzyl) (3-(1-(piperidin-4-yl)cyclopropyl) propyl)amino)picolinate (400 mg, 67.2% yield). LCMS (ESI-MS) m/z = 538.3 $[M+H]^+$.

Step 3. methyl 6-((3-(1-(1-(5-bromo-2-nitrophenyl)piperidin-4-yl)cyclopropyl)propyl)(4-methoxybenzyl)-amino)picolinate

[000586] K_2CO_3 (252 mg, 1.82 mmol) was added to a mixture of 4-bromo-2-fluoro-1-nitrobenzene (201 mg, 0.92 mmol) and methyl 6-((4-methoxybenzyl)(3-(1-(piperidin-4-yl)cyclopropyl)propyl)-amino)-picolinate (400 mg, 0.92 mmol) in ACN (5 mL). The mixture was stirred at 120 °C for 1 hour. The resulting mixture was filtered, the filter cake was washed with MeCN (3 x 30 mL). The filtrate was concentrated under reduced pressure to afford the crude methyl 6-((3-(1-(1-(5-bromo-2-nitrophenyl)piperidin-4-yl)cyclopropyl)propyl)(4-methoxybenzyl) -amino)picolinate (400 mg, 54.9% yield). LCMS (ESI-MS) m/z = 637.2 $[M+H]^+$.

Step 4. methyl 6-((3-(1-(1-(2-amino-5-bromophenyl)piperidin-4-yl)cyclopropyl)propyl)(4-methoxybenzyl)amino)picolinate

[000587] To a stirred mixture of methyl 6-((3-(1-(1-(5-bromo-2-nitrophenyl)piperidin-4-yl)cyclopropyl)propyl)(4-methoxybenzyl)-amino)picolinate (400 mg, 0.63 mmol), NH_4Cl (134 mg, 2.50 mmol) in water (2 mL) and EtOH (8 mL) was added iron powder (350 mg, 6.27 mmol). The reaction mixture was stirred at 80 °C for 1 hour. The resulting mixture was filtered, the filter cake was washed with EtOH (3 x 20 mL). The filtrate was concentrated under vacuum. The residue was dissolved in water (10 mL) and EA (5 mL). The resulting mixture was extracted with EA (3 x10 mL). The combined organic layers were washed with brine (90 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under vacuum to afford the crude product methyl 6-((3-(1-(1-(2-amino-5-bromophenyl)piperidin-4-

yl)cyclopropyl)propyl)(4-methoxybenzyl)amino)-picolinate (300 mg, 70.8% yield). LCMS (ESI-MS) m/z = 607.2 $[M+H]^+$.

Step 5. 5'-bromo-6'-(4-methoxybenzyl)spiro[cyclopropane-1,10'-3,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan]-4'-one

[000588] NaHMDS (0.25 mL, 2M in THF) in THF (2.22 mL) was added to methyl 6-((3-(1-(1-(2-amino-5-bromophenyl)piperidin-4-yl)cyclopropyl)propyl)(4-methoxybenzyl)amino)picolinate (300 mg, 0.49 mmol) in THF (3 mL) under nitrogen atmosphere at 0 °C. The mixture was stirred at 0 °C for 1 hour. The reaction mixture was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 5'-bromo-6'-(4-methoxybenzyl)spiro[cyclopropane-1,10'-3,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan]-4'-one (100 mg, 31.7% yield). LCMS (ESI-MS) m/z = 575.2 $[M+H]^+$.

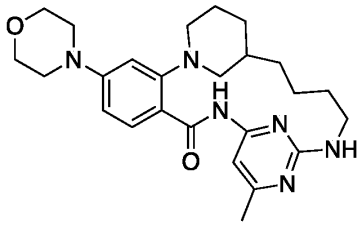
Step 6. 5'-bromospiro[cyclopropane-1,10'-3,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan]-4'-one

[000589] 5'-bromo-6'-(4-methoxybenzyl)spiro[cyclopropane-1,10'-3,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan]-4'-one (100 mg, 0.17 mmol) was added to TFA (1.5 mL). The reaction mixture was stirred at 60 °C for 1 hours. The resulting mixture was concentrated under vacuum to afford crude 5'-bromospiro[cyclopropane-1,10'-3,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacyclodecap-han]-4'-one (60 mg, 68.2% yield). LCMS (ESI-MS) m/z = 455.1 $[M+H]^+$.

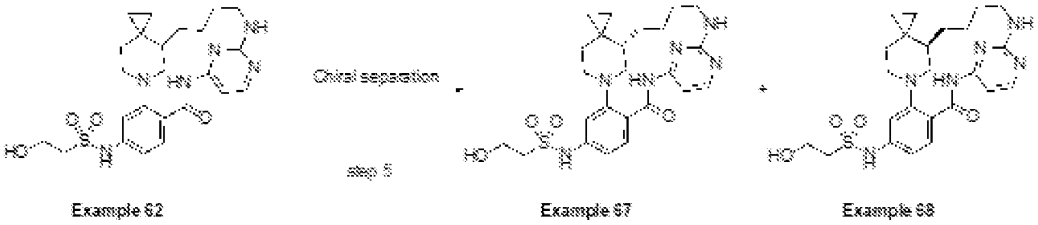
Step 7. 2-hydroxy-N-(4'-oxospiro[cyclopropane-1,10'-3,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide

[000590] tBu-XPhos Pd G3 (10 mg, 0.013 mmol) was added to a mixture of 5'-bromospiro[cyclopropane-1,10'-3,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacyclodecap-han]-4'-one (60 mg, 0.13 mmol), 2-hydroxyethanesulfonamide (19 mg, 0.16 mmol) and K_2CO_3 (36.42 mg, 0.26 mmol) in DMSO (2 mL) under nitrogen atmosphere. The mixture was stirred at 100 °C for 1 hour. The residue was concentrated and purified by Prep-HPLC with the following conditions: Column: Xselect-CSH Prep Fluoro-Phenyl OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 36% B to 57 % B in 10 min; Wave Length: 254nm/220nm nm; RT1(min): 8.68 to afford the product 2-hydroxy-N-(4'-oxospiro[cyclopropane-1,10'-3,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (26.7 mg, 39.9% yield).

Example 66. 5^6-methyl-2^5-morpholino-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one was prepared via General synthetic route 4A using intermediate C and morpholine in Step 4 that engage in a Cu-catalyzed coupling procedure described in Step 4 of Example 4 except for using DMF as solvent at 90 °C in place of dioxane at 100 °C and L-proline as a ligand. (Compound 66)



Examples 67 and 68. 2-hydroxy-N-((3'S)-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide & 2-hydroxy-N-((3'R)-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (Compound 67 and compound 68 respectively)



[000591] The racemic mixture of 2-hydroxy-N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (73 mg, 0.146 mmol) was dissolved with MeOH and purified by Chiral-prep-HPLC with the following conditions: Column: Column: CHIRAL ART Cellulose-SZ, 3*25 cm, 5 μm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 30ML/MIN mL/min; Gradient: isocratic 30; Wave Length: 254/220nm nm; RT1(min): 17.109; RT2(min): 20.23; Sample Solvent: EtOH--HPLC; Injection Volume: 0.4 mL; Number Of Runs: 9 to afford the two products:

First eluting isomer:

[000592] Enantiopure 2-hydroxy-N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (26.4 mg, 34.9% yield). LCMS (ESI-MS) m/z = 501.3 [M+H]+. 97.4% ee.

Second eluting isomer:

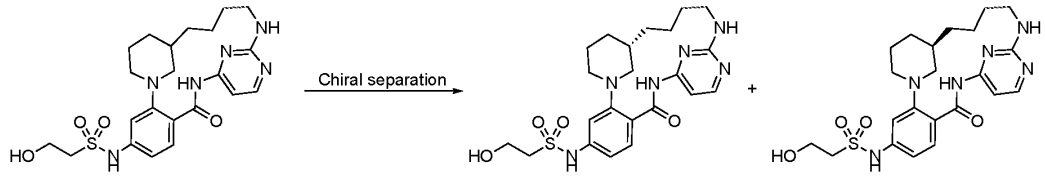
[000593] Enantiopure 2-hydroxy-N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (27.1 mg, 36.7% yield). LCMS (ESI-MS) m/z = 501.4 [M+H]+. 99.2% ee.

Table 7. 2 hour KIF18A Biochemical data for Examples 67 and 68

Compound	**KIF18A ADP-Glo IC50, nM (2h)**
First eluting isomer	+++++
Second eluting isomer	++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Examples 69 and 70. 2-hydroxy-N-((1^{3}S)-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide & 2-hydroxy-N-((1^{3}R)-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide (Compounds 69 and 70 respectively)



Example 59 Example 69 Example 70

[000594] The racemic mixture of 2-hydroxy-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide (10 mg, 0.021 mmol) was dissolved with MeOH and purified by Chiral-prep-HPLC with the following conditions: Column: CHIRAL ART Cellulose-SC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 40; Wave Length: 254/220nm nm; RT1(min): 6.881; RT2(min): 8.399; Sample Solvent: EtOH--HPLC; Injection Volume: 1.0 mL; Number Of Runs: 2 to afford the two products:

First eluting isomer:

[000595] Enantiopure 2-hydroxy-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide (2.1 mg, 20.9% yield). LCMS (ESI-MS) m/z = 475.3 [M+H]+. 100% ee.

Second eluting isomer:

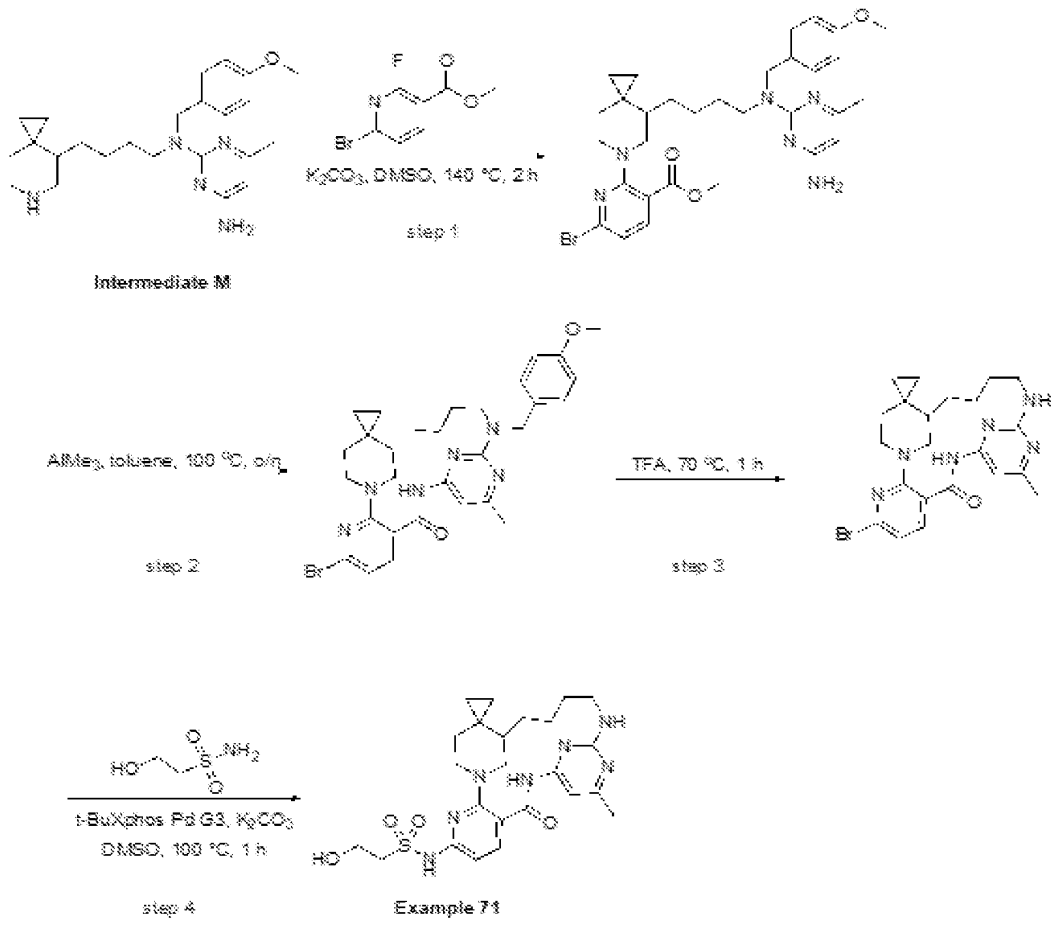
[000596] Enantiopure 2-hydroxy-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide (2.1 mg, 20.9% yield). LCMS (ESI-MS) m/z = 475.3 [M+H]+. 99.2% ee.

Table 8. 2 hour KIF18A Biochemical data for Examples 69 and 70

Compound	**KIF18A ADP-Glo IC50, nM (2h)**
First eluting isomer	++++
Second eluting isomer	++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 71. 2-hydroxy-N-(6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,3)-piperidinacyclodecaphan]-6'-yl)ethane-1-sulfonamide was prepared from Intermediate M via General synthetic route 3B following the procedure outlined below. (Compound 71)



1. **Methyl 2-(4-(4-((4-amino-6-methylpyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)-6-azaspiro[2.5] octan-6-yl)-6-bromonicotinate**

[000597] K_2CO_3 (283.44 mg, 2.05 mmol) was added to the mixture of Intermediate M (280 mg, 0.68 mmol) and methyl 6-bromo-2-fluoronicotinate (159.99 mg, 0.68 mmol) in DMSO (5 mL), the resulting mixture was heated to 140 °C and stirred for 2 hours. The reaction was quenched with water (40 mL). The resulting mixture was extracted with EA (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA = 1:1) to afford methyl 2-(4-(4-((4-amino-6-methylpyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)-6-azaspiro[2.5]octan-6-yl)-6-bromonicotinate (280 mg, 65.68 % yield). LCMS (ESI-MS) m/z = 623.2 $[M+H]^+$.

2. **6'-bromo-6'-(4-methoxybenzyl)-6'-methylspiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,3)-piperidinacyclodecaphan]-3'-one**

[000598] $AlMe_3$ (2.64 mL, 2.65 mmol, 1 M in heptane) was added to the mixture of methyl 2-(4-(4-((4-amino-6-methylpyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)-6-azaspiro[2.5]octan-6-yl)-6-bromonicotinate (550 mg, 0.88 mmol) in toluene (12 mL), the resulting mixture was heated to 100 °C and stirred overnight. The reaction was quenched with MeOH (20 mL). The resulting mixture was filtered, the filter cake was washed with MeOH (10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 2:1) to afford 6'-bromo-6'-(4-methoxybenzyl)-6'-methylspiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,3)-piperidinacyclodecaphan]-3'-one (90 mg, 17.25 % yield). LCMS (ESI-MS) m/z = 591.2 $[M+H]^+$.

3. **6'-bromo-6'-methylspiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,3)-piperidinacyclodecaphan]-3'-one**

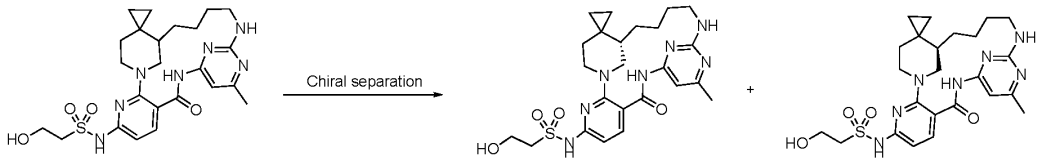
[000599] The mixture of 6'-bromo-6'-(4-methoxybenzyl)-6'-methylspiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,3)-piperidinacyclodecaphan]-3'-one (70 mg, 0.12 mmol) in TFA (3 mL) was heated to 70 °C and stirred for 1 hour. The reaction was quenched with $NaHCO_3$ (aq.)(10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford the crude product as light yellow oil. LCMS (ESI-MS) m/z = 471.1 $[M+H]^+$.

4. **2-hydroxy-N-(6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,3)-piperidinacyclodecaphan]-6'-yl)ethane-1-**

sulfonamide

[000600] 3rd Generation t-BuXPhos Pd precatalyst (11.81 mg, 0.01 mmol) was added to the mixture of 6'-bromo-6'-methylspiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,3)-piperidinacyclodecaphan] -3'-one (70 mg, 0.15 mmol), 2-hydroxyethanesulfonamide (18.58 mg, 0.15 mmol) and Cs_2CO_3 (96.76 mg, 0.3 mmol) in DMSO (1.3 mL) under nitrogen atmosphere, the resulting mixture was heated to 100 °C and stirred for 1 hour. The mixture was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 10% to 50% gradient in 10 min; detector, UV 254 nm, 220 nm to afford 2-hydroxy-N-(6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,3)-piperidinacyclodecaphan]-6'-yl)ethane-1-sulfonamide (2.1 mg, 2.72% yield). LCMS (ESI-MS) m/z = 516.4 $[M+H]^+$.

Examples 72 and 73. 2-hydroxy-N-((3'S)-6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,3)-piperidinacyclodecaphan]-6'-yl)ethane-1-sulfonamide & 2-hydroxy-N-((3'R)-6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,3)-piperidinacyclodecaphan]-6'-yl)ethane-1-sulfonamide



Example 71 Example 72 Example 73

[000601] The racemic mixture of 2-hydroxy-N-(6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,3)-piperidinacyclodecaphan]-6'-yl)ethane-1-sulfonamide (13 mg, 0.03 mmol) was separated by Prep_Chiral HPLC with the following condition: Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 50; Wave Length: 254/220nm nm; RT1(min): 3.676; RT2(min): 7.777; Sample Solvent: EtOH--HPLC; Injection Volume: 1.1 mL; Number Of Runs: 2, the desired fractions were combined and lyophilized to afford the two products.

first eluting isomer:

[000602] Enantiopure 2-hydroxy-N-(6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,3)-piperidinacyclodecaphan]-6'-yl)ethane-1-sulfonamide (2.2 mg, 16.58% yield). LCMS (ESI-MS) m/z = 516.4 $[M+H]^+$

second eluting isomer:

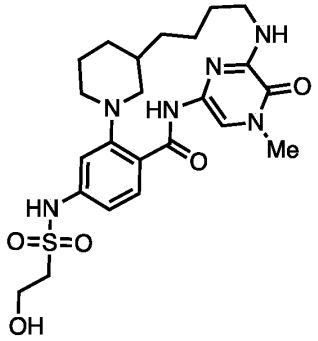
[000603] Enantiopure 2-hydroxy-N-(6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,3)-piperidinacyclodecaphan]-6'-yl)ethane-1-sulfonamide (1.7 mg, 12.75% yield), LCMS (ESI-MS) m/z = 516.4 $[M+H]^+$

Table 9. 2 hour KIF18A Biochemical data for Examples 72 and 73

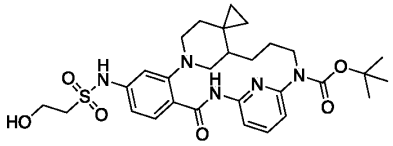
Compound	**KIF18A ADP-Glo IC50, nM (2h)**
First eluting isomer	++++
Second eluting isomer	+

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

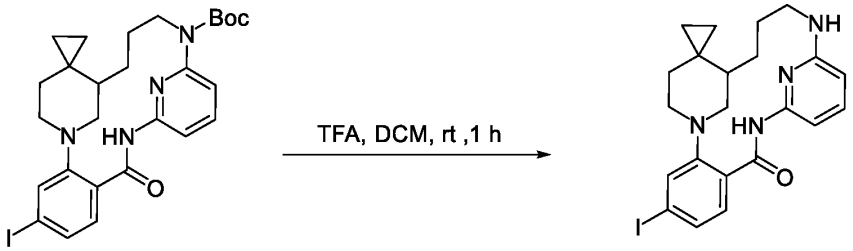
Example 74. (*E*)-2-hydroxy-*N*-(5^1-methyl-5^2,3-dioxo-5^1,5^2-dihydro-4,6-diaza-5(5,3)-pyrazina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide was prepared utilizing General Synthetic Route 6 following the procedure described in Example 146. Step 1 employed *tert*-butyl 3-(4-aminobutyl)piperidine-1-carboxylate and 3,5-dibromo-1-methylpyrazin-2(1*H*)-one. Step 5 employed 2-hydroxyethane-1-sulfonamide. (Compound 74)



Example 75. ***tert*****-butyl 5'-((2-hydroxyethyl)sulfonamido)-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane]-6'-carboxylate was prepared starting from Intermediate A, following General synthetic route 1A as outlined in Steps 1 through 8 procedures for Example 1. (Compound 75)**

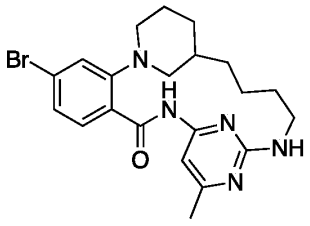


Example 76. 5'-iodospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphan]-3'-one was prepared as described below. (Compound 76)

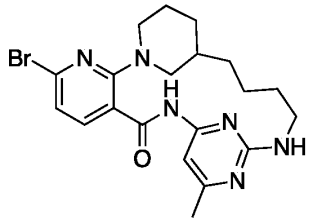


[000604] TFA (0.2 mL) was added to a stirred mixture of tert-butyl 5'-iodo-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphane]-6'-carboxylate (Example 75) (10 mg, 0.017 mmol) in DCM (0.5 mL). The resulting mixture was stirred at room temperature for 1 hour and concentrated under vacuum. The residue was purified by Prep-TLC (DCM/MeOH 10:1) to afford the desired product 5'-iodospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclononaphan]-3'-one (3.0 mg, 36.1% yield). LCMS (ESI-MS) m/z = 489.1 $[M+H]^+$,

Example 77. 2^5-bromo-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one is Intermediate C (Compound 77)

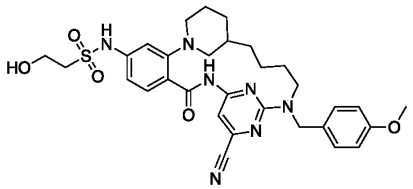


Example 78. 2^6-bromo-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,3)-piperidinacyclodecaphan-3-one was prepared via General synthetic route 3A using intermediate B and 6-bromo-2-fluoronicotinic acid in Step 1 (Compound 78)

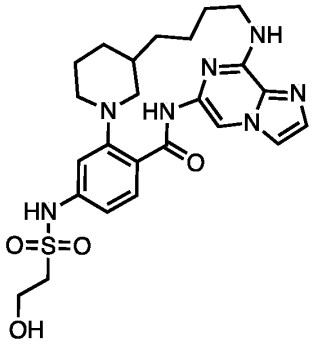


Examples 79, 80, 81. See Example 61

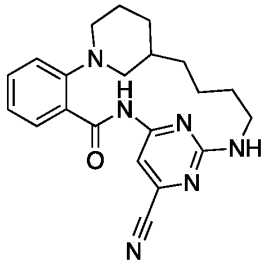
Example 82. *N*-(5^6-cyano-6-(4-methoxybenzyl)-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide was prepared via the synthetic route for example 61 using 6-amino-2-chloropyrimidine-4-carbonitrile in Step 1 (Compound 82)



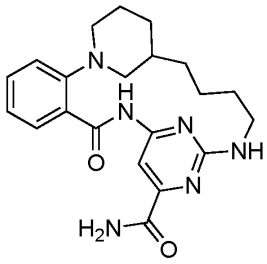
Example 83: (*E*)-2-hydroxy-*N*-(3-oxo-4,6-diaza-5(6,8)-imidazo[1,2-*a*]pyrazina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide was prepared utilizing General Synthetic Route 6. Step 1 employed *tert*-butyl 3-(4-aminobutyl)piperidine-1-carboxylate and 6-bromo-8-chloroimidazo[1,2-*a*]pyrazine. Step 5 employed 2-hydroxyethane-1-sulfonamide. (Compound 83)



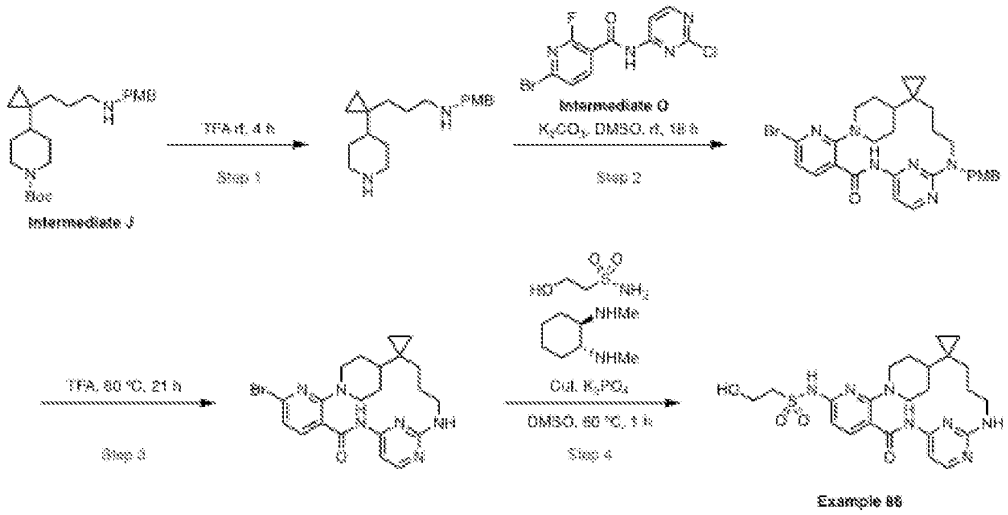
Example 84. 3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-5^{6}-carbonitrile was prepared following the synthetic route for example 61 using 6-amino-2-chloropyrimidine-4-carbonitrile in Step 1. In step 6, the reaction was heated at 130 ^{o}C for 30 min which afforded compound 84 as protodehalogenation by-product. (Compound 84)



Example 85. 3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-56-carboxamide was prepared following the synthetic route used to prepare Compound 84 starting from 2^{5}-iodo-6-(4-methoxybenzyl)-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-5^{6}-carboxamide which was a by-product formed in step 3. Example 85 is a protodehalogenation by-product in this reaction. (Compound 85)



Example 86. 2-hydroxy-*N*-(3'-oxospiro[cyclopropane-1,10'-4,6-diaza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,4)-piperidinacyclodecaphan]-6'-yl)ethane-1-sulfonamide was prepared was prepared following the synthetic route outlined below. (Compound 86)



1. *N*-(4-methoxybenzyl)-3-(1-(piperidin-4-yl)cyclopropyl)propan-1-amine

[000605] To a vial was added tert-butyl 4-(1-(3-((4-methoxybenzyl)amino)propyl)cyclopropyl)piperidine-1-carboxylate, (Intermediate J, 247 mg, 613 µmol) and TFA (4.42 g, 2.98 mL, 38.7 mmol). The reaction mixture was stirred at rt for 4 hour then concentrated in vacuo. The crude residue was diluted with sat. aq. $NaHCO_3$ and extracted with DCM (3 x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was used for the next step without further purification. LCMS M+1/Z = 303.2

2. 6'-bromo-6'-(4-methoxybenzyl)spiro[cyclopropane-1,10'-4,6-diaza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,4)-piperidinacyclodecaphan]-3'-one

[000606] To the crude residue from the previous step was added under N_2 atmosphere 6-bromo-N-(2-chloropyrimidin-4-yl)-2-fluoronicotinamide (Intermediate O, 214 mg, 645 µmol), K_2CO_3 (268 mg, 1.94 mmol), and DMSO (8.0 mL). The reaction mixture was stirred at rt. After 18 h, the reaction mixture was diluted with EtOAc and washed with brine (5 x), dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-100% 3:1 EtOAc:EtOH in heptane) provided 6-bromo-N-(2-chloropyrimidin-4-yl)-2-(4-(1-(3-((4-methoxybenzyl)amino)propyl)cyclopropyl)piperidin-1-yl)nicotinamide (211 mg, 344 µmol, 53.2 %) and 6'-bromo-6'-(4-methoxybenzyl)spiro[cyclopropane-1,10'-4,6-diaza-5(4,2)-

pyrimidina-2(2,3)-pyridina-1(1,4)-piperidinacyclodecaphan]-3'-one (16 mg, 28 μmol, 4.3 %). LCMS M+1/Z = 577.1

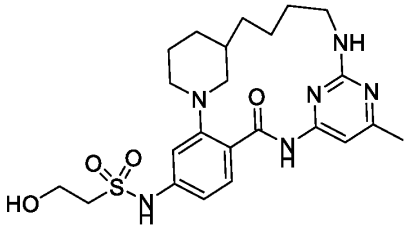
3. 6'-bromospiro[cyclopropane-1,10'-4,6-diaza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,4)-piperidinacyclodecaphan]-3'-one

[000607] A solution of 6'-bromo-6'-(4-methoxybenzyl)spiro[cyclopropane-1,10'-4,6-diaza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,4)-piperidinacyclodecaphan]-3'-one (16 mg, 28 μmol) in TFA (0.19 g, 0.13 mL, 1.7 mmol) was heated to 60 °C. After 1 h, the reaction mixture was concentrated in vacuo. The crude residue was reconstituted in DCM and washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$, and concentrated. The crude material was used for the next step without further purification. LCMS M+1/Z = 457.0

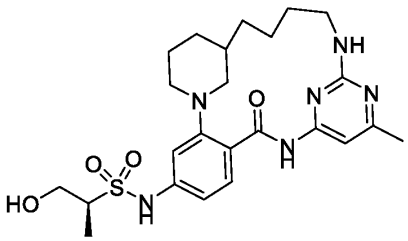
4. 2-hydroxy-*N*-(3'-oxospiro[cyclopropane-1,10'-4,6-diaza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,4)-piperidinacyclodecaphan]-6'-yl)ethane-1-sulfonamide

[000608] To the crude material from the previous step was added CuI (2.1 mg, 11 μmol), (1R,2R)-N,N'-Dimethyl-1,2-cyclohexanediamine (3.2 mg, 0.8 Eq, 22 μmol), Potassium phosphate, tribasic (29 mg, 11 μL, 0.14 mmol), and 2-hydroxyethane-1-sulfonamide (17 mg, 0.14 mmol). The reaction vial was placed under a N_2 atmosphere then DMSO (0.5 mL) was added. The reaction mixture was then heated to 80 °C. After 21 h, the reaction mixture was diluted with water and extracted with DCM (3 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification via prepHPLC (10-100% MeCN in 0.1% TFA water) followed by repurification of the provided fractions containing product via prepHPLC (10-100% MeCN in 0.1% NH_4OAc water) provided 6'-bromo-6'-(4-methoxybenzyl)spiro[cyclopropane-1,10'-4,6-diaza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,4)-piperidinacyclodecaphan]-3'-one (16 mg). LCMS M+1/Z = 502.2

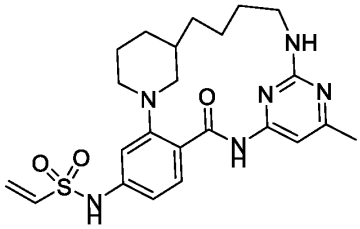
Example 87. (2R)-1-hydroxy-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)propane-2-sulfonamide was prepared via General synthetic route 4A using intermediate C and (R)-1-hydroxypropane-2-sulfonamide in Step 4 that engage in a Cu-catalyzed coupling procedure described in Step 4 of Example 4 except for using DMF as solvent at 90 °C in place of dioxane at 100 °C. (Compound 87)



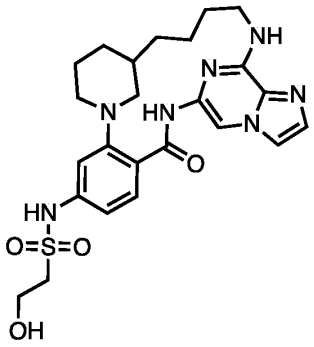
Example 88. (2S)-1-hydroxy-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)propane-2-sulfonamide was prepared via General synthetic route 4A using intermediate C and (S)-1-hydroxypropane-2-sulfonamide in Step 4 that engage in a Cu-catalyzed coupling procedure described in Step 4 of Example 4 with the except for using DMF as solvent at 90 °C in place of dioxane at 100 °C. (Compound 88)



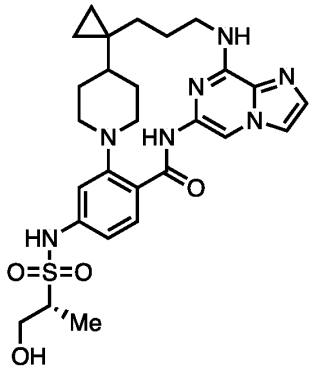
Example 89. N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethenesulfonamide was prepared via General synthetic route 4A using intermediate C and 2-fluoroethane-1-sulfonamide in Step 4 that engage in a Cu-catalyzed coupling procedure described in Step 4 of Example 4 except for using DMF as solvent at 90°C in place of dioxane at 100°C. Example 89 was an elimination by-product in this reaction. (Compound 89)



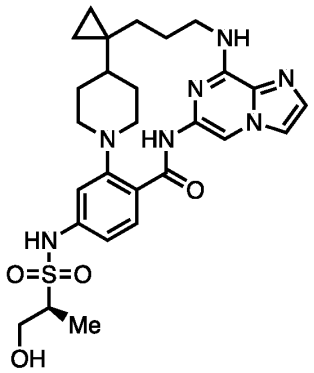
Example 90: (*E*)-2-hydroxy-*N*-(3'-oxospiro[cyclopropane-1,10'-4,6-diaza-5(6,8)-imidazo[1,2-*a*]pyrazina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide was prepared utilizing General synthetic route 6 following the procedure described in Example 146. Step 1 employed *tert*-butyl 4-(1-(3-aminopropyl)cyclopropyl)piperidine-1-carboxylate and 6-bromo-8-chloroimidazo[1,2-*a*]pyrazine. Step 5 employed 2-hydroxyethane-1-sulfonamide. (Compound 90)



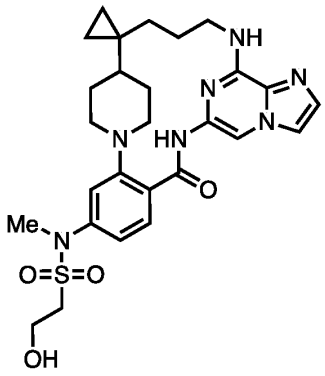
Example 91: (*R*,*E*)-1-hydroxy-*N*-(3'-oxospiro[cyclopropane-1,10'-4,6-diaza-5(6,8)-imidazo[1,2-*a*]pyrazina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)propane-2-sulfonamide was prepared utilizing General synthetic route 6 **following the procedure described in Example 146. Step 1 employed *tert*-butyl 4-(1-(3-aminopropyl)cyclopropyl)piperidine-1-carboxylate and 6-bromo-8-chloroimidazo[1,2-*a*]pyrazine. Step 5 employed (*R*)-1-hydroxypropane-2-sulfonamide. (Compound 91)**



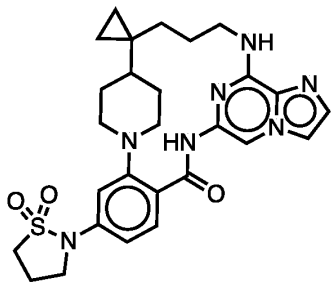
Example 92: (*S*,*E*)-1-hydroxy-*N*-(3'-oxospiro[cyclopropane-1,10'-4,6-diaza-5(6,8)-imidazo[1,2-*a*]pyrazina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)propane-2-sulfonamide was prepared utilizing General synthetic route 6 **following the procedure described in Example 146. Step 1 employed and 6-bromo-8-chloroimidazo[1,2-*a*]pyrazine. Step 5 employed (*S*)-1-hydroxypropane-2-sulfonamide. (Compound 92)**



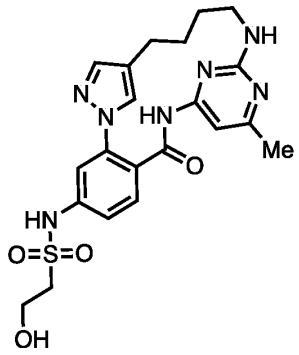
Example 93: (*E*)-2-hydroxy-*N*-methyl-*N*-(3'-oxospiro[cyclopropane-1,10'-4,6-diaza-5(6,8)-imidazo[1,2-*a*]pyrazina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide was prepared utilizing General synthetic route 6 **following the procedure described in Example 146. Step 1 employed *tert*-butyl 4-(1-(3-aminopropyl)cyclopropyl)piperidine-1-carboxylate and 6-bromo-8-chloroimidazo[1,2-*a*]pyrazine. Step 6 employed 2-hydroxy-*N*-methylethane-1-sulfonamide. (Compound 93)**



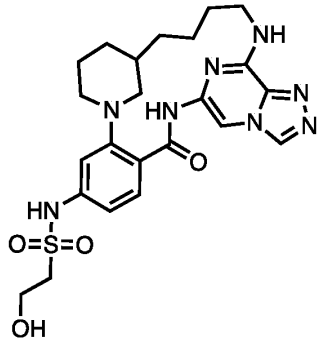
Example 94: (*E*)-5'-(1,1-dioxidoisothiazolidin-2-yl)spiro[cyclopropane-1,10'-4,6-diaza-5(6,8)-imidazo[1,2-*a*]pyrazina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one was prepared utilizing General synthetic route 6 **following the procedure described in Example 146. Step 1 employed *tert*-butyl 4-(1-(3-aminopropyl)cyclopropyl)piperidine-1-carboxylate and 6-bromo-8-chloroimidazo[1,2-*a*]pyrazine. Step 6 employed isothiazolidine 1,1-dioxide. (Compound 94).**



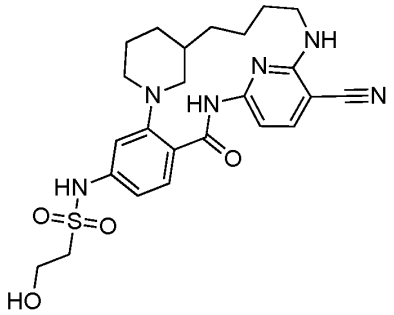
Example 95: (*Z*)-2-hydroxy-*N*-(5^{6}-methyl-3-oxo-1^{1}*H*-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-pyrazola-2(1,2)-benzenacyclodecaphane-2^{5}-yl)ethane-1-sulfonamide was prepared utilizing a modified General synthetic route **4a following the procedure described in Example 62. Step 1 employed 4-(1*H*-pyrazol-4-yl)butan-1-amine and Intermediate H. Step 2 was omitted. (Compound 95).**



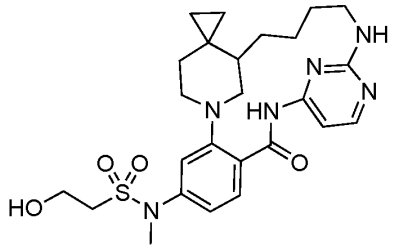
Example 96: (*E*)-2-hydroxy-*N*-(3-oxo-4,6-diaza-5(6,8)-[1,2,4]triazolo[4,3-*a*]pyrazina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^{5}-yl)ethane-1-sulfonamide was prepared utilizing General synthetic route **6 following the procedure described in Example 146. Step 1 employed *tert*-butyl 3-(4-aminobutyl)piperidine-1-carboxylate and 6-bromo-8-chloro-[1,2,4]triazolo[4,3-*a*]pyrazine. Step 6 employed 2-hydroxyethane-1-sulfonamide. (Compound 96)**



Example 97. ***N*****-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide was prepared via General synthetic route 4A from Intermediate P and *tert*-butyl 3-(4-aminobutyl)piperidine-1-carboxylate following the procedure for Example 18. (Compound 97)**

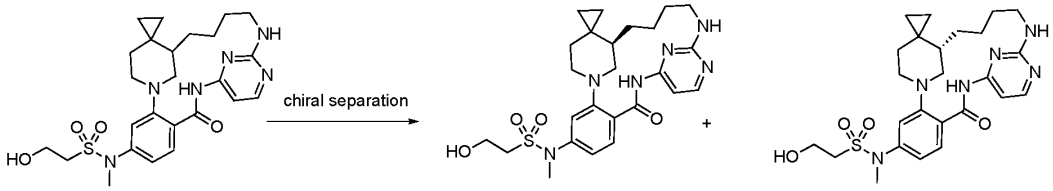


Example 98. 2-hydroxy-N-methyl-N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide was synthesized via General synthetic route 4A using intermediate E and intermediate H. In Step 4 2-hydroxy-N-methylethane-1-sulfonamide was used and a Cu-catalyzed coupling procedure described in Step 4 of Example 4 (Compound 98)



Examples 99 and 100. 2-hydroxy-N-methyl-N-((3'R)-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide & 2-hydroxy-N-methyl-N-((3'S)-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-

5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (Compound 99 and compound 100 respectively).



Example 98 Example 99 Example 100

[000609] A racemic mixture of 2-hydroxy-N-methyl-N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (30 mg, 0.058 mmol) was dissolved with MeOH and purified by Chiral-prep-HPLC with the following conditions: Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 35; Wave Length: 254/220nm nm; RT1(min): 5.83; RT2(min): 7.341; Sample Solvent: EtOH--HPLC; Injection Volume: 0.3 mL; Number of injections: 5 to afford the two products:

First eluting isomer:

[000610] Enantiopure 2-hydroxy-N-methyl-N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (8.1 mg, 26.8% yield). LCMS (ESI-MS) m/z = 515.2 $[M+H]^+$. 100% ee.

Second eluting isomer:

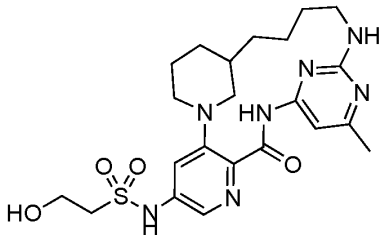
[000611] Enantiopure 2-hydroxy-N-methyl-N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (8.6 mg, 28.5% yield). LCMS (ESI-MS) m/z = 515.2 $[M+H]^+$. 99.9% ee.

Table 10. 2 hour KIF18A Biochemical data for Examples 99 and 100

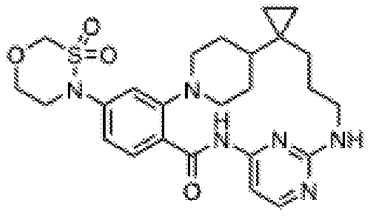
Compound	**KIF18A ADP-Glo IC50, nM (2h)**
First eluting isomer	++
Second eluting isomer	+++++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

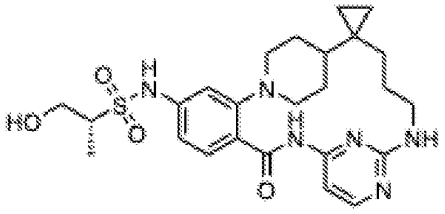
Example 101. 2-hydroxy-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-2(3,2)-pyridina-1(1,3)-piperidinacyclodecaphane-2^5-yl)ethane-1-sulfonamide was synthesized from Intermediate B and methyl 5-bromo-3-fluoropyridine-2-carboxylate using General synthetic route 3C and similar reaction procedures as in Example 4. In step 2, LiOH in THF-water was used to produce a carboxylic acid required for step 3. (Compound 101)



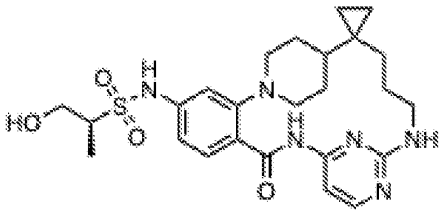
Example 102. 5'-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)spiro[cyclopropane-1,10'-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one was prepared via General synthetic route 3A from intermediate L in Step 1 and 1,3,4-oxathiazinane 3,3-dioxide in Step 4. For the latter, Pd-catalyzed coupling procedure as described in Step 4 of Example 18 was used. Alternatively, Example 102 can be synthesized via General synthetic route 4B using Intermediate J and Intermediate H in Step 1 (Compound 102).



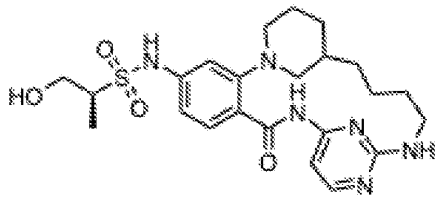
Example 103. (*R*)-1-hydroxy-*N*-(3'-oxospiro[cyclopropane-1,10'-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)propane-2-sulfonamide was prepared via General synthetic route 3A from intermediate L in Step 1 and (*R*)-1-hydroxypropane-2-sulfonamide in Step 4. For the latter, Pd-catalyzed coupling procedure as described in Step 4 of Example 18 was used. Alternatively, Example 103 can be synthesized via General synthetic route 4B using Intermediate J and Intermediate H in Step 1 (Compound 103).



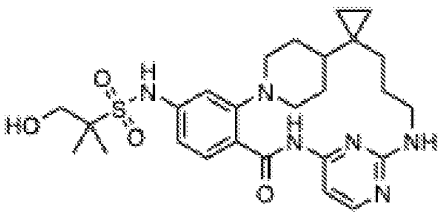
Example 104. (*S*)-1-hydroxy-*N*-(3'-oxospiro[cyclopropane-1,10'-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)propane-2-sulfonamide was prepared via General synthetic route 3A from intermediate L in Step 1 and (*S*)-1-hydroxypropane-2-sulfonamide in Step 4. For the latter, Pd-catalyzed coupling procedure as described in Step 4 of Example 18 was used. Alternatively, Example 104 can be synthesized via General synthetic route 4B using Intermediate J and Intermediate H in Step 1 (Compound 104).



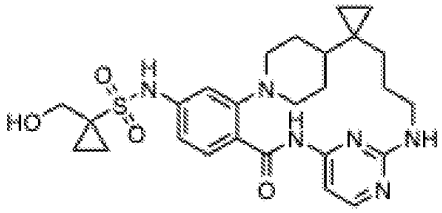
Example 105. (2*S*)-1-hydroxy-*N*-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-25-yl)propane-2-sulfonamide was prepared via General synthetic route 4A from tert-butyl 3-(4-aminobutyl)piperidine-1-carboxylate and Intermediate H, as described in procedure from Example 62, and (*S*)-1-hydroxypropane-2-sulfonamide in Step 4. For the latter, Pd-catalyzed coupling procedure as described in Step 4 of Example 18 was used (Compound 105).



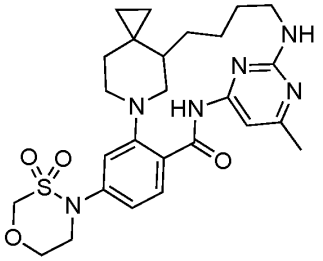
Example 106. 1-hydroxy-2-methyl-*N*-(3'-oxospiro[cyclopropane-1,10'-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)propane-2-sulfonamide was prepared via General synthetic route 3A from intermediate L in Step 1 and 1-hydroxy-2-methylpropane-2-sulfonamide in Step 4. For the latter, Pd-catalyzed coupling procedure as described in Step 4 of Example 18 was used. Alternatively, Example 106 can be synthesized via General synthetic route 4B using Intermediate J and Intermediate H in Step 1 (Compound 106).



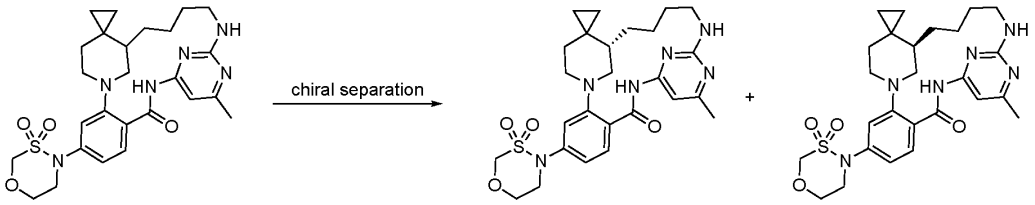
Example 107. 1-(hydroxymethyl)-*N*-(3'-oxospiro[cyclopropane-1,10'-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)cyclopropane-1-sulfonamide was prepared via General synthetic route 3A from intermediate L in Step 1 and 1-(hydroxymethyl)cyclopropane-1-sulfonamide in Step 4. For the latter, Pd-catalyzed coupling procedure as described in Step 4 of Example 18 was used. Alternatively, Example 107 can be synthesized via General synthetic route 4B using Intermediate J and Intermediate H in Step 1 (Compound 107).



Example 108. 5'-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)-6'-methylspiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one was prepared via General synthetic route 4A starting from Intermediate E and intermediate G. In step 4 1,3,4-oxathiazinane 3,3-dioxide, palladium acetate, cesium carbonate and Xantphos in dioxane at 100 C were used to produce desired Compound 108.



Examples 109 and 110. (3'S)-5'-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)-6'-methylspiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one & (3'R)-5'-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)-6'-methylspiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one (Compound 109 and compound 110 respectively)



Example 108 Example 109 Example 110

[000612] The racemic mixture of 2-hydroxy-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-2(3,2)-pyridina-1(1,3)-piperidinacyclodecaphane-2^5-yl)ethane-1-sulfonamide (40.0 mg, 0.076 mmol) was separated by Prep-Chiral-HPLC with the condition: Column: CHIRALPAK IH, 2*25 cm, 5 μm; Mobile Phase A: HEX(0.1% DEA&0.1%FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 15; Wave Length: 254/220nm nm; RT1(min): 11.768; RT2(min): 14.058; Sample Solvent: EtOH--HPLC; Injection Volume: 1.3 mL; Number of injections: 1 to afford two products:

First eluting isomer:

[000613] Enantiopure 2-hydroxy-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-2(3,2)-pyridina-1(1,3)-piperidinacyclodecaphane-2^5-yl)ethane-1-sulfonamide (10.2 mg, 25.5% yield). LCMS (ESI-MS) m/z = 527.2 $[M+H]^+$, e,e = 100%.

Second eluting isomer:

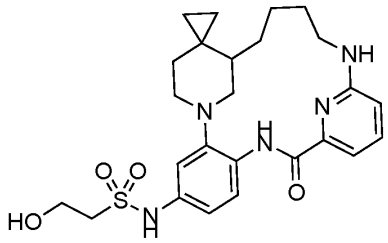
[000614] Enantiopure 2-hydroxy-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-2(3,2)-pyridina-1(1,3)-piperidinacyclodecaphane-2^5-yl)ethane-1-sulfonamide (11.1 mg, 27.8% yield). LCMS (ESI-MS) m/z =527.2 $[M+H]^+$, e,e = 100%.

Table 11. 2 hour KIF18A Biochemical data for Examples 109 and 110

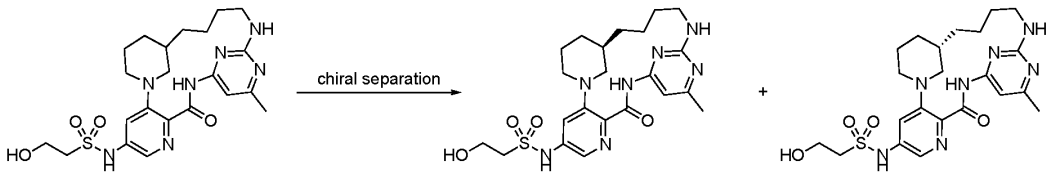
Compound	KIF18A ADP-Glo IC50, nM (2h)
First eluting isomer	+++++
Second eluting isomer	++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 111. 2-hydroxy-N-(4'-oxospiro[cyclopropane-1,4'-3,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide was synthesized from Intermediate F and methyl 6-bromopicolinate via General synthetic route 2B with exception of Step 4 where AlMe3 was employed to forge macrocyclization instead of a base following the procedure from step 2 of example 71 (Compound 111).



Examples 112 and 113. 2-hydroxy-N-((1^{3}R)-5^{6}-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-2(3,2)-pyridina-1(1,3)-piperidinacyclodecaphane-2^{5}-yl)ethane-1-sulfonamide & 2-hydroxy-N-((1^{3}S)-5^{6}-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-2(3,2)-pyridina-1(1,3)-piperidinacyclodecaphane-2^{5}-yl)ethane-1-sulfonamide (Compound 112 and compound 113 respectively)



Example 101 Example 112 Example 113

[000615] The racemic mixture of 2-hydroxy-N-(5^{6}-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-2(3,2)-pyridina-1(1,3)-piperidinacyclodecaphane-2^{5}-yl)ethane-1-sulfonamide (8 mg, 0.016 mmol) was separated by Prep-Chiral-HPLC with the condition: Column: CHIRALPAK IH, 2*25 cm, 5 μm; Mobile Phase A: HEX(0.1% DEA&0.1%FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient:

isocratic 15; Wave Length: 254/220nm nm; RT1(min): 11.768; RT2(min): 14.058; Sample Solvent: EtOH--HPLC; Injection Volume: 1.3 mL; Number of injections: 1 to afford two products:

First eluting isomer:

[000616] Enantiopure 2-hydroxy-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-2(3,2)-pyridina-1(1,3)-piperidinacyclodecaphane-2^5-yl)ethane-1-sulfonamide (1.2 mg, 13.53% yield). LCMS (ESI-MS) m/z = 578.2 $[M+H]^+$, e,e = 90.3%.

Second eluting isomer:

[000617] Enantiopure 2-hydroxy-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-2(3,2)-pyridina-1(1,3)-piperidinacyclodecaphane-2^5-yl)ethane-1-sulfonamide (1.6 mg, 16.60% yield). LCMS (ESI-MS) m/z =578.2 $[M+H]^+$, e,e = 97.1%.

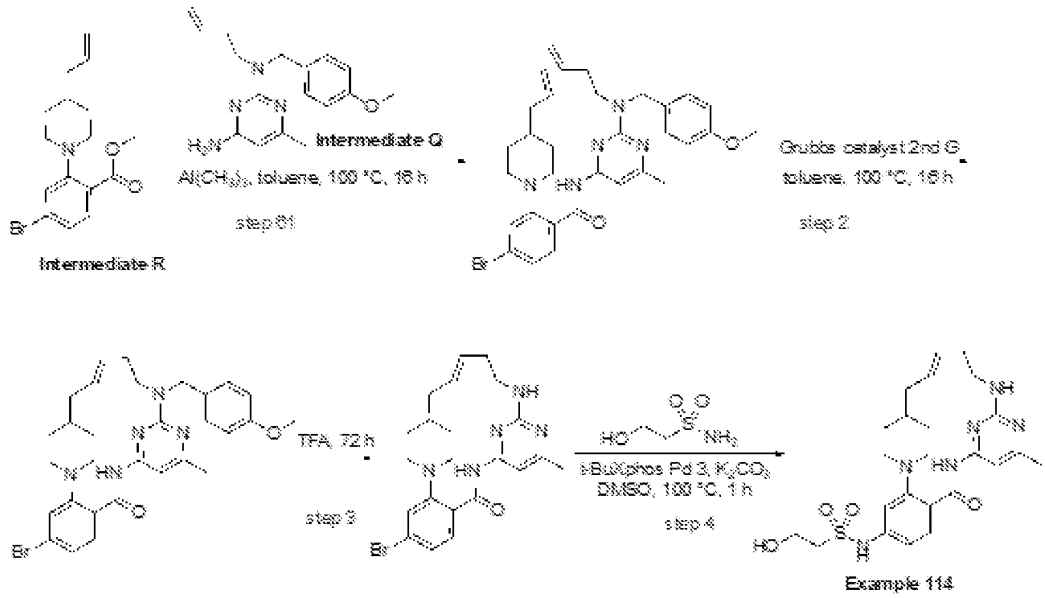
Table 12. 2 hour KIF18A Biochemical data for Examples 112 and 113 (2h)

Compound	**KIF18A ADP-Glo IC50, nM**
First eluting isomer	+
Second eluting isomer	++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 114. (E)-2^5-bromo-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one was synthesized from Intermediate Q and

Intermediate R following Steps 1-4 of General synthetic route 7A as described in the procedure below. (Compound 114)



1. **2-(4-allylpiperidin-1-yl)-4-bromo-N-(2-(but-3-en-1-yl(4-methoxybenzyl)amino)-6-methylpyrimidin-4-yl)benzamide**

[000618] $Al(CH_3)_3$ (13.3 mL, 13.3 mmol) was added to a mixture of Intermediate R (1.5 g, 4.44 mmol,) and Intermediate Q (1.32 g, 4.44 mmol) in toluene (30 mL, 282 mmol) at 0 °C. The resulting solution was heated to 100 °C and stirred for 16 hours. After cooling to room temperature, the reaction mixture was diluted with water (20 mL) and extracted with EA (50 mL x 2). The combined organic layers were washed with brine (50 mL x 2), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA/PE 1:3 to afford 2-(4-allylpiperidin-1-yl)-4-bromo-N-(2-(but-3-en-1-yl(4-methoxybenzyl)amino)-6-methylpyrimidin-4-yl)benzamide (1.3 g, 31.6% yield). LCMS (ESI-MS) m/z = 604.3 $[M+H]^+$.

2. **(E)-2^5-bromo-6-(4-methoxybenzyl)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one**

[000619] Grubbs catalyst 2nd Gen(169 mg, 0.198 mmol) was added to a mixture of 2-(4-allylpiperidin-1-yl)-4-bromo-N-(2-(but-3-en-1-yl(4-methoxybenzyl)amino)-6-methylpyrimidin-4-yl)benzamide (600 mg, 0.992 mmol) in toluene (10 mL). The resulting solution was heated to 100 °C and stirred for 16 hours. After cooling to room temperature, the reaction mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA/PE 1:3 to afford (E)-2^5-bromo-6-(4-methoxybenzyl)-

5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (350 mg, 25.9% yield). LCMS (ESI-MS) m/z = 576.3 $[M+H]^+$.

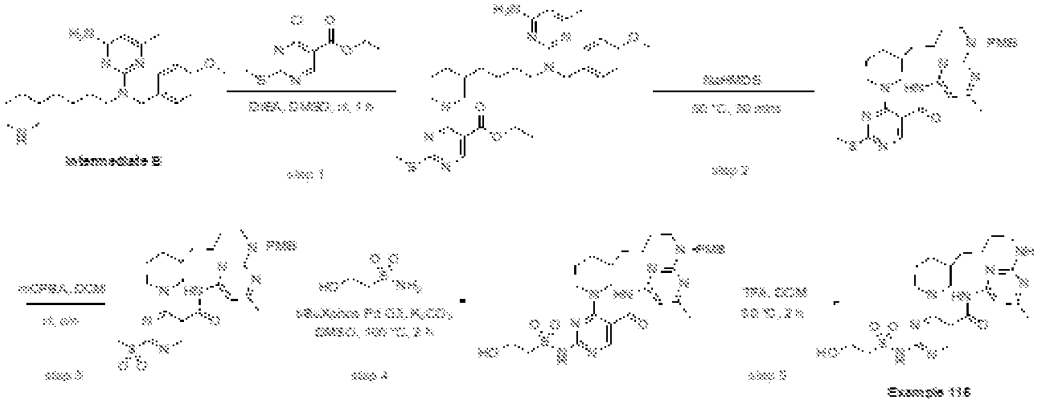
3. (E)-2^5-bromo-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one

[000620] Into a 25-mL round-bottom flask, was added (E)-2^5-bromo-6-(4-methoxybenzyl)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (300 mg, 0.52 mmol) and TFA (5 mL). The resulting solution was stirred at room temperature for 72 hours. The reaction mixture was concentrated under vacuum to afford (E)-2^5-bromo-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (240 mg crude). LCMS (ESI-MS) m/z = 456.1 $[M+H]^+$.

4. (E)-2-hydroxy-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide

[000621] Into a solution of (E)-2^5-bromo-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (240 mg, 0.526 mmol) in DMSO (2 mL) was added 2-hydroxyethanesulfonamide (197 mg, 1.58 mmol), t-BuXPhos Pd G3 (83.7 mg, 0.105 mmol) and K_2CO_3 (218 mg, 1.58 mmol). The resulting solution was heated to 100 °C and stirred for 1 hour. After cooling to room temperature, the reaction mixture was diluted with water (10 mL) and extracted with EA (10 mL x 2). The combined organic layers were combined, washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA/PE 1:1 to afford (E)-2-hydroxy-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide (50 mg, 18.6% yield). LCMS (ESI-MS) m/z = 501.3 $[M+H]^+$.

Example 115. 2-hydroxy-*N*-(5^6-methyl-3-oxo-4,6-diaza-2(4,5),5(4,2)-dipyrimidina-1(1,3)-piperidinacyclodecaphane-2^2-yl) ethane-1-sulfonamide was synthesized from Intermediate B as described below. (Compound 115)



1. ethyl 4-(3-(4-((4-amino-6-methylpyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)piperidin-1-yl)-2-(methylthio)pyrimidine-5-carboxylate

[000622] DIEA (324 mg, 2.50 mmol) was added to a stirred mixture of Intermediate B (240 mg, 0.62 mmol) and ethyl 4-chloro-2-(methylthio)pyrimidine-5-carboxylate (291 mg, 1.25 mmol) in DMSO (4 mL). The reaction was stirred at room temperature for 1 h. The resulting mixture was diluted with EA (200 ml) and washed with brine (3 x 200 ml). The organic layer was dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the ethyl 4-(3-(4-((4-amino-6-methylpyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)piperidin-1-yl)-2-(methylthio)pyrimidine-5-carboxylate (170 mg crude). LCMS (ESI-MS) m/z = 580.3 $[M+H]^+$.

2. 6-(4-methoxybenzyl)-5^6-methyl-2^2-(methylthio)-4,6-diaza-2(4,5),5(4,2)-dipyrimidina-1(1,3)-piperidinacyclodecaphan-3-one

[000623] NaHMDS (237 mg, 1.29 mmol) was added to a stirred solution of ethyl 4-(3-(4-((4-amino-6-methylpyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)piperidin-1-yl)-2-(methylthio)pyrimidine-5-carboxylate (250 mg, 0.43 mmol) in THF (1 mL) under nitrogen atmosphere. The reaction mixture was heated to 50 °C and stirred for 30 minutes. The resulting mixture was diluted with water (30 ml) and extracted with EA (2 x 30 ml). The organic layers were combined, washed with brine (2 x 30 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA/PE 1:3 to afford 6-(4-methoxybenzyl)-5^6-methyl-2^2-(methylthio)-4,6-diaza-2(4,5),5(4,2)-dipyrimidina-1(1,3)-piperidinacyclodecaphan-3-one (50 mg, 11.3% yield). LCMS (ESI-MS) m/z = 534.2 $[M+H]^+$.

3. 6-(4-methoxybenzyl)-5^6-methyl-2^2-(methylsulfonyl)-4,6-diaza-2(4,5),5(4,2)-dipyrimidina-1(1,3)-piperidinacyclodecaphan-3-one

[000624] m-CPBA (64.6 mg, 0.37 mmol) was added to a stirred solution of 6-(4-methoxybenzyl)-5^6-methyl-2^2-(methylthio)-4,6-diaza-2(4,5),5(4,2)-dipyrimidina-1(1,3)-piperidinacyclodecaphan-3-one (50 mg, 0.09 mmol) in DCM (3 mL). The resulting solution was stirred at room temperature overnight. The reaction mixture was diluted with DCM (50 ml) and washed with saturated sodium $NaHCO_3$ solution (3 x 50 ml). The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA/PE 2:1 to afford the desired product 6-(4-methoxybenzyl)-5^6-methyl-2^2-(methylsulfonyl)-4,6-diaza-2(4,5),5(4,2)-dipyrimidina-1(1,3)-piperidinacyclodecaphan-3-one (30 mg, 56.6% yield). LCMS (ESI-MS) m/z = 566.1 $[M+H]^+$.

4. 2-hydroxy-*N*-(6-(4-methoxybenzyl)-5^6-methyl-3-oxo-4,6-diaza-2(4,5),5(4,2)-dipyrimidina-1(1,3)-piperidinacyclodecaphane-2^2-yl)ethane-1-sulfonamide

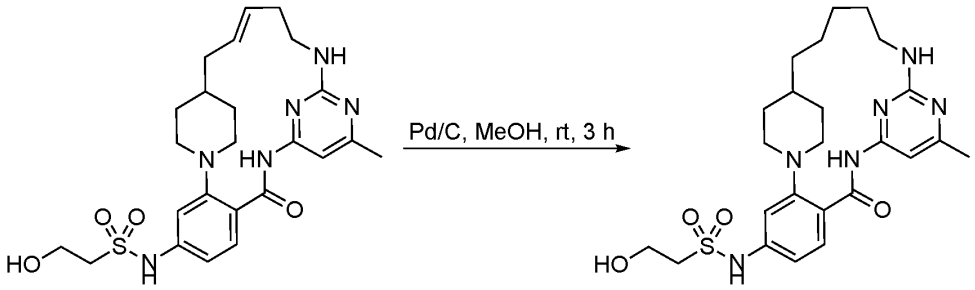
[000625] Into a solution of 6-(4-methoxybenzyl)-5^6-methyl-2^2-(methylsulfonyl)-4,6-diaza-2(4,5),5(4,2)-dipyrimidina-1(1,3)-piperidinacyclodecaphan-3-one (25 mg, 0.044 mmol) in DMSO (0.5 mL) was added 2-hydroxyethane-1-sulfonamide (16.6 mg, 0.13 mmol), K_2CO_3 (18.3 mg, 0.13 mmol) and tBuXPhos Pd G3 (7.0 mg, 0.009 mmol,). The resulting solution was heated to 100 ^oC and stirred for 2 hours. After cooling to room temperature, the resulting mixture was diluted with EA (50 ml) and washed with brine (3 x 50 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford desired product 2-hydroxy-*N*-(6-(4-methoxybenzyl)-5^6-methyl-3-oxo-4,6-diaza-2(4,5),5(4,2)-dipyrimidina-1(1,3)-piperidinacyclodecaphane-2^2-yl)ethane-1-sulfonamide (8 mg crude). LCMS (ESI-MS) m/z = 611.3 $[M+H]^+$.

5. 2-hydroxy-*N*-(5^6-methyl-3-oxo-4,6-diaza-2(4,5),5(4,2)-dipyrimidina-1(1,3)-piperidinacyclodecaphane-2^2-yl) ethane-1-sulfonamide

[000626] TFA (0.5 mL) was added to a solution of 2-hydroxy-N-(6-(4-methoxybenzyl)-5^6-methyl-3-oxo-4,6-diaza-2(4,5),5(4,2)-dipyrimidina-1(1,3)-piperidinacyclodecaphane-2^2-yl)ethane-1-sulfonamide (5 mg, 0.008 mmol) in DCM (0.5 mL). The finally mixture was heated to 50 °C and stirred for 2 hours. After cooling to room temperature, the mixture was neutralized to pH 10 with saturated sodium $NaHCO_3$ solution. The resulting mixture was diluted with water (20 ml) and extracted with EA (3 x 20 ml). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM = 1:10 to afford 2-hydroxy-N-(5^6-methyl-3-oxo-4,6-diaza-2(4,5),5(4,2)-dipyrimidina-1(1,3)-piperidinacyclodecaphane-2^2-

yl)ethane-1-sulfonamide (0.5 mg, 89.7% purity, 1.9% yield). LCMS (ESI-MS) m/z = 491.2 $[M+H]^+$.

Example 116. 2-hydroxy-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide was synthesized from Example 114 vis Step 5 of General synthetic route 7A as described below (Compound 116)

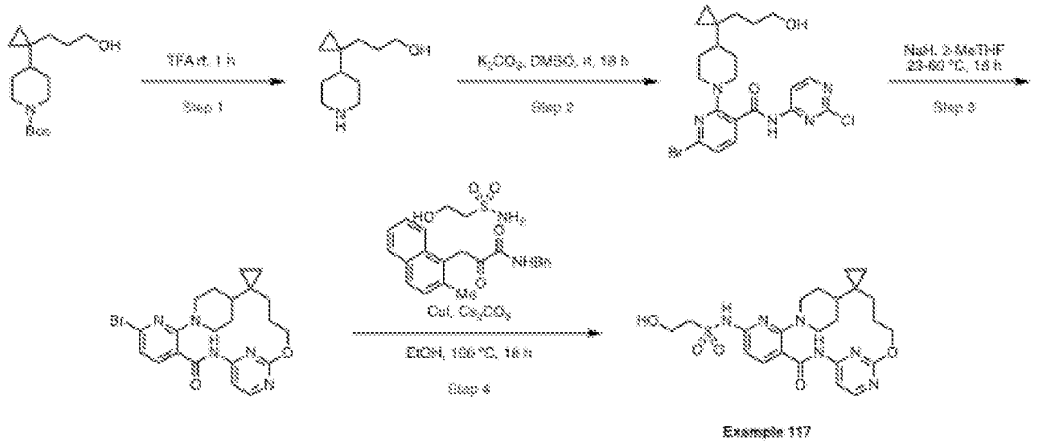


Example 114 **Example 116**

[000627] Into a solution of (E)-2-hydroxy-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide (35 mg, 0.07 mmol) in MeOH (5 mL) was added Pd/C (3.72 mg, 0.035 mmol) . The resulting solution was purged with H_2 and stirred at room temperature under 3.5 atm of H_2 for 3 hours. The reaction mixture was filtered. The filtrate was evaporated and dried under vacuum to give 2-hydroxy-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide (13.1 mg, 36.6% yield). LCMS (ESI-MS) m/z = 503.3 [M+H]+.

Example 117. 2-hydroxy-*N*-(3'-oxospiro[cyclopropane-1,10'-6-oxa-4-aza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,4)-piperidinacyclodecaphan]-6'-yl)ethane-1-sulfonamide

was prepared was prepared following the synthetic route outlined below. (Compound 117)



1. 3-(1-(piperidin-4-yl)cyclopropyl)propan-1-ol

[000628] To a vial was added tert-butyl 4-(1-(3-hydroxypropyl)cyclopropyl)piperidine-1-carboxylate (250 mg, 882 μmol), DCM (3.0 mL), and TFA (1.01 g, 680 μL, 8.82 mmol). The reaction mixture was then stirred at rt. After 1 h, the reaction mixture was concentrated in vacuo. The crude material was used for the next step without further purification. LCMS M+1/Z = 502.2

2. 6-bromo-*N*-(2-chloropyrimidin-4-yl)-2-(4-(1-(3-hydroxypropyl)cyclopropyl)piperidin-1-yl)nicotinamide

[000629] To the crude material from the previous step was added 6Intermediate O (292 mg, 882 μmol), K_2CO_3 (488 mg, 3.53 mmol), and MeCN (6.0 mL). The reaction mixture was heated to 50 °C. After 18 h, the reaction mixture was diluted with EtOAc and washed with brine (5 x), dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-100% EtOAc in heptane) provided 6-bromo-N-(2-chloropyrimidin-4-yl)-2-(4-(1-(3-hydroxypropyl)cyclopropyl)piperidin-1-yl)nicotinamide (178 mg, 40.8 %). LCMS M+1/Z = 494.0

3. 6'-bromospiro[cyclopropane-1,10'-6-oxa-4-aza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,4)-piperidinacyclodecaphan]-3'-one

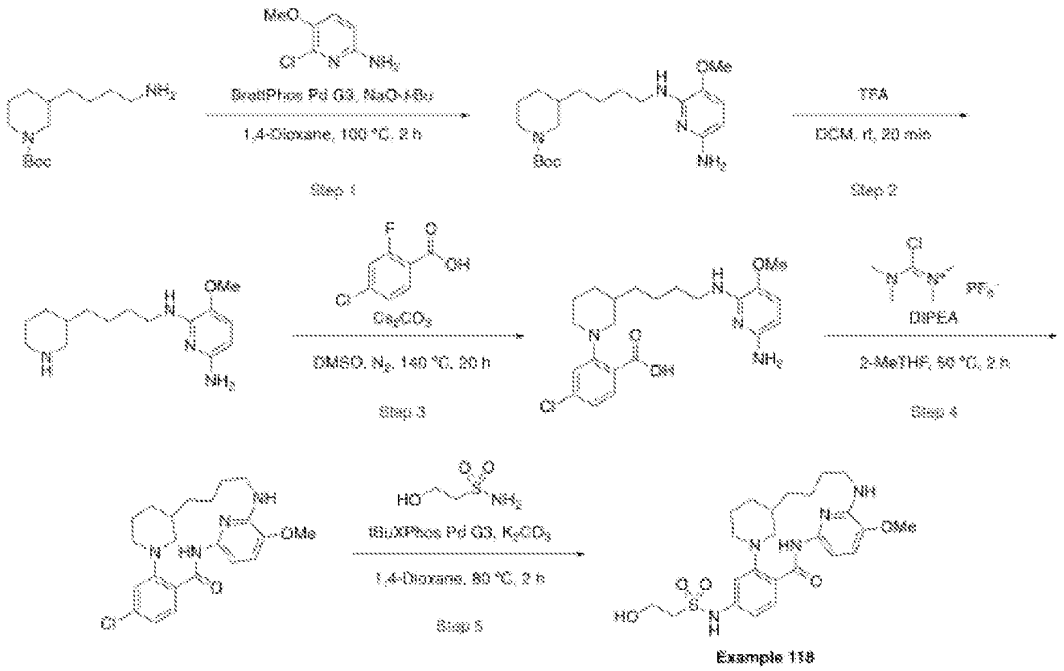
[000630] To a solution of 6-bromo-N-(2-chloropyrimidin-4-yl)-2-(4-(1-(3-hydroxypropyl)cyclopropyl)piperidin-1-yl)nicotinamide (160 mg, 323 μmol) in 2-Methyltetrahydrofuran (110 mL) at 23 °C was added NaH (38.8 mg, 60% Wt, 970 μmol). The

reaction mixture was then heated to 60 °C. After 18 h, the reaction mixture was quenched with aq. NH_4Cl then concentrated in vacuo. The crude residue was then diluted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-100% EtOAc in heptane) provided 6'-bromospiro[cyclopropane-1,10'-6-oxa-4-aza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,4)-piperidinacyclodecaphan]-3'-one (25 mg, 17 %). LCMS M+1/Z = 458.0

4. 2-hydroxy-*N*-(3'-oxospiro[cyclopropane-1,10'-6-oxa-4-aza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,4)-piperidinacyclodecaphan]-6'-yl)ethane-1-sulfonamide

[000631] To a vial was added 6'-bromospiro[cyclopropane-1,10'-6-oxa-4-aza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,4)-piperidinacyclodecaphan]-3'-one (25 mg, 55 μmol), Cuprous iodide (2.1 mg, 0.37 μL, 11 μmol), N1-Benzyl-N2-(2-methylnaphthalen-1-yl)oxalamide (6.9 mg, 22 μmol), Cs_2CO_3 (71 mg, 0.22 mmol), and 2-hydroxyethane-1-sulfonamide (34 mg, 0.27 mmol). The reaction vial was then placed under N_2 atmosphere and EtOH (2.0 mL) was added. The reaction mixture was then heated to 100 °C. After 18 h, the reaction mixture was filtered through celite and concentrated. Purification via prepHPLC (10-100% MeCN with 0.1% NH_4OAc water) followed by repurification via prepHPLC (10-100% MeCN with 0.1% TFA water) provided 2-hydroxy-N-(3'-oxospiro[cyclopropane-1,10'-6-oxa-4-aza-5(4,2)-pyrimidina-2(2,3)-pyridina-1(1,4)-piperidinacyclodecaphan]-6'-yl)ethane-1-sulfonamide 2,2,2-trifluoroacetate (2.07 mg, 5.7 %). LCMS M+1/Z = 503.1

Example 118. 2-hydroxy-*N*-(5^5-methoxy-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide was prepared was prepared following the synthetic route outlined below. (Compound 118)



1. *tert*-butyl 3-(4-((6-amino-3-methoxypyridin-2-yl)amino)butyl)piperidine-1-carboxylate

[000632] To a vial was added tert-butyl 3-(4-aminobutyl)piperidine-1-carboxylate (582 mg, 2.27 mmol), 6-chloro-5-methoxypyridin-2-amine (300 mg, 1.89 mmol), BrettPhos-Pd-G3 (85.7 mg, 94.6 μmol), and NaOtBu (273 mg, 2.84 mmol). The reaction mixture was placed under a N_2 atmosphere and 1,4-Dioxane (12 mL) was added. The reaction mixture was then heated to 100 °C. After 2 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$, diluted with EtOAc, washed with brine (5 x), dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-60% EtOAc in heptane) provided 6-chloro-5-methoxypyridin-2-amine (300 mg, 1 Eq, 1.89 mmol). LCMS M+1/Z = 379.2

2. 3-methoxy-*N*^{2}-(4-(piperidin-3-yl)butyl)pyridine-2,6-diamine

[000633] TFA (1.5 g, 1.0 mL, 13 mmol) was added to a solution of tert-butyl 3-(4-((6-amino-3-methoxypyridin-2-yl)amino)butyl)piperidine-1-carboxylate (596 mg, 1.57 mmol) in DCM (9 mL) and the reaction was stirred at rt. After 20 min, the reaction was concentrated in vacuo,

diluted with DCM, washed with sat. aq. NaHCO3 then brine, filtered, and concentrated. The crude material was used for the next step without further purification. LCMS M+1/Z = 279.2

3. 2-(3-(4-((6-amino-3-methoxypyridin-2-yl)amino)butyl)piperidin-1-yl)-4-chlorobenzoic acid

[000634] To the crude material from the previous reaction was added Cs_2CO_3 (1.54 g, 3 Eq, 4.72 mmol) and 4-chloro-2-fluorobenzoic acid (330 mg, 1.89 mmol). The reaction mixture was placed under a N_2 atmosphere and DMSO (8.0 mL) was added. The reaction mixture was then heated to 140 °C. After 20 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$, diluted with EtOAc, washed with brine (5 x), dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-100% EtOAc in heptane) provided 2-(3-(4-((6-amino-3-methoxypyridin-2-yl)amino)butyl)piperidin-1-yl)-4-chlorobenzoic acid (61 mg, 0.14 mmol, 9.0 %). LCMS M+1/Z = 433.1

4. 2^5-chloro-5^5-methoxy-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one

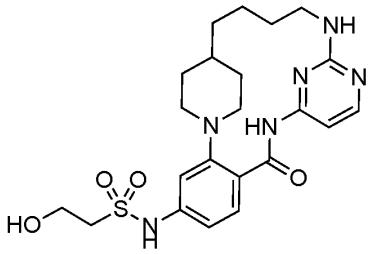
To a vial was added 2-(3-(4-((6-amino-3-methoxypyridin-2-yl)amino)butyl)piperidin-1-yl)-4-chlorobenzoic acid (60 mg, 0.14 mmol), 2-Methyltetrahydrofuran (30 mL), DIPEA (72 mg, 97 µL, 0.55 mmol), and N-(chloro(dimethylamino)methylene)-N-methylmethanaminium hexafluorophosphate(V) (58 mg, 0.21 mmol). The reaction mixture was then heated to 50 °C. After 2 h, the reaction mixture was diluted with EtOAc then washed with water and brine, dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-60% EtOAc in heptanes) provided 2^5-chloro-5^5-methoxy-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (40 mg, 70 %). LCMS M+1/Z = 415.1

5. 2-hydroxy-*N*-(5^5-methoxy-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide

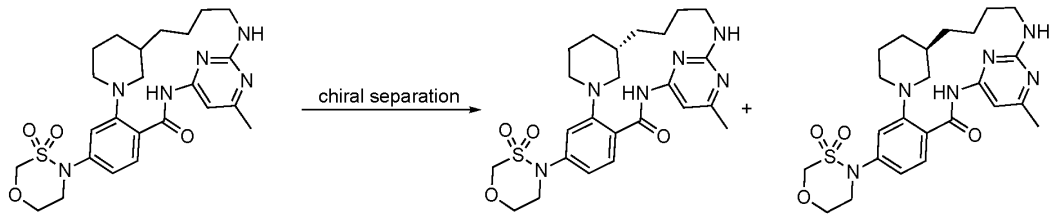
[000635] To a vial was added 2^5-chloro-5^5-methoxy-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (40 mg, 96 µmol), tBuXPhos Pd G3 (7.7 mg, 9.6 µmol), 2-hydroxyethane-1-sulfonamide (72 mg, 0.58 mmol), and K2CO3 (40 mg, 0.29 mmol). The reaction vial was placed under a N_2 atmosphere and 1,4-Dioxane (1.0 mL) was added. The reaction mixture was then heated to 80 °C. After 2 h, the reaction mixture was cooled to rt and filtered through celite. Purification via prepHPLC (10-100% MeCN in H2O with 0.1% TFA) followed by lyophilization provided 2-hydroxy-N-(5^5-methoxy-3-oxo-4,6-

diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide 2,2,2-trifluoroacetate (41 mg, 68%). LCMS M+1/Z = 504.2

Example 119. 2-hydroxy-N-(4'-oxospiro[cyclopropane-1,10'-3,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide was synthesized from Example 127 via General synthetic route 7A, Step 5, following the same procedures as described in Example 116. (Compound 119)



Examples 120 and 121. (1^3*s*)-2^5-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one and (1^3*R*)-2^5-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (Compound 120 and compound 121 respectively)



Example 55 Example 120 Example 121

[000636] The racemic mixture of 2^5-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (Example 55, 10 mg, 0.02 mmol) was dissolved with MeOH and purified by Chiral-prep-HPLC with the following conditions: Column: CHIRALPAK ID, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 50; Wave Length: 254/220nm nm; RT1(min): 7.801; RT2(min): 9.266; Sample Solvent: EtOH--HPLC; Injection Volume: 2.0 mL; Number Of Runs: 1 to afford the two products:

First eluting isomer:

[000637] Enantiopure 2^5-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (0.8 mg, 0.15% yield). LCMS (ESI-MS) m/z = 501.2 $[M+H]^+$. ee = 100%.

Second eluting isomer:

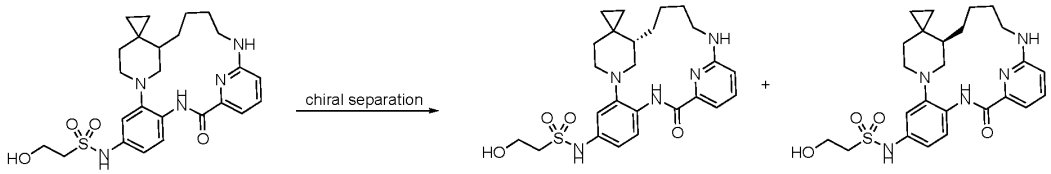
[000638] Enantiopure 2^5-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (0.9 mg, 0.17% yield). LCMS (ESI-MS) m/z = 501.2 $[M+H]^+$. ee = 100%.

Table 13. 2 hour KIF18A Biochemical data for Examples 120 and 121

Compound	**KIF18A ADP-Glo IC50, nM (2h)**
First eluting isomer	++++
Second eluting isomer	++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Examples 122 and 123. 2-hydroxy-N-((3'S)-4'-oxospiro[cyclopropane-1,4'-3,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide & 2-hydroxy-N-((3'R)-4'-oxospiro[cyclopropane-1,4'-3,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (Compound 122 and compound 123 respectively)



[000639] The racemic mixture of 2-hydroxy-N-(4'-oxospiro[cyclopropane-1,4'-3,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (20 mg, 0.04 mmol) was dissolved with MeOH and purified by Chiral-prep-HPLC with the following conditions: Column: CHIRALCEL OD-H, 2*25 mm, 5 μm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: MeOH: EtOH=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 15; Wave Length: 254/220nm nm; RT1(min): 29.018; RT2(min):

33.665; Sample Solvent: EtOH--HPLC; Injection Volume: 1.0 mL; Number Of Runs: 2 to afford the two products:

First eluting isomer:

[000640] Enantiopure 2-hydroxy-N-(4'-oxospiro[cyclopropane-1,4'-3,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (3.0 mg, 14.8% yield). LCMS (ESI-MS) m/z = 500.4 [M+H]+. 100% ee.

Second eluting isomer:

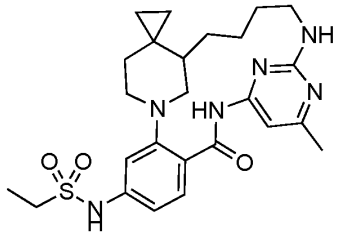
[000641] Enantiopure 2-hydroxy-N-(4'-oxospiro[cyclopropane-1,4'-3,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (3.1 mg, 15.2% yield). LCMS (ESI-MS) m/z = 500.3 [M+H]+. 100% ee.

Table 14. 2 hour KIF18A Biochemical data for Examples 122 and 123 (2h)

Compound	**KIF18A ADP-Glo IC50, nM**
First eluting isomer	++++
Second eluting isomer	++

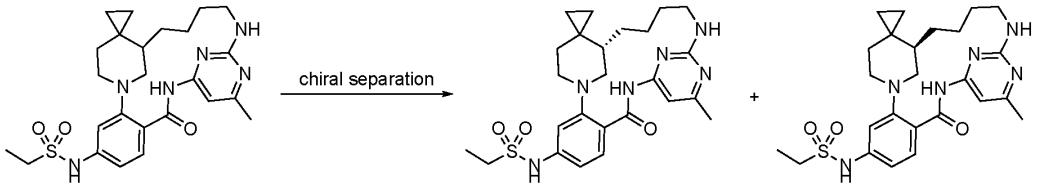
IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 124. *N*-(6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethanesulfonamide was prepared starting from Intermediate E and Intermediate G, following General synthetic route 4A following procedures outlined in Example 18. Ethanesulfonamide was used in Step 4. (Compound 124)



Examples 125 and 126. N-((3'S)-6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl) ethanesulfonamide & N-((3'R)-6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-

5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl) ethanesulfonamide (Compound 125 and compound 126 respectively)



Example 124 Example 125 Example 126

[000642] The racemic mixture of N-(6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethanesulfonamide (100 mg, 0.19 mmol) was purified by Prep-Chiral-HPLC with the following conditions: Column: CHIRALPAK IH-3, 4.6*50 mm, 3μm, Mobile Phase: Hex(0.1% DEA):(MeOH : DCM=1:1)=85:15, Flow: 1,Temperature: 25°C, Instrument: LC-96; PDA Model: SPD-M20A; Lamp: D2; Start Wavelength: 190nm; End Wavelength: 800nm; Use Cell Temp: Use; Cell Temp: 40°C to afford two products:

first eluting isomer:

[000643] Enantiopure N-(6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethanesulfonamide (38.4 mg, 38.3% yield). LCMS (ESI-MS) m/z = 499.4 $[M+H]^+$.

second eluting isomer:

[000644] Enantiopure N-(6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethanesulfonamide (35.8 mg, 95.5% purity, 34.3% yield). LCMS (ESI-MS) m/z = 499.4 $[M+H]^+$.

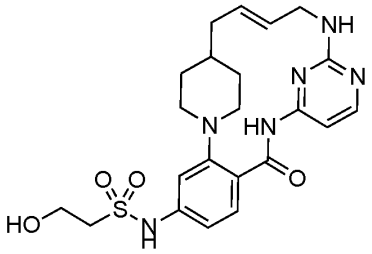
Table 15. 2 hour KIF18A Biochemical data for Examples 125 and 126

Compound	**KIF18A ADP-Glo IC50, nM (2h)**
First eluting isomer	+++++
Second eluting isomer	++

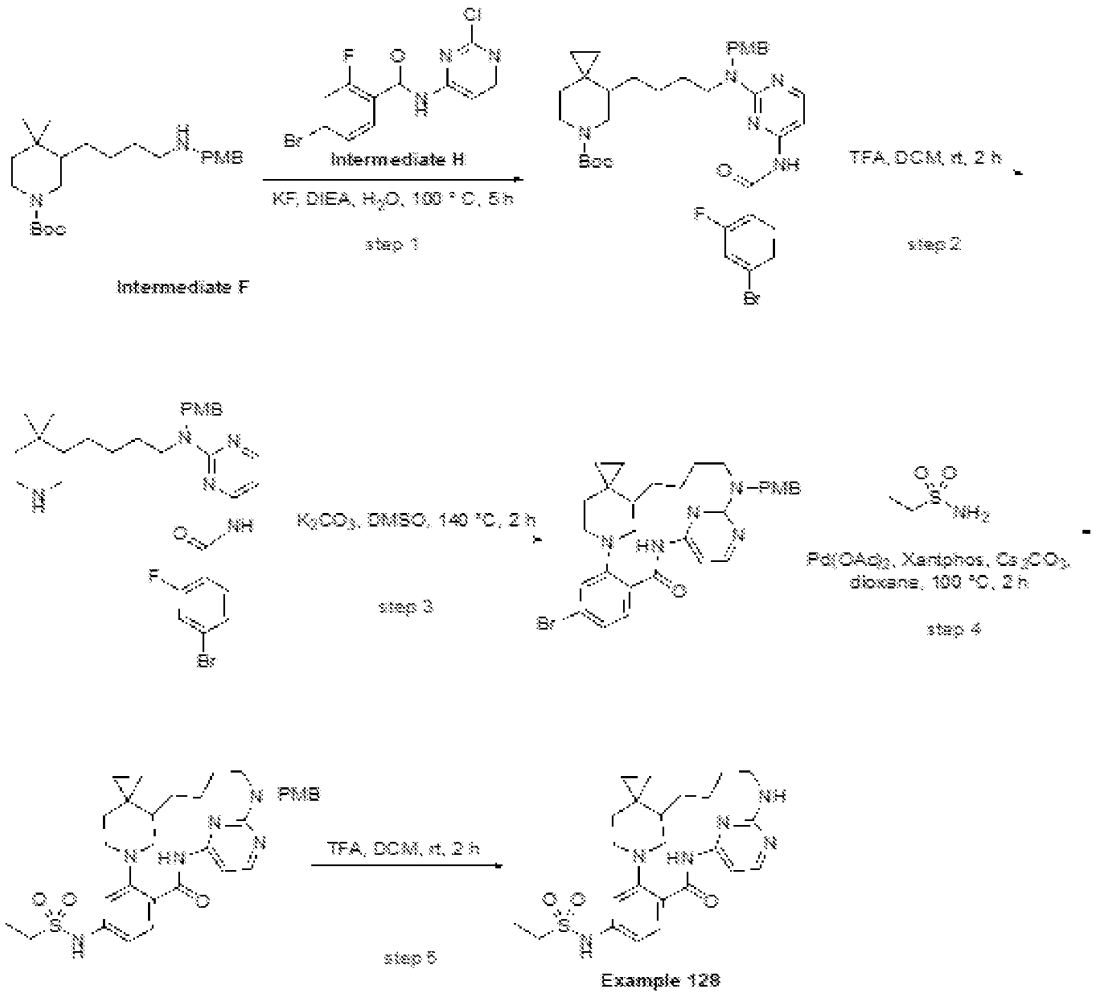
IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 127. (E)-2-hydroxy-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan-8-en-2^5-yl)ethane-1-sulfonamide was synthesized from

Intermediate S and Intermediate R via General synthetic route 7A (Steps 1-4) following same procedures as described in Example 114. (Compound 127)



Example 128. N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethanesulfonamide was prepared starting from Intermediate F and Intermediate H, following General synthetic route 4C as described in procedure below. (Compound 128)



1. **tert-butyl 4-(4-((4-(4-bromo-2-fluorobenzamido)pyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate**

[000645] To a stirred solution of tert-butyl 4-(4-((4-methoxybenzyl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate (2.00 g, 4.97 mmol) and 4-bromo-N-(2-chloropyrimidin-4-yl)-2-fluorobenzamide (1.64 g, 4.97 mmol) in H_2O (40 mL) was added KF (0.58 g, 9.94 mmol) and DIEA (1.28 g, 9.94 mmol). The resulting mixture was heated to 100 °C and stirred for 5 hours. After cooling to room temperature, the reaction mixture was diluted with H_2O (100 mL) and extracted with EA (3 x 100 mL). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with PE/EA 2 : 1 to afford the desired product tert-butyl 4-(4-((4-(4-bromo-2-fluorobenzamido)pyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate (2.20 g, 61.7% yield). LCMS (ESI-MS) m/z = 696.2 $[M+H]^+$.

2. **N-(2-((4-(6-azaspiro[2.5]octan-4-yl)butyl)(4-methoxybenzyl)amino)pyrimidin-4-yl)-4-bromo-2-fluorobenzamide**

[000646] TFA (3 mL) was added to a stirred mixture of tert-butyl 4-(4-((4-(4-bromo-2-fluorobenzamido)pyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate (2.20 g, 3.16 mmol) in DCM (30 mL). The resulting mixture was stirred at room temperature for 2 hours and concentrated to afford the product N-(2-((4-(6-azaspiro[2.5]octan-4-yl)butyl)(4-methoxybenzyl)amino)pyrimidin-4-yl)-4-bromo-2-fluorobenzamide (1.70 g, crude). LCMS (ESI-MS) m/z = 596.2 $[M+H]^+$.

3. **5'-bromo-6'-(4-methoxybenzyl)spiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one**

[000647] K_2CO_3 (1.18 g, 8.55 mmol) was added to a mixture of N-(2-((4-(6-azaspiro[2.5]octan-4-yl)butyl)(4-methoxybenzyl)amino)pyrimidin-4-yl)-4-bromo-2-fluorobenzamide (1.70 g, 2.85 mmol) in DMSO (85 mL). The resulting mixture was heated to 140 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was diluted with water (200 mL) and extracted with EA (2 x 200 mL). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the product 5'-bromo-6'-(4-methoxybenzyl)spiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one (1.10 g, crude). LCMS (ESI-MS) m/z = 576.2 $[M+H]^+$.

4. **N-(6'-(4-methoxybenzyl)-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-**

1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethanesulfonamide

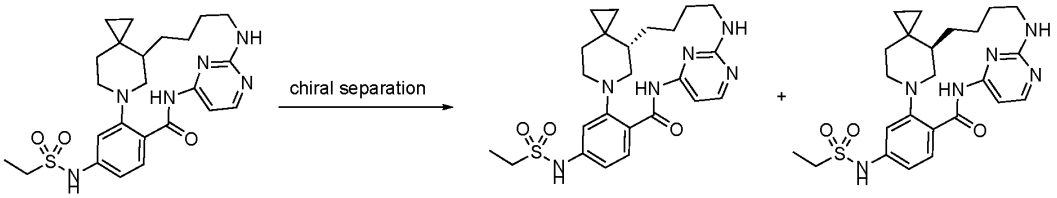
[000648] Into a solution of 5'-bromo-6'-(4-methoxybenzyl)spiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one (1.00 g, 1.73 mmol) in dioxane (15 mL) was added ethanesulfonamide (280 mg, 2.60 mmol), $Pd(OAc)_2$ (80 mg, 0.35 mmol), Xantphos (400 mg, 0.69 mmol) and Cs_2CO_3 (1.70 g, 5.20 mmol) under nitrogen atmosphere. The resulting solution was heated to 100 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was diluted with water (10 mL) and extracted with EA (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with EA/PE 1:1 to afford the desired product N-(6'-(4-methoxybenzyl)-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethanesulfonamide (400 mg, 37.3% yield). LCMS (ESI-MS) m/z = 605.3 $[M+H]^+$.

5. N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethanesulfonamide

[000649] TFA (5 mL) was added to a stirred mixture of N-(6'-(4-methoxybenzyl)-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethanesulfonamide (10 mg, 0.017 mmol) in DCM (1 mL). The resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by prep-HPLC with the following conditions: Column: Xbridge Prep OBD C18 Column, 30*150mm, 5μm; Mobile Phase A: Water(10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 38% B to 68 % B in 10 min; Wave Length: 254nm/220nm nm; RT1(min): 8.68 to afford N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethanesulfonamide (3.7 mg, 45.62% yield). LCMS (ESI-MS) m/z = 485.2 $[M+H]^+$.

Examples 129 and 130. N-((3'S)-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethanesulfonamide and N-((3'R)-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-

piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethanesulfonamide. (Compound 129 and compound 130 respectively)



Exmaple 128 Example 129 Example 130

[000650] The racemic mixture of N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethanesulfonamide (120 mg, 0.25 mmol) was dissolved with MeOH and purified by PREP-SFC with the following conditions: Column: CHIRALPAK IH 3*25 cm, 5um; Mobile Phase A: CO_2, Mobile Phase B: MeOH(1%-2M-NH_3-MeOH); Flow rate: 90 mL/min; Gradient: isocratic 42% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 6.5; RT2(min): 9.02; Sample Solvent: MEOH; Injection Volume: 3 mL; Number Of Runs: 6 to afford the two products:

First eluting isomer:

[000651] Enantiopure N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethanesulfonamide (37.1 mg, 30.85% yield). LCMS (ESI-MS) m/z = 485.2 $[M+H]^+$. ee = 100%.

Second eluting isomer:

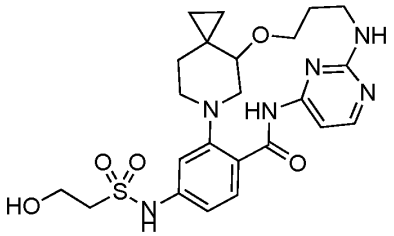
[000652] Enantiopure N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethanesulfonamide (41.6 mg, 34.56% yield). LCMS (ESI-MS) m/z = 485.2 $[M+H]^+$. ee = 100%.

Table 16. 2 hour KIF18A Biochemical data for Examples 129 and 130

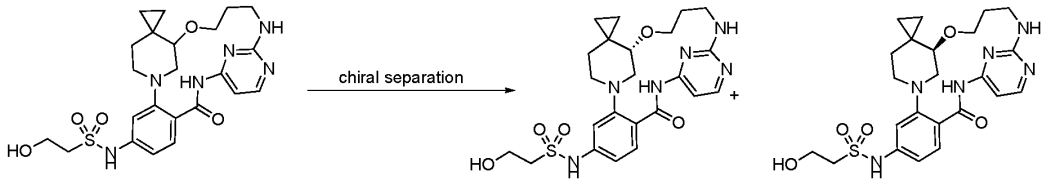
Compound	**KIF18A ADP-Glo IC50, nM (2h)**
First eluting isomer	+++++
Second eluting isomer	+

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 131. 2-hydroxy-N-(3'-oxospiro[cyclopropane-1,4'-10-oxa-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide was prepared starting from Intermediate T and Intermediate H, following General synthetic route 4A as described in procedure in Example 62. (Compound 131)



Examples 132 and 133. 2-hydroxy-N-((3'S)-3'-oxospiro[cyclopropane-1,4'-10-oxa-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide & 2-hydroxy-N-((3'R)-3'-oxospiro[cyclopropane-1,4'-10-oxa-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (Compound 132 and compound 133 respectively)



[000653] The racemic mixture of 2-hydroxy-N-(3'-oxospiro[cyclopropane-1,4'-10-oxa-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (16.5 mg, 0.033 mmol) was dissolved with MeOH and purified by Prep-SFC with the following conditions: Column: CHIRALPAK IH 5*25 cm, 5um; Mobile Phase A: CO2, Mobile Phase B: MeOH(1%-2M-NH_3-MeOH); Flow rate: 90 mL/min; Gradient: isocratic 40% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 4.6; RT2(min): 7.37; Sample Solvent: MEOH; Injection Volume: 4 mL; Number Of Runs: 2 to afford the two products:

First eluting isomer:

[000654] Enantiopure 2-hydroxy-N-(3'-oxospiro[cyclopropane-1,4'-10-oxa-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (4.9 mg, 29.6% yield). LCMS (ESI-MS) m/z = 503.1 $[M+H]^+$. 100% ee.

Second eluting isomer:

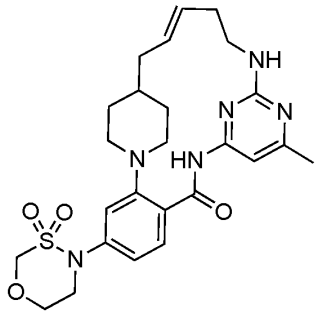
[000655] Enantiopure 2-hydroxy-N-(3'-oxospiro[cyclopropane-1,4'-10-oxa-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (5.2 mg, 31.5% yield). LCMS (ESI-MS) m/z = 503.1 $[M+H]^+$. 98.8% ee.

Table 17. 2 hour KIF18A Biochemical data for Examples 132 and 133

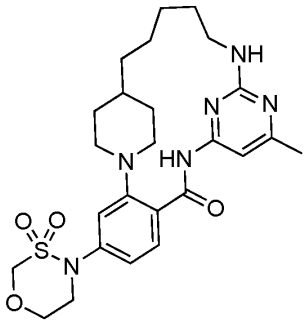
Compound	**KIF18A ADP-Glo IC50, nM** (2h)
First eluting isomer	++++
Second eluting isomer	+

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

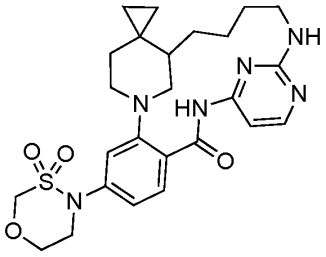
Example 134. (E)-2^5-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one was synthesized from Intermediate Q and Intermediate R following Steps 1-4 of General synthetic route 7A as described in the for Example 114 with 1,3,4-oxathiazinane 3,3-dioxide used in step 4. (Compound 134)



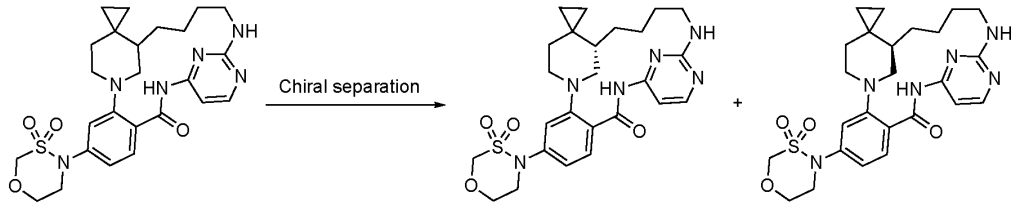
Example 135. 2^5-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-3-one was synthesized from Example 134 via General synthetic route 7A, Step 5, following the same procedures as described in Example 116. (Compound 135)



Example 136. 5'-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)spiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one was prepared starting from Intermediate E and Intermediate H, following General synthetic route 4A as described in procedure outlined for example 62 with 1,3,4-oxathiazinane 3,3-dioxide used in step 4. (Compound 136)



Example 137 and 138. (3'R)-5'-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)spiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one & (3'S)-5'-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)spiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one (Compound 137 and compound 138 respectively)



Example 136 Example 137 Example 138

[000656] The racemic mixture of 5'-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)spiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one (30 mg, 0.05 mmol) was purified by Prep-Chiral-HPLC with the following conditions: Column: CHIRALPAK IF-3, 4.6*50 mm,3 um, Mobile Phase: Hex(0.2%FA):(MeOH: DCM=1:1)=60:40, Flow: 1 mL/min, Temperature: 25C, Instrument: LC-95; PDA Model: SPD-M20A; Lamp: D2; Start Wavelength: 190nm; End Wavelength: 800nm; Use Cell Temp: Use; Cell Temp: 40°C to afford two products: as a white solid and (3'S)-5'-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)spiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one as a white solid.

first eluting isomer:

[000657] Enantiopure 5'-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)spiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one (7.7 mg, 27.3% yield). LCMS (ESI-MS) m/z = 513.1 $[M+H]^+$.

second eluting isomer:

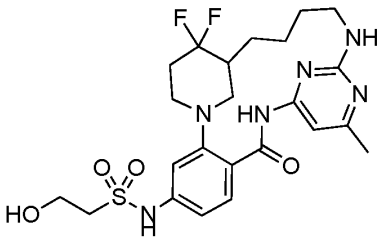
[000658] Enantiopure 5'-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)spiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one (4.3 mg, 15.1% yield), LCMS (ESI-MS) m/z = 513.1 $[M+H]^+$.

Table 18. 2 hour KIF18A Biochemical data for Examples 137 and 138

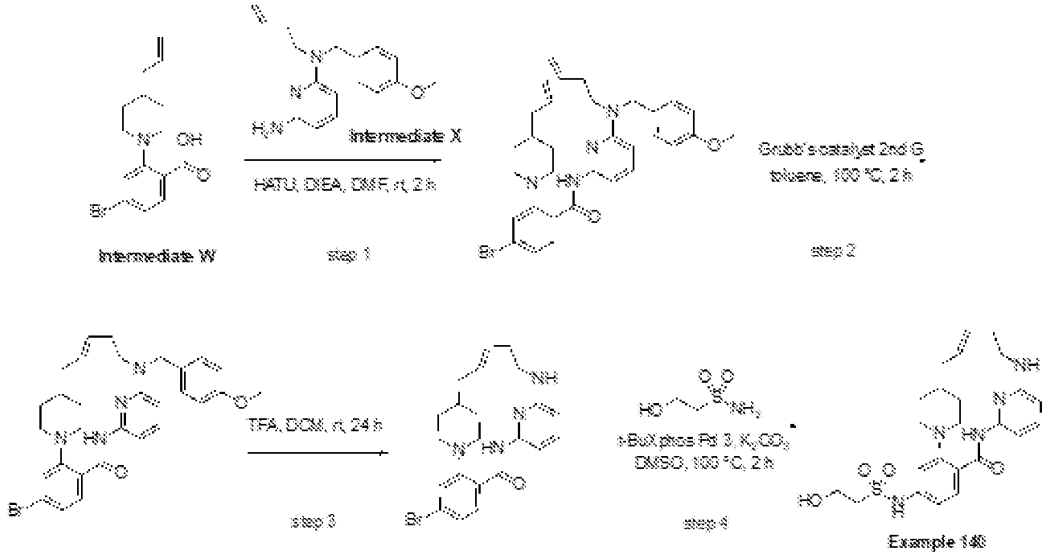
Compound	**KIF18A ADP-Glo IC50, nM (2h)**
First eluting isomer	++++
Second eluting isomer	+

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 139. N-(1^4,1^4-difluoro-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide was prepared starting from Intermediate G and Intermediate U, following General synthetic route 4A as described in procedure outlined in Example 62. (Compound 139)



Example 140. (E)-2-hydroxy-N-(3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide was synthesized via General synthetic route 7B, from Intermediate X and Intermediate W following the procedure outlined below. (Compound 140)



1. 2-(4-allylpiperidin-1-yl)-4-bromo-N-(6-(but-3-en-1-yl(4-methoxybenzyl)amino)pyridin-2-yl)benzamide

[000659] To a stirred solution of Intermediate W (250 mg, 0.88 mmol) in anhydrous DMF (2.5 mL) was added Intermediate X (286 mg, 0.88 mmol), HATU (503 mg, 1.32 mmol) and DIEA (342 mg, 2.65 mmol). The resulting mixture was stirred at room temperature for 2 hours, diluted with water (10 mL) and extracted with EA (3 x 10 mL). The combined organic layers were washed with brine (30 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA 4 : 1 to afford the desired product 2-(4-allylpiperidin-1-yl)-4-bromo-N-(6-(but-3-en-1-yl(4-methoxybenzyl)amino)pyridin-2-yl)benzamide (200 mg, 38.1% yield). LCMS (ESI-MS) m/z = 589.2 $[M+H]^+$.

2. (E)-2^5-bromo-6-(4-methoxybenzyl)-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one

[000660] To a stirred solution of 2-(4-allylpiperidin-1-yl)-4-bromo-N-(6-(but-3-en-1-yl(4-methoxybenzyl)amino)pyridin-2-yl)benzamide (192 mg, 0.33 mmol) in anhydrous toluene (2 mL) was added Grubb's catalyst 2nd G (55 mg, 0.065 mmol). The resulting mixture was heated to 100 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was

diluted with water (10 mL) and extracted with EA (3 x 10 mL). The combined organic layers were washed with brine (30 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE/EA 4 : 1 to afford the desired product (E)-2^5-bromo-6-(4-methoxybenzyl)-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (130 mg, 70.4% yield). LCMS (ESI-MS) m/z = 561.2 $[M+H]^+$.

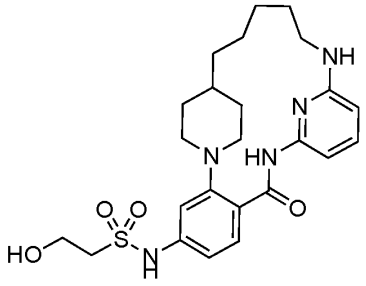
3. (E)-2^5-bromo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one

[000661] TFA (10 mL) was added to a stirred mixture of (E)-2^5-bromo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (130 mg, 0.23 mmol) in DCM (1 mL). The resulting mixture was stirred at room temperature for 24 hours and concentrated to afford the crude product (E)-2^5-bromo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (80 mg crude). LCMS (ESI-MS) m/z = 441.1 $[M+H]^+$.

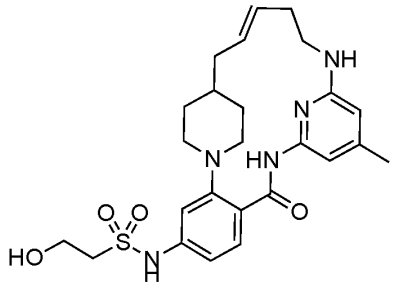
4. (E)-2-hydroxy-N-(3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide

[000662] To a solution of (E)-2^5-bromo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (40 mg, 0.091 mmol) in DMSO (4 mL) was added 2-hydroxyethanesulfonamide (23 mg, 0.18 mmol), t-BuXPhos Pd G3 catalyst (14 mg, 0.018 mmol) and K_2CO_3 (38 mg, 0.27 mmol) under nitrogen atmosphere. The resulting solution was heated to 100 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was diluted with water (10 mL) and extracted with EA (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by reversed-phase flash chromatography with the following conditions: Column: XBridge Prep RP OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 36% B to 66% B in 10min; Wave Length: 254nm/220nm nm; RT1(min): 8.9 to afford the desired product (E)-2-hydroxy-N-(3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide (60 mg, 14.0% yield). LCMS (ESI-MS) m/z = 486.2 $[M+H]^+$. Purity = 97.4%.

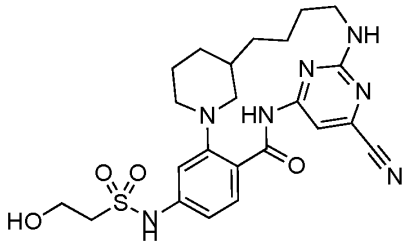
Example 141. 2-hydroxy-N-(3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide was synthesized from Example 140 via General synthetic route 7A, Step 5, following the same procedures as described in Example 116. (Compound 141)



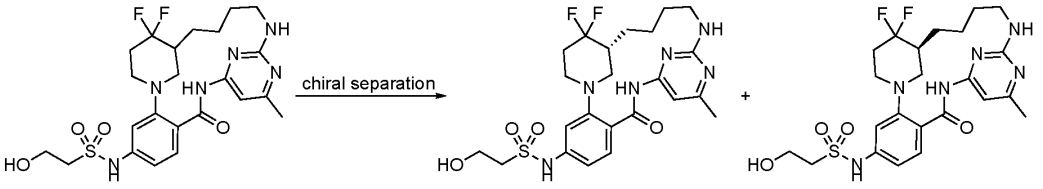
Example 142. (E)-2-hydroxy-N-(5^4-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide was prepared via General synthetic route 7B, from Intermediate V and Intermediate W following the procedure described for example 140. (Compound 142)



Example 143. N-(5^6-cyano-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide was synthesized via General synthetic route 4A, from Intermediate Y and *tert*-butyl 3-(4-aminobutyl)piperidine-1-carboxylate as described in the procedure for Example 62. (Compound 143)



Examples 144 and 145. N-((1^{3}R)-1^4,1^4-difluoro-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide & N-((1^{3}S)-1^4,1^4-difluoro-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide (Compound 144 and compound 145 respectively)



Example 139 Example 144 Example 145

[000663] The racemic mixture of N-(1^4,1^4-difluoro-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide (17 mg, 0.032 mmol) was dissolved with MeOH and purified by Chiral-prep-HPLC with the following conditions: Column: (R, R)-WHELK-O1 3*25 cm, 5um; Mobile Phase A: CO2, Mobile Phase B: ACN: MeOH=1: 1(1%-2M-NH3-MeOH); Flow rate: 90 mL/min; Gradient: isocratic 40% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 6.42; RT2(min): 7.33; Sample Solvent: MEOH; Injection Volume: 0.8 mL to afford the two products:

First eluting isomer:

[000664] Enantiopure N-(1^4,1^4-difluoro-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide (5.7 mg, 33.3%). LCMS (ESI-MS) m/z = 525.2 $[M+H]^+$. 100% ee.

Second eluting isomer:

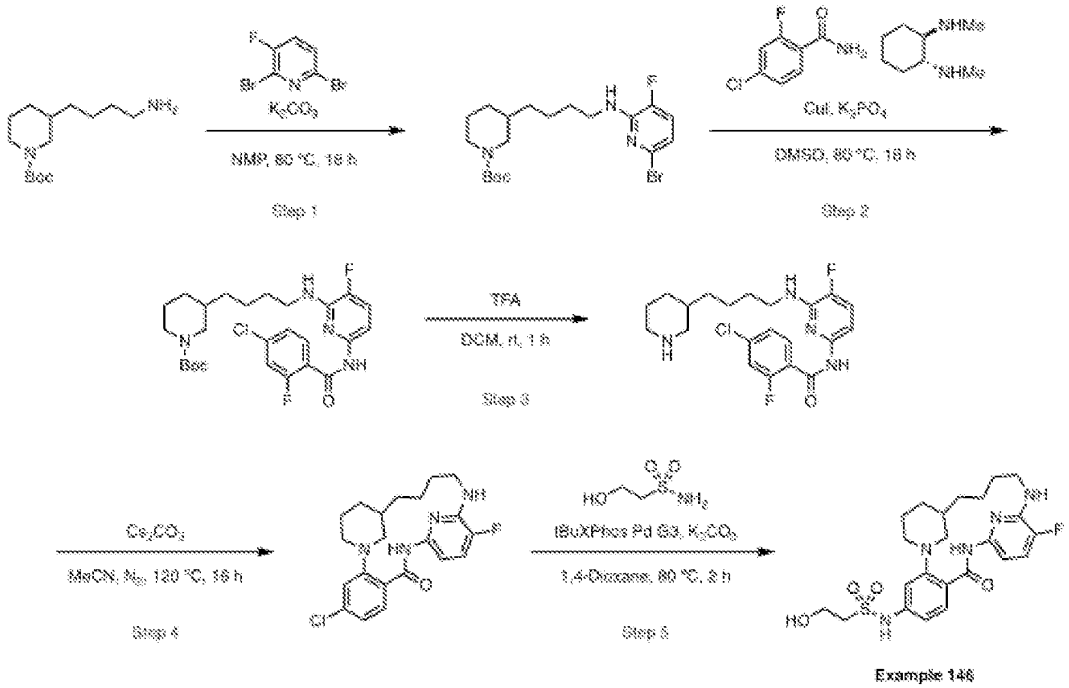
[000665] Enantiopure N-(1^4,1^4-difluoro-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide (5.5 mg, 31.5%). LCMS (ESI-MS) m/z = 525.1 $[M+H]^+$, 100% ee.

Table 19. 2 hour KIF18A Biochemical data for Examples 144 and 145

Compound	**KIF18A ADP-Glo IC50, nM (2h)**
First eluting isomer	+++++
Second eluting isomer	+++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 146. ***N*-(5^5-fluoro-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide was prepared via General synthetic route 6 as described below. (Compound 146)**



1. *tert*-butyl 3-(4-((6-bromo-3-fluoropyridin-2-yl)amino)butyl)piperidine-1-carboxylate

[000666] To a vial was added tert-butyl 3-(4-aminobutyl)piperidine-1-carboxylate (640 mg, 2.50 mmol), K2CO3 (1.03 g, 7.49 mmol), 2,6-dibromo-3-fluoropyridine (763 mg, 3.00 mmol) and NMP (12 mL) under N_2. The reaction mixture was then heated to 80 °C. After 18 h, the reaction mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-40% EtOAc in heptane) provided tert-butyl 3-(4-((6-bromo-3-fluoropyridin-2-yl)amino)butyl)piperidine-1-carboxylate (519 mg, 48.3 %). LCMS M+1/Z = 430.1

2. *tert*-butyl 3-(4-((6-(4-chloro-2-fluorobenzamido)-3-fluoropyridin-2-yl)amino)butyl)piperidine-1-carboxylate

[000667] To a vial was added tert-butyl 3-(4-((6-bromo-3-fluoropyridin-2-yl)amino)butyl)piperidine-1-carboxylate (515 mg, 1.20 mmol), CuI (228 mg, 1.20 mmol), (1R,2r)-N,N-dimethyl-1,2-cyclohexanediamine (170 mg, 1.20 mmol), Potassium phosphate, tribasic (762 mg, 297 µL, 3.59 mmol) and DMSO (10 mL). The reaction mixture was then heated to 80 °C. After 18 h, the reaction mixture was diluted with EtOAc and washed with water, then brine (5 x), dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-30% EtOAc in heptane) provided tert-butyl 3-(4-((6-(4-chloro-2-fluorobenzamido)-3-fluoropyridin-2-yl)amino)butyl)piperidine-1-carboxylate (383 mg, 61.2 %). LCMS M+1/Z = 523.2

3. 4-chloro-2-fluoro-*N*-(5-fluoro-6-((4-(piperidin-3-yl)butyl)amino)pyridin-2-yl)benzamide

[000668] To tert-butyl 3-(4-((6-(4-chloro-2-fluorobenzamido)-3-fluoropyridin-2-yl)amino)butyl)piperidine-1-carboxylate (383 mg, 1 Eq, 732 µmol) in DCM (5.0 mL) was added TFA (1.67 g, 1.13 mL, 20 Eq, 14.6 mmol). The reaction mixture was stirred at rt. After 1 h, the reaction mixture was neutralized with sat. aq. $NaHCO_3$, dried over $MgSO_4$, and concentrated. The crude material was used for the next step without further purification. LCMS M+1/Z = 423.1

4. 2^5-chloro-5^5-fluoro-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one

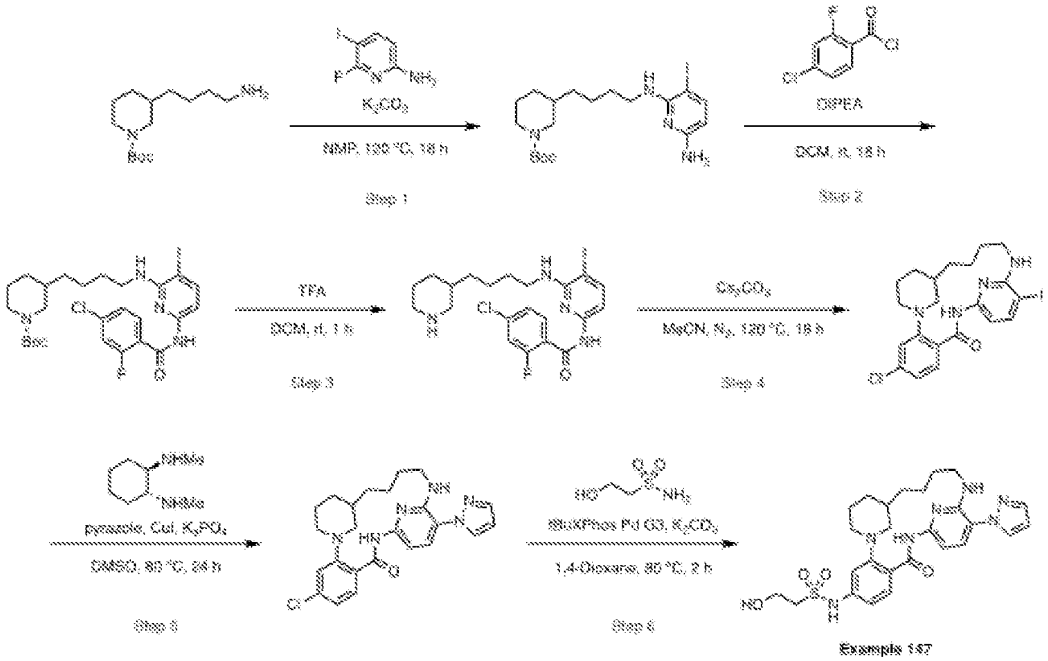
[000669] To the crude material from the previous step was added MeCN (80 mL) and Cs_2CO_3 (716 mg, 2.20 mmol) under N_2. The reaction mixture was then heated to 120 °C. After 16 h, the reaction was cooled to rt and diluted with EtOAc then washed with brine (5 x), dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-50% EtOAc in heptanes) provided 2^5-chloro-5^5-fluoro-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (99 mg, 34 %). LCMS M+1/Z = 403.1

5. *N*-(5^5-fluoro-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide

[000670] To a vial was added 25-chloro-55-fluoro-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (20 mg, 50 µmol), tBuXPhos Pd G3 (3.9 mg, 5.0 µmol), 2-hydroxyethane-1-sulfonamide (47 mg, 0.37 mmol), and K_2CO_3 (21 mg, 0.15

mmol). The reaction was placed under a N_2 atmosphere and 1,4-Dioxane (0.25 mL) was added. The reaction mixture was then heated to 80 °C. After 2 h, the reaction mixture was cooled to rt and filtered through celite. Purification via prepHPLC (10-100% MeCN in H_2O with 0.1% TFA) followed by neutralization and extraction of the fractions containing product mass provided N-(55-fluoro-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-25-yl)-2-hydroxyethane-1-sulfonamide (19.4 mg, 72 %). LCMS M+1/Z = 492.2

Example 147. 2-hydroxy-*N*-(3-oxo-5^5-(1*H*-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide was synthesized as described below (Compound 147)



1. *tert*-butyl 3-(4-((6-amino-3-iodopyridin-2-yl)amino)butyl)piperidine-1-carboxylate

[000671] To a vial was added tert-butyl 3-(4-aminobutyl)piperidine-1-carboxylate (500 mg, 1.95 mmol), K_2CO_3 (809 mg, 5.85 mmol), 6-fluoro-5-iodopyridin-2-amine (487 mg, 2.05 mmol) and NMP (10 mL). The reaction mixture was then heated to 120 °C. After 18 h, the reaction mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification via Isco

column chromatography (0-100% EtOAc in heptane) provided tert-butyl 3-(4-((6-amino-3-iodopyridin-2-yl)amino)butyl)piperidine-1-carboxylate (122 mg, 13.2 %). LCMS M+1/Z = 474.1

2. *tert*-butyl 3-(4-((6-(4-chloro-2-fluorobenzamido)-3-iodopyridin-2-yl)amino)butyl)piperidine-1-carboxylate

[000672] To a vial was added tert-butyl 3-(4-((6-amino-3-iodopyridin-2-yl)amino)butyl)piperidine-1-carboxylate (122 mg, 257 μmol), DIPEA (99.7 mg, 134 μL, 772 μmol), DCM (10 mL), and 4-Chloro-2-fluoro-benzoylchloride (54.6 mg, 37.3 μL, 283 μmol). The reaction mixture was then stirred at rt. After 18 h, the reaction mixture was diluted with water and extracted with DCM (3 x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-100% EtOAc in heptane) provided tert-butyl 3-(4-((6-(4-chloro-2-fluorobenzamido)-3-iodopyridin-2-yl)amino)butyl)piperidine-1-carboxylate (83.3 mg, 51.3 %). LCMS M+1/Z = 631.1

3. 4-chloro-2-fluoro-*N*-(5-iodo-6-((4-(piperidin-3-yl)butyl)amino)pyridin-2-yl)benzamide

[000673] To tert-butyl 3-(4-((6-(4-chloro-2-fluorobenzamido)-3-iodopyridin-2-yl)amino)butyl)piperidine-1-carboxylate (83 mg, 0.13 mmol) in DCM (2.0 mL) was added TFA (0.30 g, 0.20 mL, 2.6 mmol). The reaction mixture was stirred at rt. The reaction mixture was stirred at rt. After 1 h, the reaction mixture was neutralized with sat. aq. $NaHCO_3$, dried over $MgSO_4$, and concentrated. The crude material was used for the next step without further purification. LCMS M+1/Z = 530.1

4. 2^5-chloro-5^5-iodo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one

[000674] To the crude material from the previous step was added MeCN (24.0 mL) and Cs_2CO_3 (0.17 g, 0.53 mmol) under N_2. The reaction mixture was then heated to 120 °C in a sealed pressure tube. After 18 h, the reaction was cooled to rt and diluted with EtOAc then washed with brine, dried over MgSO4, and concentrated. Purification via Isco column chromatography (0-45% EtOAc in heptanes) provided 2^5-chloro-5^5-iodo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (30 mg, 45 %). LCMS M+1/Z = 511.0

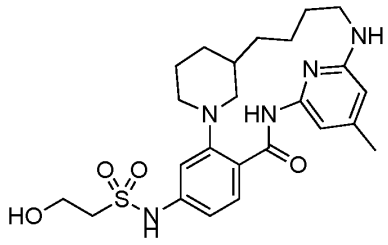
5. 2^5-chloro-5^5-(1*H*-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one

[000675] To a vial was added 2^5-chloro-5^5-iodo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (30 mg, 59 µmol), CuI (5.6 mg, 29 µmol), trans-(1R,2R)-N,N'-Bismethyl-1,2-cyclohexanediamine HCl (5.2 mg, 29 µmol), Potassium phosphate, tribasic (44 mg, 17 µL, 0.21 mmol) and DMSO (3.0 mL) under N_2. The reaction mixture was then heated to 80 °C. After 24 h, the reaction mixture was diluted with EtOAc and washed with water, then brine (5 x), dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-30% EtOAc in heptane) provided 2^5-chloro-5^5-(1H-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (21.5 mg, 81 %). LCMS M+1/Z = 451.2

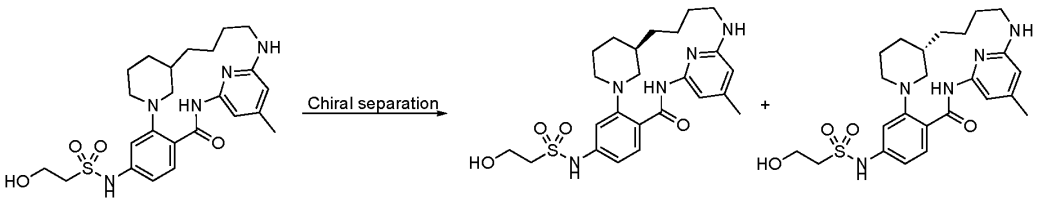
6. 2-hydroxy-*N*-(3-oxo-5^5-(1*H*-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide

[000676] To a vial was added 2^5-chloro-5^5-(1H-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (21 mg, 47 µmol), tBuXPhos Pd G3 (3.7 mg, 4.7 µmol), 2-hydroxyethane-1-sulfonamide (44 mg, 0.35 mmol), and K_2CO_3 (19 mg, 0.14 mmol). The reaction was placed under a N_2 atmosphere and 1,4-Dioxane (0.25 mL) was added. The reaction mixture was then heated to 80 °C. After 30 min, the reaction mixture was cooled to rt and filtered through celite. Purification via prepHPLC (10-100% MeCN in H_2O with 0.1% TFA) followed by lyophilization provided 2-hydroxy-N-(3-oxo-55-(1H-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-25-yl)ethane-1-sulfonamide 2,2,2-trifluoroacetate (14.1 mg, 45 %). LCMS M+1/Z = 540.2.

Example 148. 2-hydroxy-*N*-(5^4-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzena-cyclodecaphane-2^5-yl)ethane-1-sulfonamide was synthesized from Intermediate Z and methyl 5-bromo-3-fluoropyridine-2-carboxylate using General synthetic route 3C and similar reaction procedures as described for Example 101. (Compound 148)



Examples 149 and 150. 2-hydroxy-*N*-((1^{3}R)-54-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamid & 2-hydroxy-*N*-((1^{3}S)-54-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide. (Compound 149 and compound 150 respectively)



[000677] The racemic mixture of 2-hydroxy-N-(5^4-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-25-yl)ethane-1-sulfonamide (20 mg, 0.04 mmol) was purified by Prep-Chiral-HPLC with the following conditions: Column : CHIRALPAK ID-3, Column Size : 4.6*50 mm,3 um, Mobile Phase : Hex(0.2%FA):(MeOH:DCM=1:1)=75:25, Flow : 1 mL/min, Temperature °C: 25, Instrument : LC-95,PDA Model : SPD-M20A, Lamp : D2, Start Wavelength : 190 nm, End WAvelength : 800 nm, Use Cell Temp. : Use, Cell Temp. °C: 40 to afford two products:

first eluting isomer:

[000678] Enantiopure 2-hydroxy-N-(5^4-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-25-yl)ethane-1-sulfonamide (2.5 mg, , 12.6% yield). LCMS (ESI-MS) m/z = 488.2 $[M+H]^+$.

second eluting isomer:

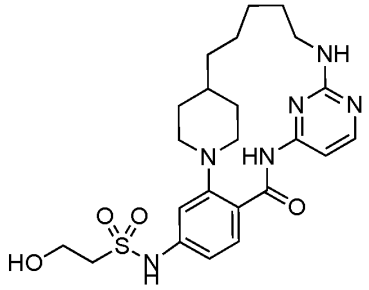
[000679] Enantiopure 2-hydroxy-N-(5^4-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-25-yl)ethane-1-sulfonamide (25 mg, 31.6% yield). LCMS (ESI-MS) m/z =488.2 $[M+H]^+$,

Table 20. 2 hour KIF18A Biochemical data for Examples 149 and 150

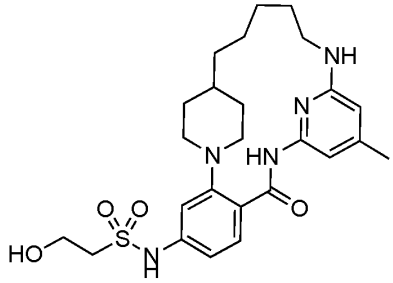
Compound	**KIF18A ADP-Glo IC50, nM (2h)**
First eluting isomer	++
Second eluting isomer	+++++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

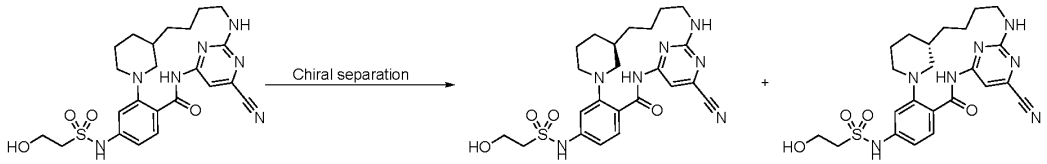
Example 151. 2-hydroxy-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide was synthesized from Example 162 via General synthetic route 7A, Step 5, following the same procedures as described in Example 116. (Compound 151)



Example 152. 2-hydroxy-N-(5^4-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide was synthesized from Example 142 via General synthetic route 7A, Step 5, following the same procedures as described in Example 116. (Compound 152)



Examples 153 and 154. N-((1^{3}R)-5^6-cyano-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide & N-((1^{3}S)-5^6-cyano-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide. (Compound 153 and compound 154 respectively)



[000680] The racemic mixture of N-(5^6-cyano-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide was

dissolved with MeOH and purified by Chiral-prep-HPLC with the following conditions: Column: CHIRALPAK IE, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 40; Wave Length: 254/220nm nm; RT1(min): 10.913; RT2(min): 13.532; Sample Solvent: EtOH--HPLC; Injection Volume: 0.9 mL; Number Of Runs: 5. to afford the two products:

First eluting isomer:

[000681] Enantiopure N-(5^6-cyano-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide (6.1 mg, 26.5% yield).). LCMS (ESI-MS) m/z =500.1 $[M+H]^+$.

Second eluting isomer:

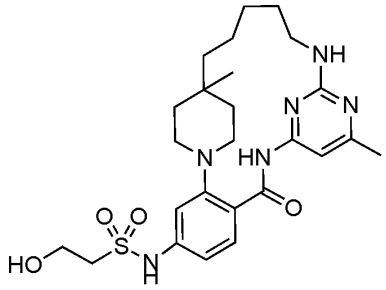
[000682] Enantiopure N-(5^6-cyano-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide (5.8 mg, 25.3% yield) as a white solid. The structure on the scheme is just assumed. LCMS (ESI-MS) m/z =500.1 $[M+H]^+$.

Table 21. 2 hour KIF18A Biochemical data for Examples 153 and 154

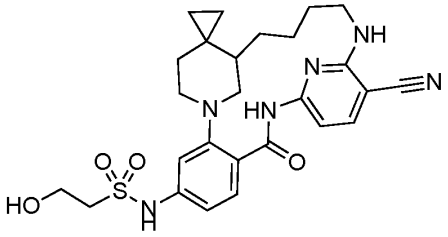
Compound	**KIF18A ADP-Glo IC50, nM (2h)**
First eluting isomer	+
Second eluting isomer	++++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

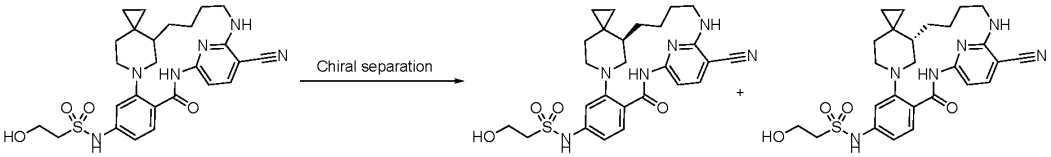
Example 155. N-(1^4,5^6-dimethyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide was synthesized from Example 165 via General synthetic route 7A, Step 5, following the same procedure as described in Example 116. (Compound 155)



Example 156. N-(5'-cyano-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)-2-hydroxyethane-1-sulfonamide was synthesized via General synthetic route 4B using Intermediate P and Intermediate F in Step 1 and 2-hydroxyethane-1-sulfonamide in Step 4, following procedures described in Example 166. (Compound 156)



Examples 157 and 158. N-((3'R)-5'-cyano-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)-2-hydroxyethane-1-sulfonamide and N-((3'S)-5'-cyano-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)-2-hydroxyethane-1-sulfonamide (Compound 157 and compound 158 respectively)



[000683] The racemic mixture of N-(5'-cyano-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)-2-hydroxyethane-1-sulfonamide (20 mg, 0.04 mmol) was dissolved with MeOH (2 mL) and purified by PREP-SFC with the following conditions: Column: CHIRALPAKIG3; Mobile Phase A : Hex (0.2% FA) : (EtOH : DCM = 1 : 1) = 55 : 45; Flow rate: 1mL/min; Gradient: isocratic ; Injection Volume: 1μl mL to afford the two products:

First eluting isomer:

[000684] Enantiopure N-(5'-cyano-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)-2-hydroxyethane-1-sulfonamide (3.2 mg, 15.8% yield). LCMS (ESI-MS) m/z = 525.2 $[M+H]^+$. ee = 99.9%.

Second eluting isomer:

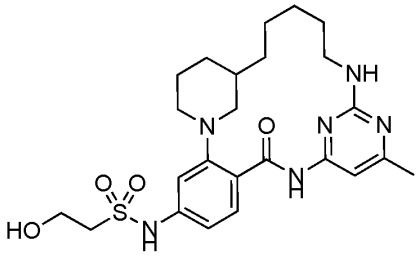
[000685] Enantiopure N-(5'-cyano-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)-2-hydroxyethane-1-sulfonamide (2.4 mg, 11.9% yield). LCMS (ESI-MS) m/z = 525.2 $[M+H]^+$. ee = 98.1%.

Table 22. 2 hour KIF18A Biochemical data for Examples 157 and 158

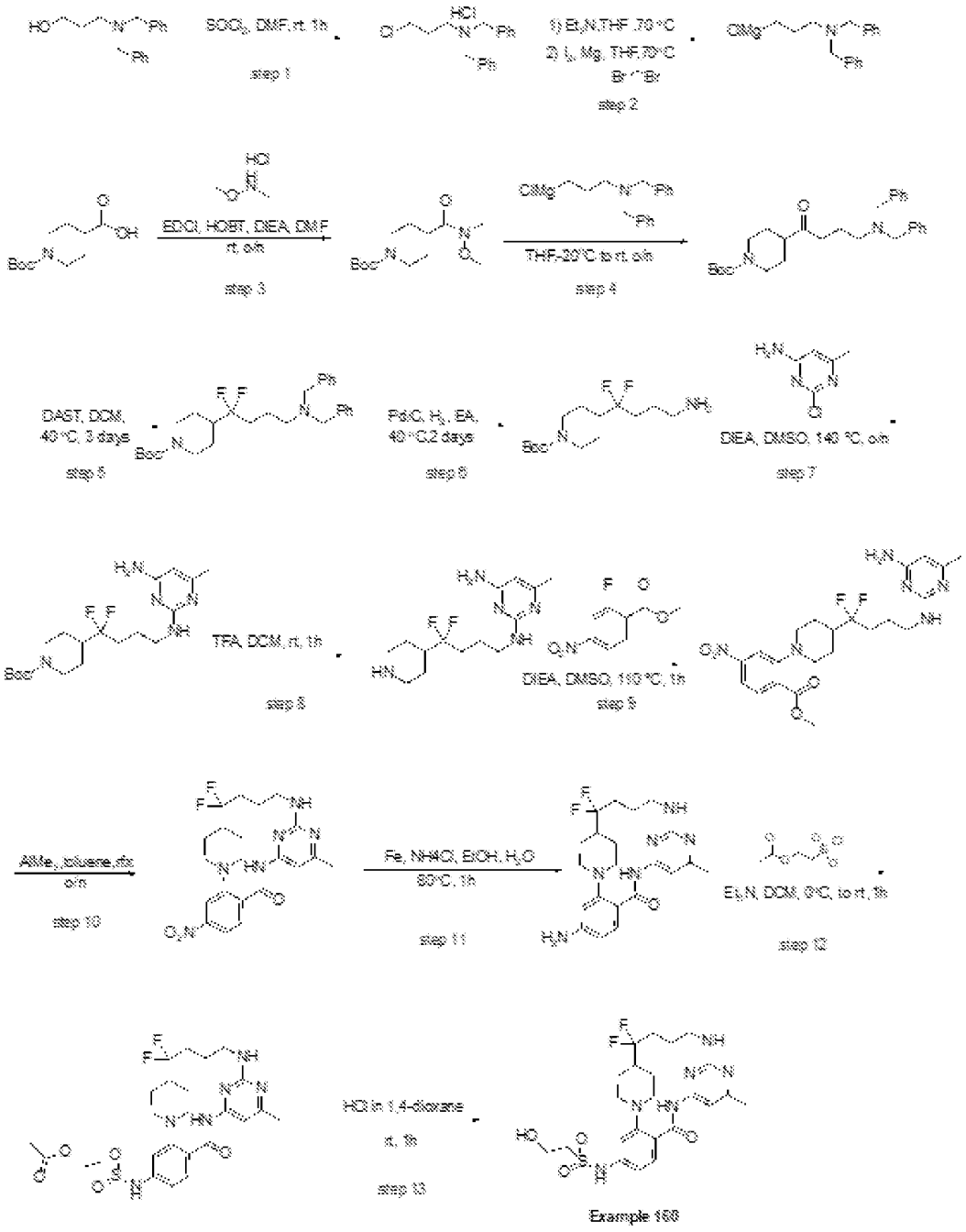
Compound	**KIF18A ADP-Glo IC50, nM (2h)**
First eluting isomer	++
Second eluting isomer	+++++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 159. 2-hydroxy-*N*-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide was synthesized via General synthetic route 4A as described in procedure from Example 18 using tert-butyl 3-(5-aminopentyl)piperidine-1-carboxylate and Intermediate G in Step 1. (Compound 159)



Example 160. N-(10,10-difluoro-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide was synthesized as described below. (Compound 160)



1. ***N,N*-dibenzyl-3-chloropropan-1-amine hydrochloride**

[000686] $SOCl_2$ (9 mL, 124 mmol) was added slowly to 3-(dibenzylamino)propan-1-ol (10 g, 39.1 mmol) and DMF (286 mg, 3.9 mmol) while being cooled by an ice batch. The mixture was stirred at room temperature for 1 hour. The resulting mixture was concentrated under vacuum to afford the crude product *N,N*-dibenzyl-3-chloropropan-1-amine hydrochloride (10 g, 74.0% yield). LCMS (ESI-MS) m/z =274.1 $[M+H]^+$.

2. (3-(dibenzylamino)propyl)magnesium chloride

[000687] Et_3N (8.81 g, 87 mmol) was added to N,N-dibenzyl-3-chloropropan-1-amine hydrochloride (9 g, 29 mmol) in Et_2O (50 mL).The mixture was stirred at room temperature for 1 hour. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (50mL) at room temperature. The resulting mixture was extracted with EA (3 x 30 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford *N,N*-dibenzyl-3-chloropropan-1-amine, free base (1g crude). A mixture of Mg (3.0 g) and I_2 (0.3 g) in THF (60 mL) was heated to 70°C under nitrogen atmosphere then dibromomethane (1.51 mL) and *N,N*-dibenzyl-3-chloropropan-1-amine (1.0 g crude) in THF (2 mL) was added to the mixture. The mixture was stirred at 70°C for 1 hour. The mixture was allowed to cool down to room temperature to afford the solution (3-(dibenzylamino)propyl)magnesium chloride in THF(~0.5 M, 50 mL).

3. *tert*-butyl 4-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate

[000688] DIEA (39.0 g, 307 mmol) was added to *N,O*-dimethylhydroxylamine hydrochloride (10.0 g, 102 mmol), 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (23.5 g, 102 mmol), EDCI (23.0 g, 153 mmol) and HOBT (20.8 g, 153 mmol) in DMF (200 mL). The reaction mixture was stirred at room temperature overnight. The mixture was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 10% to 40% gradient in 10 min; detector, UV 220 nm to afford tert-butyl 4-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (6.0 g, 17.1% yield). LCMS (ESI-MS) m/z = 273.3 $[M+H]^+$.

4. (*tert*-butyl 4-(4-(dibenzylamino)butanoyl)piperidine-1-carboxylate

[000689] A solution of (3-(dibenzylamino)propyl)magnesium chloride (50 mL, ~0.5M) was added slowly to *tert*-butyl 4-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (8.00 g, 29.4 mmol) in THF (40 mL) under nitrogen atmosphere at -20°C. The mixture was stirred at room temperature overnight. The reaction was quenched with sat. NH_4Cl (aq.) (200 mL) at room temperature. The resulting mixture was extracted with EA (3 x 200 mL). The combined organic layers were washed with brine (600 mL), dried over anhydrous Na_2SO_4. After

filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford (*tert*-butyl 4-(4-(dibenzylamino)butanoyl)piperidine-1-carboxylate (4 g, 24.1% yield). LCMS (ESI-MS) m/z = 451.3 $[M+H]^+$.

5. *tert*-butyl 4-(4-(dibenzylamino)-1,1-difluorobutyl)piperidine-1-carboxylate

[000690] DAST (14.3 g, 88.7 mmol) was added to (tert-butyl 4-(4-(dibenzylamino)butanoyl)piperidine-1-carboxylate (4 g, 8.87 mmol) in DCM (40 mL) under nitrogen atmosphere. The mixture was stirred at 40°C for 3 days. The reaction was quenched with sat. NH_4Cl (aq.) (120 mL) at 0 °C. The resulting mixture was extracted with DCM (3 x 40 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford *tert*-butyl 4-(4-(dibenzylamino)-1,1-difluorobutyl)piperidine-1-carboxylate (2 g, 38.1% yield). LCMS (ESI-MS) m/z = 473.3 $[M+H]^+$.

6. *tert*-butyl 4-(4-amino-1,1-difluorobutyl)piperidine-1-carboxylate

[000691] Pd/C (0.45 g, 0.42 mmol, 10% Pd on carbon) was added to a mixture of tert-butyl 4-(4-(dibenzylamino)-1,1-difluorobutyl)piperidine-1-carboxylate (2 g, 4.23 mmol) in EA (40 mL) under nitrogen atmosphere. The mixture was stirred at room temperature for 2 days under hydrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with EA (3 x 30 mL). The filtrate was concentrated under reduced pressure to afford the crude product *tert*-butyl 4-(4-amino-1,1-difluorobutyl)piperidine-1-carboxylate (900 mg, 65.4% yield). LCMS (ESI-MS) m/z = 291.3 $[M+H]^+$.

7. *tert*-butyl 4-(4-((4-amino-6-methylpyrimidin-2-yl)amino)-1,1-difluorobutyl)piperidine-1-carboxylate

[000692] DIEA (2.43 g, 18.8 mmol) was added to a mixture of 2-chloro-6-methylpyrimidin-4-amine (900 mg, 6.26 mmol) and tert-butyl 4-(4-amino-1,1-difluorobutyl)piperidine-1-carboxylate (1.83 g, 6.26 mmol) in DMSO (10 mL). The mixture was stirred at 140 °C overnight. The reaction was quenched with water (30 mL) at room temperature. The resulting mixture was extracted with EA (3 x 30 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford *tert*-butyl 4-(4-((4-amino-6-methylpyrimidin-2-yl)amino)-1,1-difluorobutyl)piperidine-1-carboxylate (450 mg, 14.3% yield). LCMS (ESI-MS) m/z = 400.2 $[M+H]^+$.

8. N^2-(4,4-difluoro-4-(piperidin-4-yl)butyl)-6-methylpyrimidine-2,4-diamine

[000693] TFA (1 mL) was added to *tert*-butyl 4-(4-((4-amino-6-methylpyrimidin-2-yl)amino)-1,1-difluoro-butyl)piperidine-1-carboxylate (450 mg, 1.13 mmol) in DCM (5 mL). The reaction mixture was stirred at room temperature for 1 hour. The resulting mixture was concentrated under vacuum to afford the crude product N^2-(4,4-difluoro-4-(piperidin-4-yl)butyl)-6-methylpyrimidine-2,4-diamine (400 mg, 94.9% yield). LCMS (ESI-MS) m/z = 300.0 $[M+H]^+$.

9. methyl 2-(4-(4-((4-amino-6-methylpyrimidin-2-yl)amino)-1,1-difluorobutyl)piperidin-1-yl)-4-nitrobenzoate

[000694] DIEA (778 mg, 6.02 mmol) was added to a mixture of methyl 2-fluoro-4-nitrobenzoate (266 mg, 2.00 mmol) and N^2-(4,4-difluoro-4-(piperidin-4-yl)butyl)-6-methylpyrimidine-2,4-diamine (400 mg, 2.00 mmol) in DMSO (5 mL). The mixture was stirred at 140 °C for 3 hours. The reaction was quenched with water at room temperature. The resulting mixture was extracted with EA (3 x 20 mL). The combined organic layers were washed with brine (80 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (7:1) to afford methyl 2-(4-(4-((4-amino-6-methylpyrimidin-2-yl)amino)-1,1-difluorobutyl)piperidin-1-yl)-4-nitrobenzoate (300 mg, 24.9% yield). LCMS (ESI-MS) m/z = 479.2 $[M+H]^+$.

10. 10,10-difluoro-5^6-methyl-2^5-nitro-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan-3-one

[000695] $AlMe_3$ (1.25 mL, 1.88 mmol, 1.5 M in toluene) was added to a mixture of methyl 2-(4-(4-((4-amino-6-methylpyrimidin-2-yl)amino)-1,1-difluorobutyl)piperidin-1-yl)-4-nitrobenzoate (300 mg, 0.63 mmol) in toluene (3 mL). The mixture was stirred at 100°C overnight. The mixture was concentrated and purified by silica gel column chromatography, eluted with PE / EA (7:1) to afford the product 10,10-difluoro-5^6-methyl-2^5-nitro-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (30 mg, 8.57% yield). LCMS (ESI-MS) m/z = 447.2 $[M+H]^+$.

11. 2^5-amino-10,10-difluoro-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan-3-one

[000696] Fe (37 mg, 0.67 mmol) was added to a stirred mixture of 10,10-difluoro-5^6-methyl-2^5-nitro-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (30 mg, 0.067 mmol) and NH_4Cl (14 mg, 0.26 mmol) in EtOH (1.5 mL) and water (0.5 mL). The mixture was stirred at 80 °C for 1 hour. The resulting mixture was filtered, the filter cake

was washed with EtOH (3 x 3 mL). The filtrate was concentrated under reduced pressure. The residue was dissolved in water (3 mL) and EA (3 mL). The resulting mixture was extracted with EA (3 x 5 mL). The combined organic layers were washed with brine (3 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford the crude product 2^5-amino-10,10-difluoro-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (25 mg, 89.3% yield). LCMS (ESI-MS) m/z = 417.2 $[M+H]^+$.

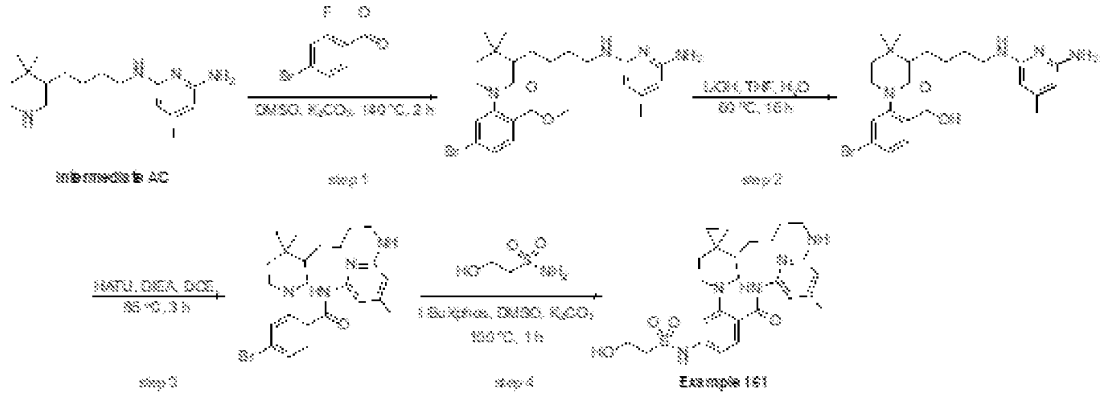
12. 2-(N-(10,10-difluoro-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)sulfamoyl)ethyl acetate

[000697] 2-(chlorosulfonyl)ethyl acetate (25 mg, 0.14 mmol) was added to a mixture of Et_3N (49 mg, 0.48 mmol) and 2^5-amino-10,10-difluoro-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphan-3-one (66.9 mg, 0.16 mmol) in DCM (1 mL) at ice bath. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was purified by Prep-TLC (PE / EA 1:1) to afford 2-(N-(10,10-difluoro-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycl-odecaphane-2^5-yl)sulfamoyl)ethyl acetate (15 mg, 15.8% yield). LCMS (ESI-MS) m/z = 567.2 $[M+H]^+$.

13. N-(10,10-difluoro-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide

[000698] HCl (2 mL, 2 mol/L in 1,4-dioxane) was added to 2-(N-(10,10-difluoro-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycl-odecaphane-2^5-yl)sulfamoyl)ethyl acetate (15 mg, 0.026 mmol). The mixture was stirred at room temperature for 1 hour. The resulting mixture was concentrated under vacuum. The residue was dissolved in DCM (2 mL) and sat. $NaHCO_3$ (aq.) (3 mL). The resulting mixture was extracted with DCM (2 x 3 mL). The combined organic layers were washed with brine (6 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford the crude product. The residue was purified by Prep-HPLC with the following conditions: Column: Welch Ultimate XB-Phenyl, 30*250 mm, 10μm; Mobile Phase A: Water (10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 28% B to 58% B in 10min; Wave Length: 254nm/220nm nm; RT1(min): 9.5 to afford the product N-(10,10-difluoro-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide (4.05 mg, 28.4% yield). LCMS (ESI-MS) m/z = 525.1 $[M+H]^+$.

Example 161. 2-hydroxy-N-(4'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide was synthesized via General synthetic route 3D using Intermediate AC and methyl 4-bromo-2-fluorobenzoate in Step 1 as described in the procedure below. (Compound 161)



1. methyl 2-(4-(4-((6-amino-4-methylpyridin-2-yl)amino)butyl)-6-azaspiro[2.5]octan-6-yl)-4-bromobenzoate

[000699] K_2CO_3 (575 mg, 4.16 mmol) was added to a stirred mixture of Intermediate AC (200 mg, 0.693 mmol) methyl 4-bromo-2-fluorobenzoate (242 mg, 1.04 mmol) in DMSO (3 mL) . The resulting mixture was heated to 140 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was diluted with H_2O (10 mL) and extracted with EA (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH 10:1 to afford methyl 2-(4-(4-((6-amino-4-methylpyridin-2-yl)amino)butyl)-6-azaspiro[2.5]octan-6-yl)-4-bromobenzoate (150 mg, 96.1% yield). LCMS (ESI-MS) m/z = 501.1$[M+H]^+$.

2. 2-(4-(4-((6-amino-4-methylpyridin-2-yl)amino)butyl)-6-azaspiro[2.5]octan-6-yl)-4-bromobenzoic acid

[000700] LiOH (45 mg, 1.90 mmol) was added to a stirred mixture of methyl 2-(4-(4-((6-amino-4-methylpyridin-2-yl)amino)butyl)-6-azaspiro[2.5]octan-6-yl)-4-bromobenzoate (150 mg, 0.32 mmol) in water (1 mL) and THF (3 mL). The resulting mixture was heated to 60 °C and stirred for 16 hours. After cooling to room temperature, the resulting mixture was filtered, the filter cake was washed with THF (2 x 6 mL). The filtrate was concentrated under reduced pressure to afford the crude product 2-(4-(4-((6-amino-4-methylpyridin-2-yl)amino)butyl)-6-

azaspiro[2.5]octan-6-yl)-4-bromobenzoic acid (110 mg crude). LCMS (ESI-MS) m/z = 487.1 $[M+H]^+$.

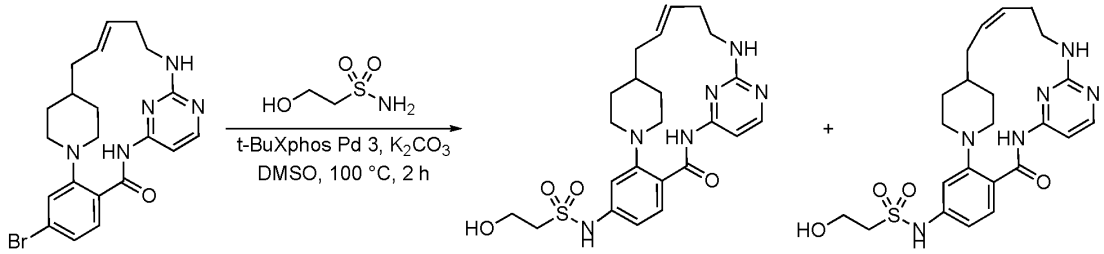
3. **5'-bromo-4'-methylspiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one**

[000701] DIEA (87.5 mg, 0.678 mmol) was added to a stirred mixture of HATU (129mg, 0.339 mmol) and t 2-(4-(4-((6-amino-4-methylpyridin-2-yl)amino)butyl)-6-azaspiro[2.5]octan-6-yl)-4-bromobenzoic acid (110 mg, 0.226 mmol) in DCE (2 mL). The resulting mixture was heated to 85 °C and stirred for 3 hours. After cooling to room temperature, the reaction mixture was diluted with H_2O (2 mL) and extracted with EA (2 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with PE / EA 6:1 to afford 5'-bromo-4'-methylspiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one (40 mg, 37.8yield). LCMS (ESI-MS) m/z = 469.1 $[M+H]^+$.

4. **2-hydroxy-N-(4'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide**

[000702] K_2CO_3 (11.8 mg, 0.086 mmol) was added to a stirred mixture of 5'-bromo-4'-methylspiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one (20 mg, 0.043 mmol), 2-hydroxyethanesulfonamide (16.0 mg, 0.129 mmol) and tBuXPhos Pd G3 (3.38 mg, 0.004 mmol) in DMSO (2 mL) under nitrogen atmosphere. The resulting mixture was heated to 100 °C and stirred for 1 hour. After cooling to room temperature, the reaction mixture was diluted with H_2O (2 mL) and extracted with EA (2 x 2 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by Prep-HPLC with the following conditions: Column: XBridge Prep RP OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 43% B to 73% B in 10min; Wave Length: 254nm/220nm nm; RT1(min): 9.1 to afford 2-hydroxy-N-(4'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (1.9 mg, 8.6% yield). LCMS (ESI-MS) m/z = 514.2 $[M+H]^+$.

Examples 162 and 167. (E)-2-hydroxy-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)ethane-1-sulfonamide & (Z)-2-Thydroxy-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)ethane-1-sulfonamide were synthesized from Intermediate AA and Intermediate R via General synthetic route 7A (Steps 1-4) following same procedures as described in Example 114. In Step 4 E- and Z- isomers of the final product were separated as described below. (Compound 162 and compound 167 respectively)



Example 162 Example 167

[000703] T-BuXPhos-Pd-G3 (71.8 mg, 0.090 mmol) was added to a mixture of (E)-2[5]-bromo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (200 mg, 0.45 mmol) and K_2CO_3 (187.5 mg, 1.35 mmol) in DMSO (3 mL). After cooling to room temperature, the resulting mixture was diluted with ethyl acetate (500 ml) and washed with brine (3 x 500 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford a crude product (80 mg). 40 mg of the crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep RP OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 25% B to 55% B in 10min; Wave Length: 254nm/220nm nm; RT1(min): 9.2) to afford a pure mixture (12 mg). The mixture was then purified by Prep-CHIRAL-HPLC with the following conditions (Column: (R, R)-WHELK-O1-Kromasil, 2.12*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 50; Wave Length: 254/220nm nm; RT1(min): 7.728; RT2(min): 10.365; Sample Solvent: EtOH--HPLC; Injection Volume: 0.9 mL; Number Of Runs: 5) to afford the two products:

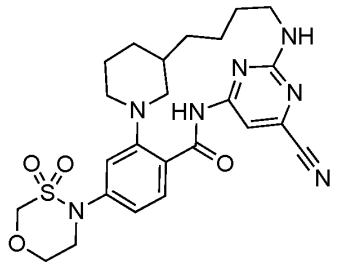
First eluting isomer:

[000704] (E)-2-hydroxy-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)ethane-1-sulfonamide (5.0 mg, 41.6% yield). LCMS (ESI-MS) m/z = 487.1 $[M+H]^+$. 98.4% purity.

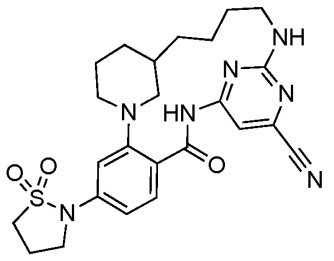
Second eluting isomer:

[000705] (Z)-2-hydroxy-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)ethane-1-sulfonamide (1.45 mg, 12% yield). LCMS (ESI-MS) m/z = 487.1 $[M+H]^+$.

Example 163. 2^5-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-5^6-carbonitrile was synthesized via General synthetic route 4A, from Intermediate Y and *tert*-butyl 3-(4-aminobutyl)piperidine-1-carboxylate as described in the procedure for Example 62. 1,3,4-oxathiazinane 3,3-dioxide was used as a nucleophile in step 4. (Compound 163)

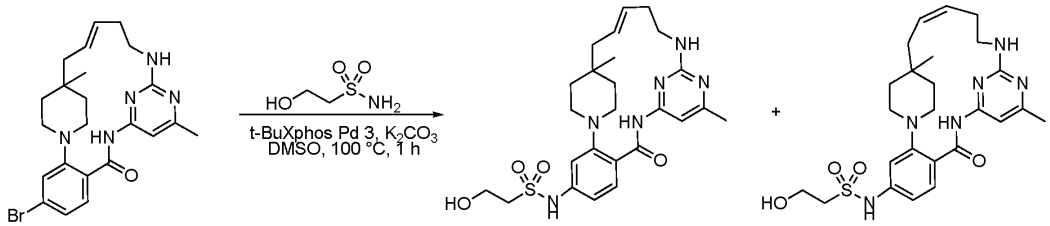


Example 164. 2^5-(1,1-dioxidoisothiazolidin-2-yl)-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-5^6-carbonitrile was synthesized via General synthetic route 4A, from Intermediate Y and *tert*-butyl 3-(4-aminobutyl)piperidine-1-carboxylate as described in the procedure for Example 62. Isothiazolidine 1,1-dioxide was used as a nucleophile in step 4. (Compound 164)



Examples 165 and 168. (E)-N-(1^4,5^6-dimethyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide

& (Z)-N-(1^4,5^6-dimethyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide were synthesized from Intermediate AB and Intermediate Q via General synthetic route 7A (Steps 1-4) following same procedures as described in Example 114. In Step 4 E- and Z- isomers of the final product were separated as described below. (Compound 165 and compound 168 respectively)



Example 165 Example 168

[000706] Into a solution of (E)-2^5-bromo-1^4,5^6-dimethyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (20 mg, 0.043 mmol) in DMSO (3 mL) was added 2-hydroxyethanesulfonamide (10.6 mg, 0.086 mmol) ,3rd t-BuXPhos precatalyst (3.38 mg, 0.004 mmol) and K_2CO_3 (17.6 mg, 0.129 mmol) . The resulting solution was heated to 140 °C and stirred for 1 hour. After cooling to room temperature, the reaction mixture was diluted with water (10 mL), extracted with EA (15 mL x 2). The organic layers were combined, washed with brine (15 mL x 2), dried with anhydrous Na_2SO_4, filtered and evaporated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA/PE 3:1 to give a light yellow solid (20 mg). This solid was dissolved in MeOH (1 mL) and purified with the following conditions: Column: (R, R)-WHELK-O1-Kromasil, 2.12*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 50; Wave Length: 254/220nm nm; RT1(min): 6.192; RT2(min): 9.289; Sample Solvent: EtOH--HPLC; Injection Volume: 2.0 mL; Number Of Runs: 3 to afford to afford the two products:

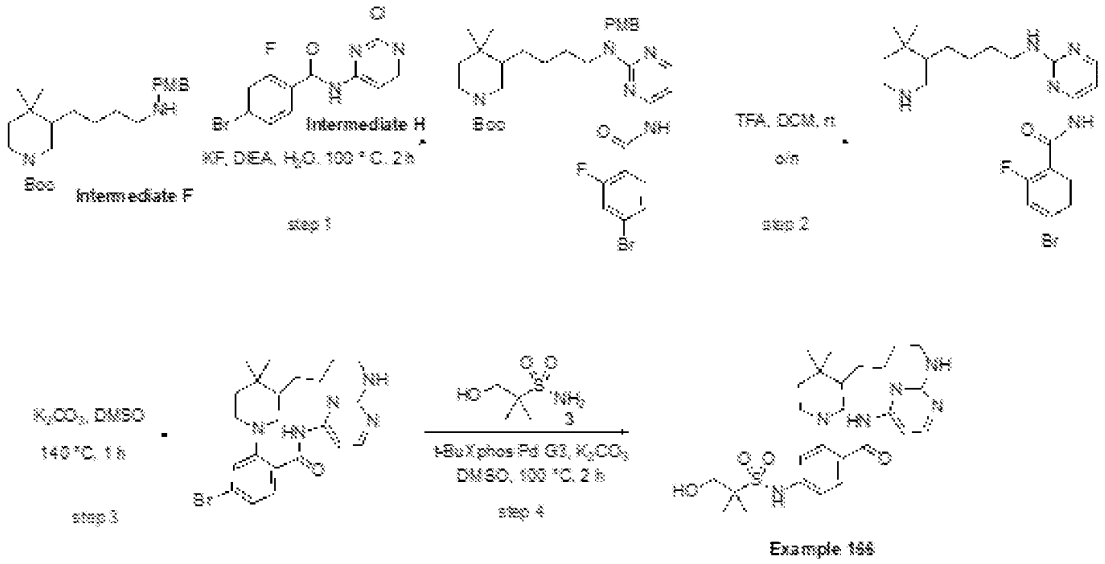
First eluting isomer:

[000707] (E)-N-(1^4,5^6-dimethyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide (5.9 mg, 26.9%). LCMS (ESI-MS) m/z = 515.2 [M+H]+.

Second eluting isomer:

[000708] (Z)-N-(1^4,5^6-dimethyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide (1.1 mg, 5.0%). LCMS (ESI-MS) m/z = 515.2 [M+H]+.

Example 166. 1-hydroxy-2-methyl-N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)propane-2-sulfonamide was synthesized via General synthetic route 4B from Intermediate H and Intermediate F in Step 1 as described in the procedures below. (Compound 166)



1. tert-butyl 4-(4-((4-(4-bromo-2-fluorobenzamido)pyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate

[000709] DIEA (644 mg, 4.98 mmol) and KF (292 mg, 4.98 mmol) were added to a stirred solution of Intermediate F (1.00 g, 2.49 mmol) and Intermediate H (819 mg, 2.49 mmol) in H_2O (10 mL). The resulting mixture was heated to 100 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was diluted with H_2O (40 mL) and extracted with EA (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column, eluted with PE/EA 2 : 1 to afford tert-butyl 4-(4-((4-(4-bromo-2-fluorobenzamido)pyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate (800 mg, 46.3% yield). LCMS (ESI-MS) m/z = 696.2 $[M+H]^+$.

2. N-(2-((4-(6-azaspiro[2.5]octan-4-yl)butyl)amino)pyrimidin-4-yl)-4-bromo-2-fluorobenzamide

[000710] TFA (5 mL) was added to a stirred mixture of tert-butyl 4-(4-((4-(4-bromo-2-fluorobenzamido)pyrimidin-2-yl)(4-methoxybenzyl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate (750 mg, 1.08 mmol) in DCM (10 mL). The resulting solution was stirred at room

temperature overnight and concentrated under vacuum to afford N-(2-((4-(6-azaspiro[2.5]octan-4-yl)butyl)amino)pyrimidin-4-yl)-4-bromo-2-fluorobenzamide (580 mg crude). LCMS (ESI-MS) m/z = 476.1 $[M+H]^+$.

3. 5'-bromospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one

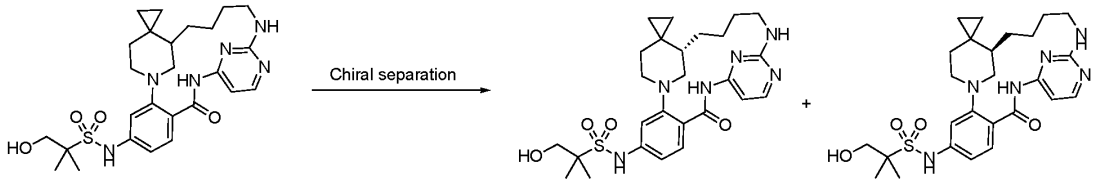
[000711] K_2CO_3 (464 mg, 3.36 mmol) was added to a mixture of N-(2-((4-(6-azaspiro[2.5]octan-4-yl)butyl)amino)pyrimidin-4-yl)-4-bromo-2-fluorobenzamide (530 mg, 1.12 mmol) in DMSO (5 mL). The resulting mixture was heated to 140 °C and stirred for 1 hour. After cooling to room temperature, the reaction mixture was diluted with water (30 mL) and extracted with EA (2 x 30 mL). The combined organic layers were washed with brine (60 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the product 5'-bromospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one (500 mg crude). LCMS (ESI-MS) m/z = 456.1 $[M+H]^+$.

4. 1-hydroxy-2-methyl-N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)propane-2-sulfonamide

[000712] T-BuXPhos-Pd-G3 (69.6 mg, 0.09 mmol,) was added to a solution of 5'-bromospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one (200 mg, 0.44 mmol), 1-hydroxy-2-methylpropane-2-sulfonamide (120 mg, 0.78 mmol) and K_2CO_3 (181.7 mg, 1.31 mmol) in DMSO (1 mL). The resulting mixture was stirred at 100 °C for 2 hours. After cooling to room temperature, the resulting mixture was diluted with ethyl acetate (50 ml) and washed with brine (3 x 50 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep RP OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 38% B to 68% B in 10min; Wave Length: 254nm/220nm nm; RT1(min): 9.1) to afford 1-hydroxy-2-methyl-N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)propane-2-sulfonamide (13 mg, 5.6% yield). LCMS (ESI-MS) m/z = 529.2 $[M+H]^+$.

Examples 169 and 170. 1-hydroxy-2-methyl-N-((3's)-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)propane-2-sulfonamide & 1-hydroxy-2-methyl-N-((3'R)-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-

5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)propane-2-sulfonamide (Compound 169 and compound 170 respectively)



Example 166 Example 169 Example 170

[000713] The racemic mixture of 1-hydroxy-2-methyl-N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)propane-2-sulfonamide (11 mg) was dissolved with MeOH and purified by PREP-CHIRAL-HPLC with the following conditions: Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 45; Wave Length: 254/220nm nm; RT1(min): 5.879; RT2(min): 10.363; Sample Solvent: EtOH--HPLC; Injection Volume: 1.6 mL; Number Of Runs: 2. to afford the two products:

First eluting isomer:

[000714] Enantiopure 1-hydroxy-2-methyl-N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)propane-2-sulfonamide (3.36 mg, 30.3% yield) LCMS (ESI-MS) m/z = 529.2 $[M+H]^+$.

Second eluting isomer:

[000715] Enantiopure 1-hydroxy-2-methyl-N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)propane-2-sulfonamide (3.67 mg, 33.1% yield). LCMS (ESI-MS) m/z = 529.2 $[M+H]^+$.

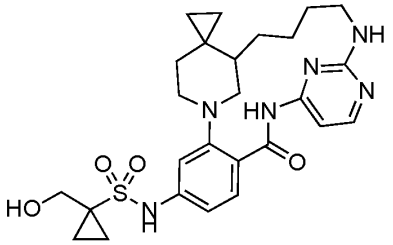
Table 23. 2 hour KIF18A Biochemical data for Examples 169 and 170

Compound	**KIF18A ADP-Glo IC50, nM (2h)**
First eluting isomer	++++
Second eluting isomer	++

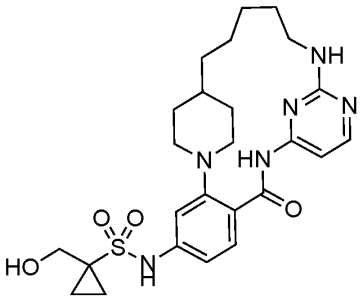
IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 171. 1-(hydroxymethyl)-N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)cyclopropane-1-

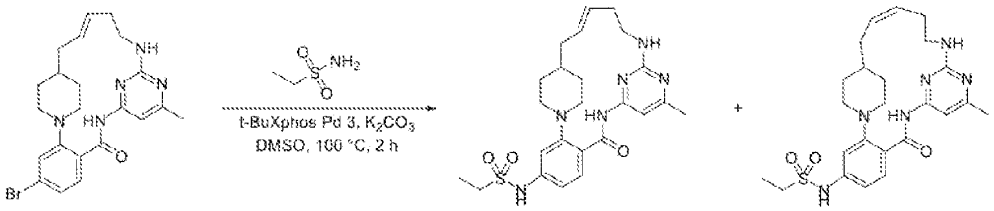
sulfonamide was synthesized via General synthetic route 4B using Intermediate F and Intermediate H in Step 1 and 1-(hydroxymethyl)cyclopropane-1-sulfonamide in Step 4, following procedures described in Example 166. (Compound 171)



Example 172. 1-(hydroxymethyl)-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)cyclopropane-1-sulfonamide synthesized from Intermediate AA and Intermediate R via General synthetic route 7A (Steps 1-5) following same procedures as described in Example 114 and Example 116. In Step 4 1-(hydroxymethyl)cyclopropane-1-sulfonamide was used. (Compound 172)



Examples 173 and 174. (E)-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide & (Z)-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)ethanesulfonamide were synthesized from Intermediate Q and Intermediate R via General synthetic route 7A (Steps 1-4) following same procedures as described in Example 114. In Step 4 E- and Z- isomers of the final product were separated as described below (Compound 173 and compound 174 respectively).



Example 173 Example 174

[000716] To a solution of (E)-2^5-bromo-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (130 mg, 0.28 mmol) in DMSO (2 mL) was added t-BuXPhos Pd G3 (45.2 mg, 0.06 mmol), ethanesulfonamide (46.7 mg, 0.43 mmol) and K_2CO_3 (118.1 mg, 0.85 mmol). The resulting mixture was heated to 100 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (50 ml) and washed with brine (3 x 50 ml). The organic layer was dried over anhydrousNa_2SO_3, filtered and concentrated under vacuum to afford a crude product (60 mg). 40 mg of the crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 35% B to 65% B in 10min; Wave Length: 254nm/220nm nm; RT1(min): 9.1) to afford a pure mixture. Then the pure mixture was purified by Prep-CHIRAL-HPLC with the following conditions (Column: (R, R)-WHELK-O1-Kromasil, 2.12*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 40; Wave Length: 254/220nm nm; RT1(min): 8.976; RT2(min): 14.361; Sample Solvent: EtOH--HPLC; Injection Volume: 2.0 mL; Number Of Runs: 2) to afford the two products:

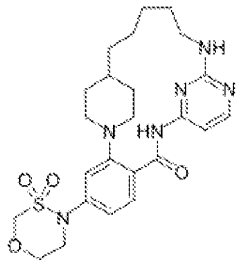
First eluting isomer:

[000717] (E)-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)ethanesulfonamide (11.39 mg, 8.2% yield). LCMS (ESI-MS) m/z = 485.1 $[M+H]^+$.

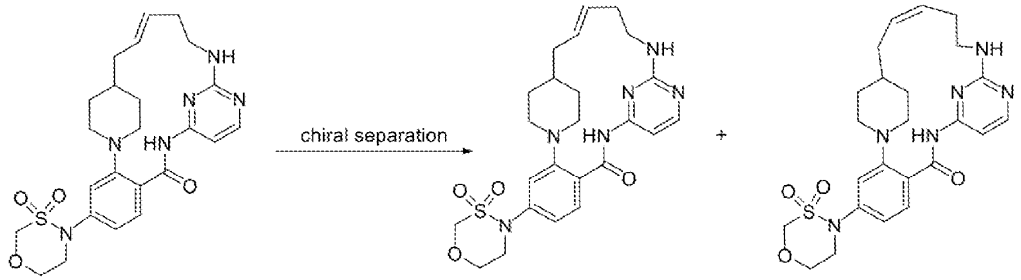
Second eluting isomer:

[000718] (Z)-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)ethanesulfonamide (1.99 mg, 1.4% yield). LCMS (ESI-MS) m/z = 485.1 $[M+H]^+$.

Example 175. 2^5-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-3-one was synthesized from Example 176 as described in procedure for preparation of Example 183 (Compound 175).



Examples 176 and 185. (*E*)-2^5-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one & (*Z*)-25-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one were synthesized from Intermediate Q and Intermediate R via General synthetic route 7A (Steps 1-4) following same procedures as described in Example 114. E- and Z- isomers of the final product were separated as described below (Compound 176 and compound 185 respectively)



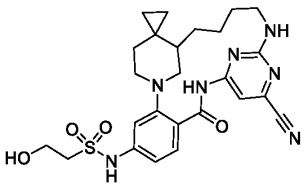
Example 176 **Example 185**

[000719] 2^5-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one(30 mg, 0.060 mmol) was purified by Prep-Chiral-HPLC with the following conditions: Column: (R, R)WhelkO1; Mobile Phase A: Hex(0.1%DEA): (EtOH: DCM=1: 1)=45: 55; Flow rate: 1 mL/min; Gradient: isocratic ; Injection Volume: 1μl mL to afford two products:

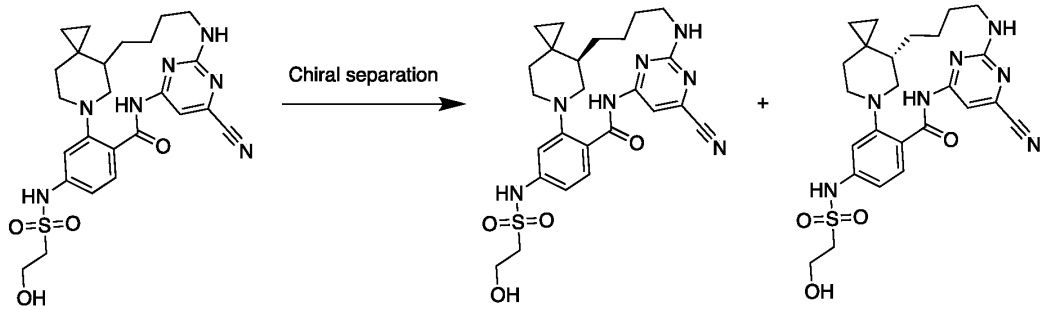
[000720] First eluting isomer: (*E*)-2^5-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (3.6 mg, 36.0% yield) LCMS (ESI-MS) m/z = 499.2 $[M+H]^+$.

[000721] Second eluting isomer: (*Z*)-2^5-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (0.2 mg, 2.0% yield), LCMS (ESI-MS) m/z = 499.2 $[M+H]^+$.

Example 177. N-(6'-cyano-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)-2-hydroxyethane-1-sulfonamide was synthesized via General synthetic route 4A, from Intermediate Y and intermediate E as described in the procedure for Example 62. 2-hydroxyethanesulfonamide was used as a nucleophile in step 4.



Examples 178 and 179. N-((3'R)-6'-cyano-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)-2-hydroxyethane-1-sulfonamide & N-((3'S)-6'-cyano-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)-2-hydroxyethane-1-sulfonamide were synthesized from Example 177 as described below (Compound 178 and compound 179 respectively).



[000722] N-(6'-cyano-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)-2-hydroxyethane-1-sulfonamide (16 mg) was

dissolved with MeOH and purified by Chiral-prep-HPLC with the following conditions: Column: CHIRAL ART Cellulose-SZ, 3*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 30ML/MIN mL/min; Gradient: isocratic 40; Wave Length: 254/220nm nm; RT1(min): 11.365; RT2(min): 16.61; Sample Solvent: EtOH--HPLC; Injection Volume: 1.7 mL; Number Of Runs: 3, to afford the two products:

First eluting isomer:

[000723] Enantiopure N-(6'-cyano-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)-2-hydroxyethane-1-sulfonamide (5.12 mg, 32% yield), LCMS (ESI-MS) m/z =526.2 $[M+H]^+$.

Second eluting isomer:

[000724] Enantiopure N-(6'-cyano-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)-2-hydroxyethane-1-sulfonamide (4.26 mg, 26.6% yield), LCMS (ESI-MS) m/z =526.2 $[M+H]^+$.

Table 24 KIF18A Biochemical data (2h assay) for Examples 178 and 179

Compound	**KIF18A ADP-Glo IC50, nM (2h)**
First eluting isomer	+
Second eluting isomer	+++++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

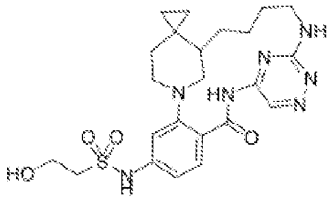
Table 24A KIF18A Biochemical data (24h assay) for Examples 178 and 179

Compound	**KIF18A ADP-Glo IC50, nM (24h)**
First eluting isomer	++++
Second eluting isomer	+++++

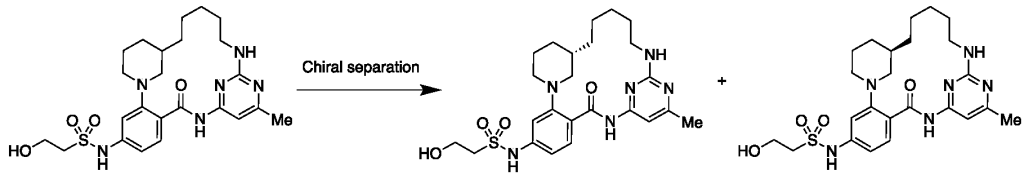
IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 180. 2-hydroxy-N-(3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(5,3)-triazina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide was synthesized via General synthetic route 4A, from Intermediate AI and intermediate E as

described in the procedure for Example 62. 2-hydroxyethanesulfonamide was used as a nucleophile in step 4. (Compound 180).



Examples 181 and 182. 2-hydroxy-N-((1^{3}R)-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide and 2-hydroxy-N-((1^{3}S)-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide were prepared via chiral separation of Example 159 as described below (Compound 181 and compound 182 respectively).



[000725] 2-hydroxy-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide (200 mg, 0.40 mmol) was separated by Prep-Chiral HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient (B%): isocratic 60; Wave Length: 254/220nm nm; RT1(min): 4.462; RT2(min): 11.872; Sample Solvent: EtOH--HPLC; Injection Volume: 1.7 mL; Number Of Runs: 2) to afford two products:

[000726] First eluting isomer: enantiopure 2-hydroxy-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide (51.5 mg, 25.8% yield), LCMS (ESI-MS) m/z =503.2 $[M+H]^+$

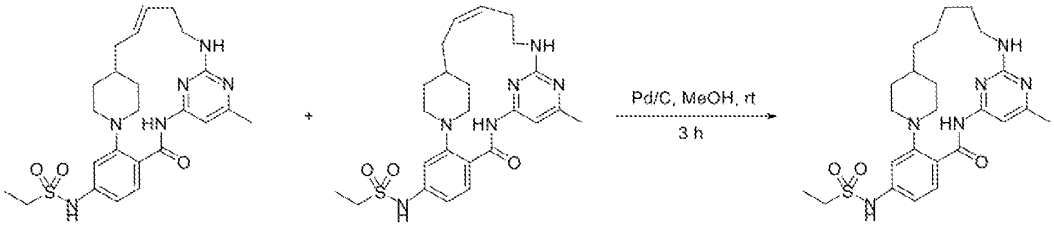
[000727] Second eluting isomer: 2 enantiopure 2-hydroxy-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide (49.2 mg, 24.6% yield), LCMS (ESI-MS) m/z =503.3 $[M+H]^+$

Table 25 KIF18A Biochemical data (2h assay) for Examples 181 and 182

Compound	KIF18A ADP-Glo IC50, nM (2h)
First eluting isomer	+++++
Second eluting isomer	++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 183. N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethanesulfonamide was synthesized from the crude product of Example 173 and 174 as described below (Compound 183).

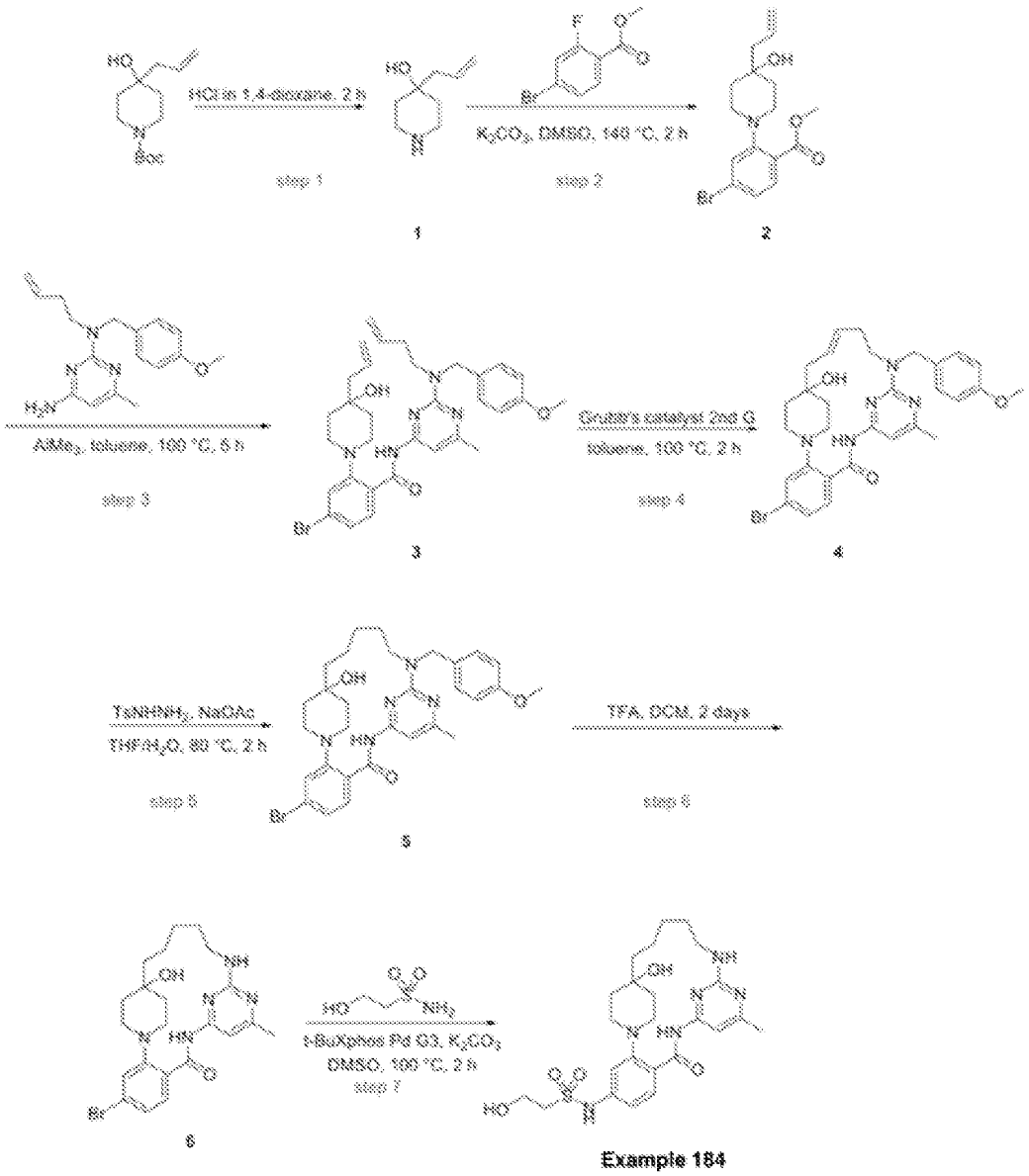


Example 183

[000728] 20 mg of the crude product from preparation of example 173 and 174 was dissolved in MeOH (2 mL) and treat with Pd/C under hydrogen atmosphere for 3 hours. The reaction mixture was filtered off and the filtrate was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Prep Shield RP18 OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10nmol/LNH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 46% B to76 % B in 10 min; Wave Length: 254nm/220nm nm; RT1(min): 8.55) to afford N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethanesulfonamide (7.13 mg, 39.1% yield).

[000729] LCMS (ESI-MS) m/z = 487.1 $[M+H]^+$.

Example 184. 2-hydroxy-N-(1^4-hydroxy-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide was synthesized as described below (Compound 184).



Step 1. 4-allylpiperidin-4-ol

[000730] tert-butyl 4-allyl-4-hydroxypiperidine-1-carboxylate (3 g, 12.4 mmol) was added HCl (4M) in 1,4-dioxane (10 mL). The resulting mixture was stirred at room temperature for 2 hours and concentrated to afford the crude product 4-allylpiperidin-4-ol (1.7 g mg crude), LCMS (ESI-MS) m/z = 142.1 $[M+H]^+$.

Step 2. methyl 2-(4-allyl-4-hydroxypiperidin-1-yl)-4-bromobenzoate

[000731] K_2CO_3 (151 mg, 1.09 mmol) was added to a mixture of 4-allylpiperidin-4-ol (1.7 mg, 12.1 mmol) and methyl 4-bromo-2-fluorobenzoate (2.8 g, 12.1 mmol) in DMSO (20 mL). The resulting mixture was heated to 140 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was diluted with water (20 mL) and extracted with EA (2 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with PE / EA 1 / 1 to afford methyl 2-(4-allyl-4-hydroxypiperidin-1-yl)-4-bromobenzoate (2 g, 47.0% yield), LCMS (ESI-MS) m/z = 353.1 $[M+H]^+$.

Step 3. 2-(4-allyl-4-hydroxypiperidin-1-yl)-4-bromo-N-(2-(but-3-en-1-yl(4-methoxybenzyl)amino)-6-methylpyrimidin-4-yl)benzamide

[000732] $AlMe_3$ (4.25 mL, 2M) was added to a stirred mixture of methyl 2-(4-allyl-4-hydroxypiperidin-1-yl)-4-bromobenzoate (1 g, 2.83 mmol) and N^2-(but-3-en-1-yl)-N^2-(4-methoxybenzyl)-6-methylpyrimidine-2,4-diamine (844 mg, 2.83 mmol) in toluene (10 mL). The resulting mixture was heated to 100 °C and stirred for 5 hours. After cooling to room temperature, the reaction mixture was diluted with water (20 mL) and extracted with EA (2 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with PE / EA 1 : 1 to afford 2-(4-allyl-4-hydroxypiperidin-1-yl)-4-bromo-N-(2-(but-3-en-1-yl(4-methoxybenzyl)amino)-6-methylpyrimidin-4-yl)benzamide (650 mg, 36.2% yield), LCMS (ESI-MS) m/z = 620.2 $[M+H]^+$.

Step 4. (E)-2^5-bromo-1^4-hydroxy-6-(4-methoxybenzyl)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one

[000733] To a stirred solution of 2-(4-allyl-4-hydroxypiperidin-1-yl)-4-bromo-N-(2-(but-3-en-1-yl(4-methoxybenzyl)amino)-6-methylpyrimidin-4-yl)benzamide (650 mg, 1.05 mmol) in anhydrous toluene (1 mL) was added Grubb's catalyst 2nd G (180 mg, 0.21 mmol). The resulting mixture was heated to 100 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was diluted with water (5 mL) and extracted with EA (2 x 5 mL). The combined organic layers were washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified with silica gel column, eluted with PE / EA 4 : 1 to afford the desired product 2^5-bromo-14-hydroxy-6-(4-

methoxybenzyl)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (400 mg, 64.5% yield), LCMS (ESI-MS) m/z = 592.2 $[M+H]^+$.

Step 5. 2^5-bromo-1^4-hydroxy-6-(4-methoxybenzyl)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-3-one

[000734] 2^5-bromo-14-hydroxy-6-(4-methoxybenzyl)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (400 mg, 0.68 mmol) was added 4-methylbenzenesulfonohydrazide (57 mg, 2.04 mmol) and NaOAc (167 mg, 2.04 mmol) in THF (2 mL) and H_2O (2 mL). The resulting solution was heated to 80 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was diluted with water (5 mL) and extracted with EA (2 x 5 mL). The combined organic layers were washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified with silica gel column, eluted with PE / EA 2 : 1 to afford the desired product 2^5-bromo-1^4-hydroxy-6-(4-methoxybenzyl)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-3-one (250 mg, 62.3% yield), LCMS (ESI-MS) m/z = 594.2 $[M+H]^+$.

Step 6. 2^5-bromo-1^4-hydroxy-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-3-one

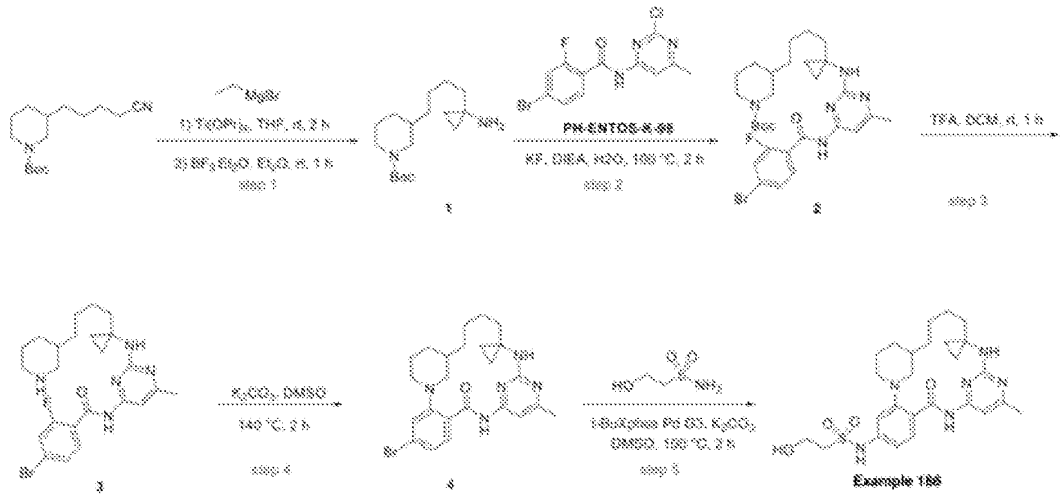
[000735] TFA (10 mL) was added to a stirred mixture of 2^5-bromo-1^4-hydroxy-6-(4-methoxybenzyl)-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-3-one (100 mg, 0.17 mmol) in DCM (1 mL). The resulting mixture was stirred at room temperature for 2 days and concentrated to afford the crude product 2^5-bromo-1^4-hydroxy-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-3-one (50 mg crude), LCMS (ESI-MS) m/z = 474.1 $[M+H]^+$.

Step 7. 2-hydroxy-N-(1^4-hydroxy-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide

[000736] Into a solution of 2^5-bromo-1^4-hydroxy-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-3-one (50 mg, 0.11 mmol) in DMSO (0.5 mL) was added 2-hydroxyethanesulfonamide (27 mg,0.22 mmol), t-BuXPhos Pd G3 catalyst (16 mg, 0.022 mmol) and K_2CO_3 (46 mg, 0.33 mmol) under nitrogen atmosphere. The resulting solution was heated to 100 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was diluted with water (2 mL) and extracted with EA (2 x 2 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered

and concentrated under vacuum to afford the crude product. The residue was purified by reversed-phase flash chromatography with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 13% B to 43% B in 10min; Wave Length: 254nm/220nm nm; RT1(min): 9.5 to afford the desired product 2-hydroxy-N-(1^4-hydroxy-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide (4.9 mg, 8.8% yield), LCMS (ESI-MS) m/z = 519.2 $[M+H]^+$.

Example 186. 2-hydroxy-N-(6'-methyl-3'-oxospiro[cyclopropane-1,7'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan]-5'-yl)ethane-1-sulfonamide was synthesized as described below (Compound 186).



Step 1. tert-butyl 3-(4-(1-aminocyclopropyl)butyl)piperidine-1-carboxylate

[000737] A solution of tert-butyl 3-(4-cyanobutyl)piperidine-1-carboxylate (700 mg, 2.63 mmol) and tetrakis(propan-2-yloxy)titanium (821 mg, 2.9 mmol) in THF (20 mL) was treated with Ethylmagnesium bromide (3.0M in Diethyl ether) (1.75 mL, 5.26 mmol) at room temperature for 2 h under nitrogen atmosphere. Then Boron trifluoride in diethyl ether solution (746 mg, 5.26 mmol) in THF (10 mL) added to the mixture at room temperature and the resulting mixture was stirred at room temperature for another 1 h. The reaction was quenched with 10% NaOH solution and extracted with EA (2 x 50 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous Na2SO4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA

/ PE 1 : 3 to afford tert-butyl 3-(4-(1-aminocyclopropyl)butyl)piperidine-1-carboxylate (300 mg, 78% yield). LCMS (ESI-MS) m/z = 297.2 $[M+H]^+$.

Step 2. tert-butyl 3-(4-(1-((4-(4-bromo-2-fluorobenzamido)-6-methylpyrimidin-2-yl)amino)cyclopropyl)butyl)piperidine-1-carboxylate

[000738] DIEA (436 mg, 3.37 mmol) was added to a mixture of tert-butyl 3-(4-(1-aminocyclopropyl)butyl)piperidine-1-carboxylate (250 mg, 0.84 mmol), Intermediate G (291 mg, 0.84 mmol) and KF (196 mg, 3.37 mmol) in Water (5 mL). The resulting mixture was stirred at 100 °C for 2 hours. The resulting mixture was diluted with water (100 ml) and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were dried over anhydrous sodium sulfate, concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA / PE 1 : 3 to afford tert-butyl 3-(4-(1-((4-(4-bromo-2-fluorobenzamido)-6-methylpyrimidin-2-yl)amino)cyclopropyl)butyl)piperidine-1-carboxylate (60 mg, 51% yield). LCMS (ESI-MS) m/z = 604.2 $[M+H]^+$.

Step 3. 4-bromo-2-fluoro-N-(6-methyl-2-((1-(4-(piperidin-3-yl)butyl)cyclopropyl)amino)pyrimidin-4-yl)benzamide

[000739] TFA (1 mL) was added to a solution of tert-butyl 3-(4-(1-((4-(4-bromo-2-fluorobenzamido)-6-methylpyrimidin-2-yl)amino)cyclopropyl)butyl)piperidine-1-carboxylate (60 mg, 0.099 mmol) in DCM (4 mL). The resulting mixture was stirred at room temperature for 2 hours. The resulting mixture was concentrated under vacuum to afford 4-bromo-2-fluoro-N-(6-methyl-2-((1-(4-(piperidin-3-yl)butyl)cyclopropyl)amino)pyrimidin-4-yl)benzamide (50 mg crude), LCMS (ESI-MS) m/z = 504.2 $[M+H]^+$.

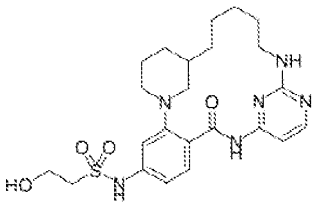
Step 4. 5'-bromo-6'-methylspiro[cyclopropane-1,7'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan]-3'-one

[000740] K_2CO_3 (41 mg, 0.30 mmol) was added to a mixture of 4-bromo-2-fluoro-N-(6-methyl-2-((1-(4-(piperidin-3-yl)butyl)cyclopropyl)amino)pyrimidin-4-yl)benzamide (50 mg, 0.099 mmol) in DMSO (5 mL). The resulting mixture was stirred at 140 °C for 2 hours before being concentrated under vacuum to afford 5'-bromo-6'-methylspiro[cyclopropane-1,7'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan]-3'-one (40 mg, crude), LCMS (ESI-MS) m/z = 484.2 $[M+H]^+$.

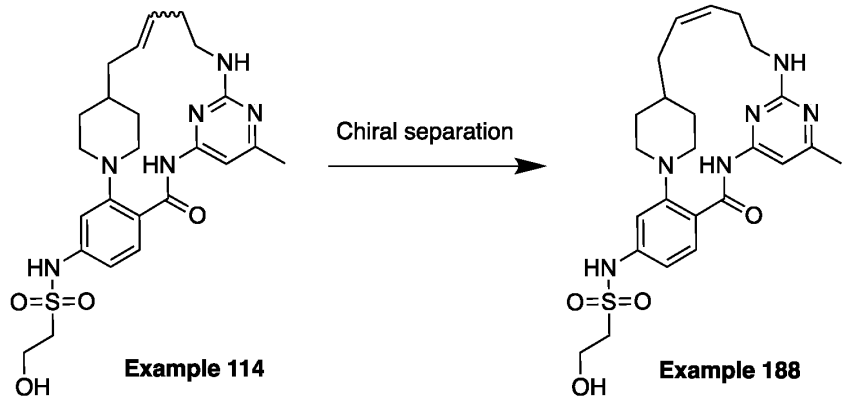
Step 5. 2-hydroxy-N-(6'-methyl-3'-oxospiro[cyclopropane-1,7'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan]-5'-yl)ethane-1-sulfonamide

[000741] Into a solution of 5'-bromo-6'-methylspiro[cyclopropane-1,7'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan]-3'-one (10 mg, 0.021 mmol) in DMSO (2 mL) was added 2-hydroxyethanesulfonamide (3.87 mg, 0.032 mmol) , t-BuXPhos Pd G3 (1.64 mg, 0.002 mmol) and K_2CO_3 (8.56 mg, 0.063 mmol). The resulting solution was stirred at 100 °C for 2 hours. After cooling to room temperature, the reaction mixture was diluted with water (5 mL), extracted with EA (5 mL x 2). The combined organic layers were washed with brine (2 x 5 mL), dried with anhydrous Na_2SO_4, evaporated under vacuum to give a crude. The residue was dissolved in MeOH, and purified with Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 35% B to 65% B in 7 min; Wave Length: 254nm/220nm nm; RT1(min): 6.68 to give 2-hydroxy-N-(6'-methyl-3'-oxospiro[cyclopropane-1,7'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan]-5'-yl)ethane-1-sulfonamide (1.8 mg), LCMS (ESI-MS) m/z = 529.3 $[M+H]^+$.

Example 187. 2-hydroxy-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-25-yl)ethane-1-sulfonamide was synthesized via General synthetic route 4A, from Intermediate H and tert-butyl 3-(5-aminopentyl)piperidine-1-carboxylate as described in the procedure for Example 62. 2-hydroxyethanesulfonamide was used as a nucleophile in step 4 (Compound 187)

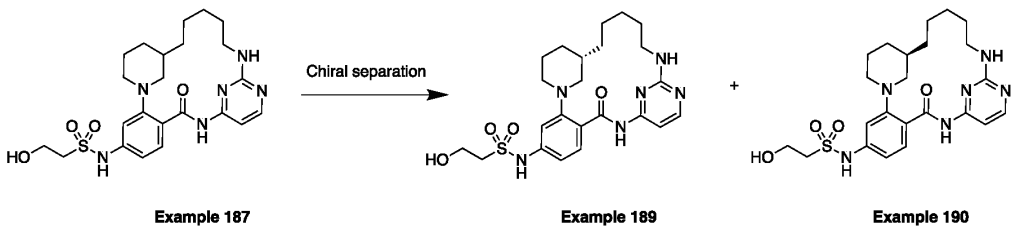


Example 188. (Z)-2-hydroxy-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide was synthesized by chiral separation of Example 114 step 4 material as described below (Compound 188).



[000742] Example 114 (100 mg, 0.20 mmol) was dissolved with MeOH and purified by Chiral-HPLC with the following conditions: Column: (R, R)-WHELK-O1-Kromasil, 2.12*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 40; Wave Length: 254/220nm nm; RT1(min): 9.105; RT2(min): 14.006; Sample Solvent: EtOH--HPLC; Injection Volume: 0.5 mL; Number Of Runs: 4 to afford (Z)-2-hydroxy-N-(56-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)ethane-1-sulfonamide (5.3 mg, 5.3% yield). LCMS (ESI-MS) m/z = 501.2 $[M+H]^+$.

Examples 189 and 190. 2-hydroxy-N-((1^{3}R)-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyc-loundecaphane-2^5-yl)ethane-1-sulfonamide and 2-hydroxy-N-((1^{3}S)-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide were prepared via chiral separation of Example 187 as described below (Compound 189 and compound 190 respectively).



[000743] Example 187 was separated by Prep-Chiral-HPLC with the following conditions: Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 50; Wave Length: 254/220nm nm; RT1(min): 6.606; RT2(min): 12.601; Sample Solvent: EtOH--HPLC; Injection Volume: 0.6 mL; Number of runs: 2 to afford two products:

[000744] First eluting isomer: enantiopure 2-hydroxy-*N*-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide, LCMS (ESI-MS) m/z = 489.2 [M+H]+.

[000745] Second eluting isomer: enantiopure 2-hydroxy-*N*-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide, LCMS (ESI-MS) m/z = 489.2 [M+H]+.

Table 26. KIF18A Biochemical data (2h assay) for Examples 189 and 190

Compound	**KIF18A ADP-Glo IC50, nM (2h)**
First eluting isomer	+++++
Second eluting isomer	++

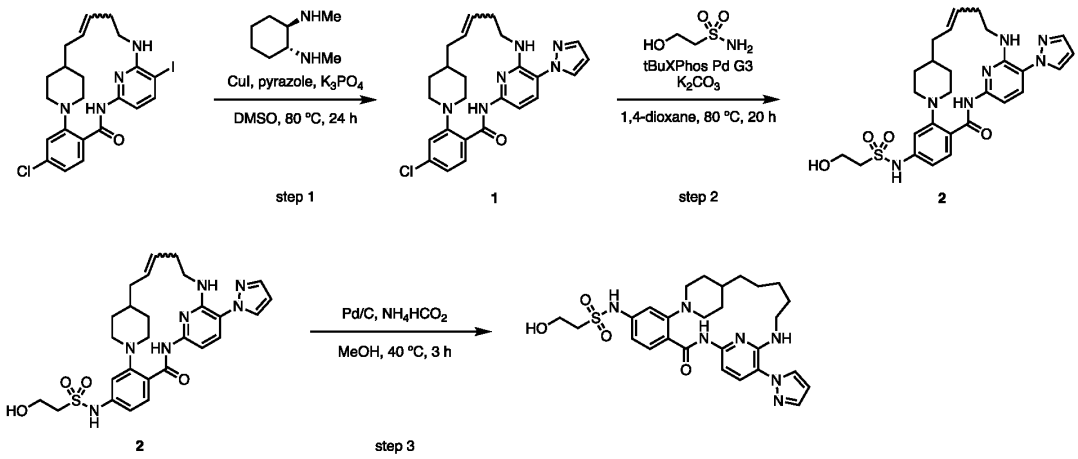
IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Table 26A KIF18A Biochemical data (24h assay) for Examples 189 and 190

Compound	**KIF18A ADP-Glo IC50, nM (24)**
First eluting isomer	+++++
Second eluting isomer	++++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 192. 2-hydroxy-*N*-(3-oxo-5^5-(1*H*-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide (Compound 192)



Step 1. 2^5-chloro-5^5-(1H-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one

[000746] To a vial was added 2^5-chloro-5^5-iodo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (40 mg, 77 μmol), CuI (7.3 mg, 38 μmol), *trans*-*N*,*N*'-dimethylcyclohexane-1,2-diamine HCl (6.8 mg, 38 μmol), K_3PO_4 (57 mg, 0.27 mmol) and DMSO (3.0 mL) under N_2. The reaction was then heated to 80 °C. After 24 hour, the reaction mixture was diluted with EtOAc and washed with water, then brine (3 x), dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-30% EtOAc in heptane) provided 2^5-chloro-5^5-(1*H*-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (24.6 mg, 69 %). LCMS (ESI-MS) m/z = 463.1 $[M+H]^+$.

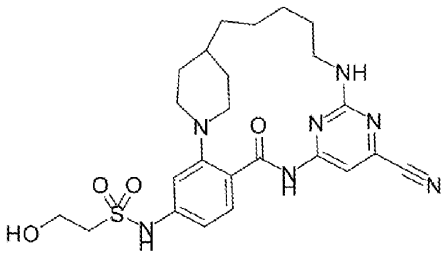
Step 2. 2-hydroxy-*N*-(3-oxo-5^5-(1*H*-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide

[000747] To a vial was added 2^5-chloro-5^5-(1*H*-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (24 mg, 52 μmol), tBuXPhos Pd G3 (4.1 mg, 5.2 μmol), 2-hydroxyethane-1-sulfonamide (49 mg, 0.39 mmol), and K_2CO_3 (21 mg, 0.16 mmol). The reaction vial was placed under a N_2 atmosphere and 1,4-dioxane (1.0 mL) was added. The reaction mixture was then heated to 80 °C. After 1.5 hour, the reaction was cooled to rt, diluted with EtOAc, filtered through celite, and concentrated. Purification via prepHPLC (10-100% MeCN in H_2O with 0.1% TFA) followed by neutralization and extraction provided 2-hydroxy-*N*-(3-oxo-5^5-(1*H*-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide (17 mg, 59 %). LCMS (ESI-MS) m/z = 552.2 $[M+H]^+$.

Step 3. 2-hydroxy-*N*-(3-oxo-5^5-(1*H*-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide

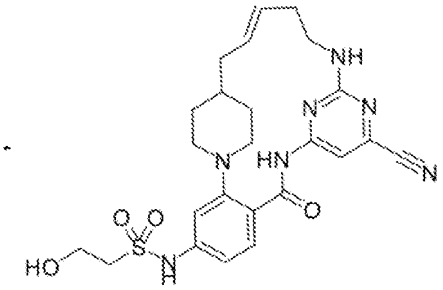
[000748] To a vial was added 2-hydroxy-N-(3-oxo-5^5-(1*H*-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide (17 mg, 31 μmol), Pd/C (8.2 mg, 10% Wt, 7.7 μmol), ammonium formate (58 mg, 0.92 mmol), and MeOH (2.0 mL). The reaction mixture was then heated to 40 °C. After 3 hour, the reaction mixture was cooled to rt, diluted with EtOAc, filtered through celite, and concentrated. Purification via prepHPLC (10-100% MeCN in H_2O with 0.1% TFA) followed by neutralization and extraction provided 2-hydroxy-*N*-(3-oxo-5^5-(1*H*-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide (11 mg, 63 %). LCMS (ESI-MS) m/z = 554.2 $[M+H]^+$.

Example 191. N-(5^6-cyano-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide was synthesized from Example 193 following the same procedure as described in Step 5 of Example 184. (Compound 191)

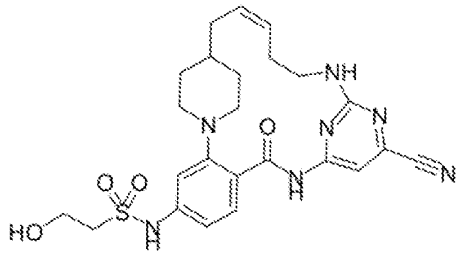


Examples 193 and 194. (E)-N-(5^6-cyano-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide & (Z)-N-(5^6-cyano-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide were synthesized from Intermediate AJ and Intermediate W using General synthetic route 7B, steps 1-4

and the procedure described for example 140, except conditions for Step 1 were the same as for preparing Intermediate G (Compound 193 and Compound 194 respectively).

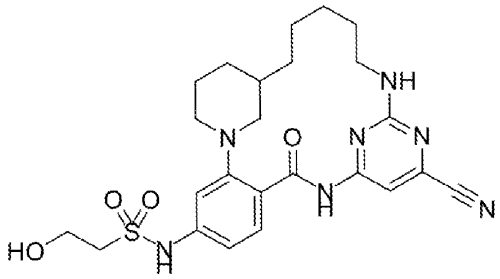


Example 193



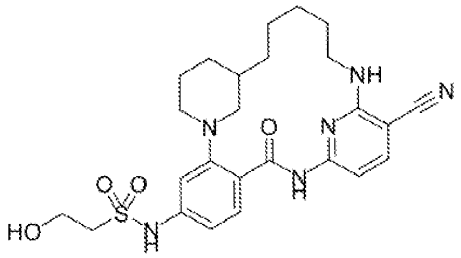
Example 194

Example 195. N-(5^6-cyano-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide was synthesized from Intermediate Y and tert-butyl 3-(5-aminopentyl)piperidine-1-carboxylate following General synthetic route 4A and the procedure described for Example 62 (Compound 195).

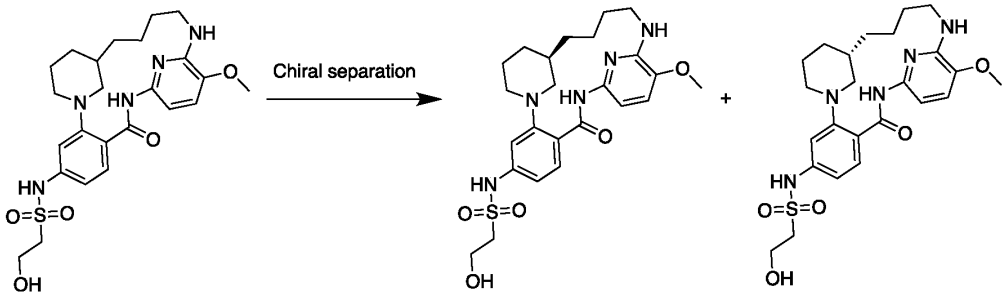


Example 196. *N*-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide was synthesized from Intermediate P and tert-butyl 3-(5-aminopentyl)piperidine-1-carboxylate following

General synthetic route 4A and the procedure described for Example 18 (Compound 196).



Examples 197 and 198. 2-hydroxy-N-((1^{3}R)-5^5-methoxy-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide & 2-hydroxy-N-((1^{3}S)-5^5-methoxy-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide were prepared by Chiral separation of Example 118 as described below (Compound 197 and compound 198 respectively).



Example 118 Example 197 Example 198

[000749] 2-hydroxy-N-(5^5-methoxy-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide (29 mg, 0.058 mmol) was dissolved with MeOH and purified by Chiral-prep-HPLC with the following conditions: Column: (R, R)-WHELK-O1-Kromasil, 2.12*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 70; Wave Length: 254/220nm nm; RT1(min): 5.123; RT2(min): 8.613; Sample Solvent: EtOH--HPLC; Injection Volume: 2.0 mL; Number Of Runs: 2 to afford the two products:

First eluting isomer:

[000750] Enantiopure 2-hydroxy-N-(5^5-methoxy-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide (5.12 mg, 17.5%). LCMS (ESI-MS) m/z = 504.2 $[M+H]^+$.

Second eluting isomer:

[000751] Enantiopure 2-hydroxy-N-(5^5-methoxy-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphane-2^5-yl)ethane-1-sulfonamide (4.67 mg, 16.1%). LCMS (ESI-MS) m/z = 504.2 $[M+H]^+$.

Table 27. KIF18A Biochemical data (2h assay) for Examples 197 and 198

Compound	**KIF18A ADP-Glo IC50, nM (2h)**
First eluting isomer	+
Second eluting isomer	++++

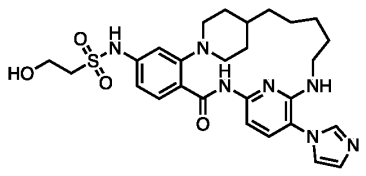
IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Table 27A. KIF18A Biochemical data (24h assay) for Examples 197 and 198

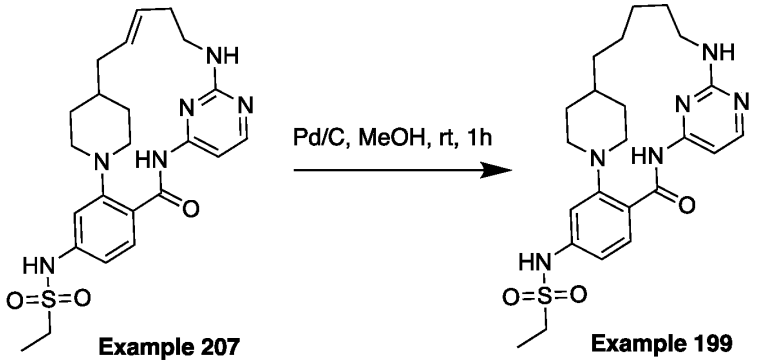
Compound	**KIF18A ADP-Glo IC50, nM (24h)**
First eluting isomer	+++
Second eluting isomer	++++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 200. *N*-(5^5-(1*H*-imidazol-1-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide was synthesized following the procedure for example 192 using imidazole in step 1. (Compound 200)



Example 199. (N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-25-yl)ethanesulfonamide was synthesized from Example 207 as described below (Compound 199).

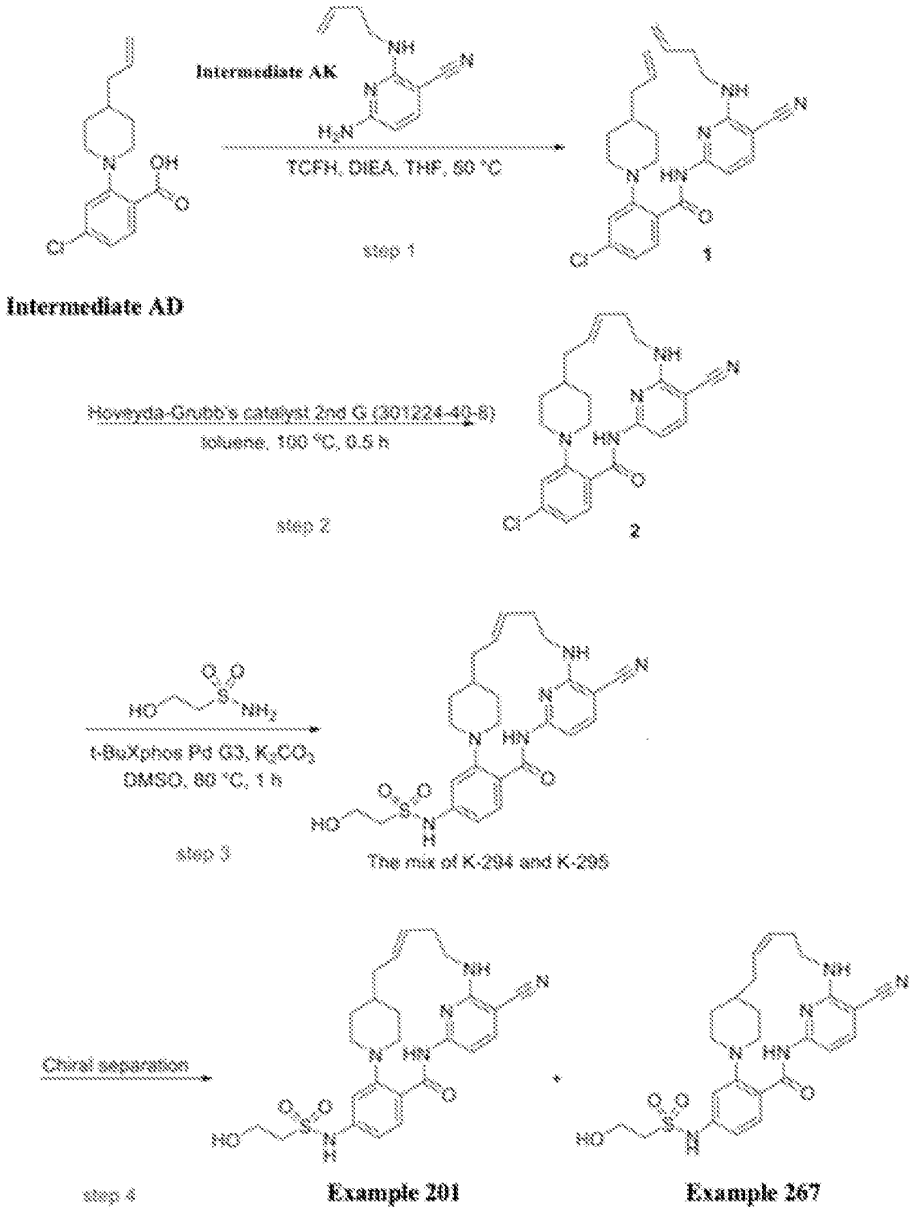


Example 207 **Example 199**

[000752] Pd/C (25 mg, 10% Pd on carbon) was added to Example 207 (15 mg, 0.032 mmol) in MeOH (1 mL). The reaction mixture was stirred at room temperature for 1 hour under hydrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with MeOH (3 x 10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions:Column: XBridge Prep Shield RP18 OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10nmol/LNH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 44% B to74 % B in 10 min; Wave Length: 254nm/220nm nm; RT1(min): 9.07 to afford (N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-25-yl)ethanesulfonamide (2.6 mg, 17.26% yield). LCMS (ESI-MS) m/z = 473.2 [M+H]+.

Examples 201 and 267. (E)-N-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide and (Z)-N-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide were synthesized

from Intermediate AD and intermediate AK following General synthetic route 8 as described below (Compound 201 and Compound 267 respectively).



1. **2-(4-allylpiperidin-1-yl)-N-(6-(but-3-en-1-ylamino)-5-cyanopyridin-2-yl)-4-chlorobenzamide**

[000753] DIEA (3 g, 0.02 mol) was added to the mixture of Intermediate AD (2 g, 7 mmol), Intermediate AK (1 g, 7 mmol) and N,N,N',N'-Tetramethylchloroformamidinium-hexafluor (3 g, 0.01 mol) in THF (20 mL). The mixture was stirred at 50 °C for 1 hour. The reaction mixture was diluted with water (60 mL). The resulting mixture was extracted with EA (3 x 60 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA / PE 1:4 to afford 2-(4-allylpiperidin-1-yl)-N-(6-(but-3-en-1-ylamino)-5-cyanopyridin-2-yl)-4-chlorobenzamide (1.5 g, 50.0 % yield). LCMS (ESI-MS) m/z =450.2 $[M+H]^+$.

2. **2^5-chloro-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-ene-5^5-carbonitrile**

[000754] Dichloro(1,3-dimesityl-2-imidazolidinylidene)(2-isopropoxybenzylidene)ruthenium (0.19 g, 0.31 mmol) was added to 2-(4-allylpiperidin-1-yl)-N-(6-(but-3-en-1-ylamino)-5-cyanopyridin-2-yl)-4-chlorobenzamide (1.4 g, 3.1 mmol) in toluene (1 mL) under nitrogen atmosphere. The mixture was stirred at 100°C for 0.5 hour. The reaction mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with EA / PE 1 : 10 to afford 2^5-chloro-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-ene-5^5-carbonitrile (700 mg, 53.0 % yield). LCMS (ESI-MS) m/z =422.2 $[M+H]^+$.

3. **N-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide**

[000755] tBuXPhos Pd G3 (73.8 mg, 83.0 μmol) was added to the mixture of 2-hydroxyethane-1-sulfonamide (311 mg, 2.49 mmol) and 2^5-chloro-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-ene-5^5-carbonitrile (350 mg, 0.83 mmol) in DMSO (4 mL) under nitrogen atmosphere. The mixture was stirred at 80 °C for 1 hour. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with EA (3 x 30 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with MeOH / DCM 1:10 to afford N-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide (200 mg, 47.2 % yield). LCMS (ESI-MS) m/z =511.2 $[M+H]^+$.

4. **(E)-N-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-**

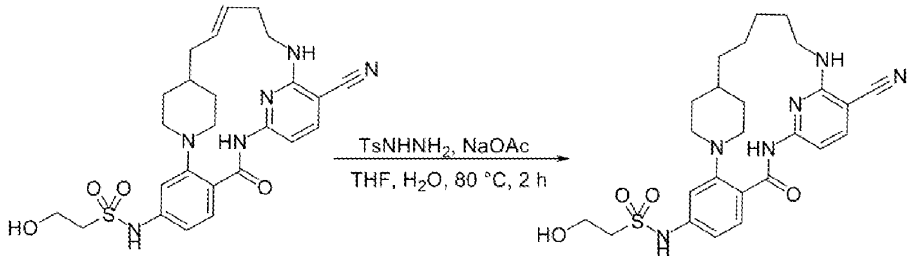
benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide and (Z)-N-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide

[000756] N-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide (200 mg,0.39 mmol) was purified by Prep-Chiral-HPLC with the following conditions (Column: (R, R)-WHELK-O1-Kromasil, 2.12*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)-HPLC, Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 40; Wave Length: 254/220nm nm; RT1(min): 10.351; RT2(min): 15.526; Sample Solvent: EtOH--HPLC; Injection Volume: 2.2 mL; Number Of Runs: 10) to afford

[000757] First eluting isomer: (E)-N-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide (78.8 mg, 38.1 % yield). LCMS (ESI-MS) m/z =511.2 $[M+H]^+$.

[000758] Second eluting isomer: (Z)-N-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide (27.6 mg, 13.7 %,) as an off-white solid. LCMS (ESI-MS) m/z =511.2 $[M+H]^+$.

Example 202. N-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide was prepared from Example 238 using the procedure described below (Compound 202).

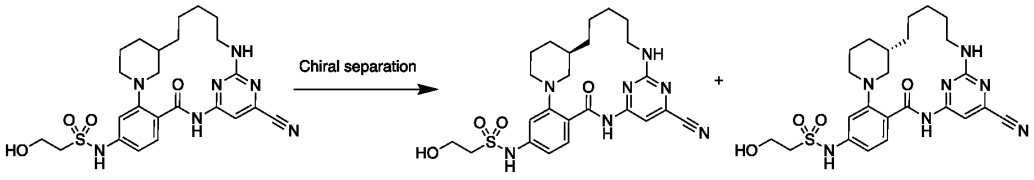


Example 238 **Example 202**

[000759] (E)-2^5-bromo-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-ene-5^5-carbonitrile (6 mg, 0.012 mmol) was added 4-methylbenzenesulfonohydrazide (7 mg, 0.036 mmol) and NaOAc (3 mg, 0.036 mmol) in THF (1 mL) and H_2O (1 mL). The resulting solution was heated to 80 °C and stirred for 2 hours. The residue was purified by reversed-phase flash chromatography with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min;

Gradient: 41% B to 71% B in 8min; Wave Length: 254nm/220nm nm; RT1(min): 6.55 to afford N-(5[5]-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2[5]-yl)-2-hydroxyethane-1-sulfonamide (1.03 mg, 17.1% yield). LCMS (ESI-MS) m/z = 513.2 $[M+H]^+$.

Examples 203 and 204. N-((1[3]R)-5[6]-cyano-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2[5]-yl)-2-hydroxyethane-1-sulfonamide & N-((1[3]S)-5[6]-cyano-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2[5]-yl)-2-hydroxyethane-1-sulfonamide were prepared by Chiral separation of Example 195 as described below (Compound 203 and compound 204 respectively)



Example 195 Example 203 Example 204

[000760] N-(5[6]-cyano-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2[5]-yl)-2-hydroxyethane-1-sulfonamide (98 mg, 0.191 mmol) was dissolved in MeOH and purified with the following conditions: Column: CHIRALPAK IM, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 40; Wave Length: 254/220nm nm; RT1(min): 9.352; RT2(min): 12.575; Sample Solvent: EtOH--HPLC; Injection Volume: 1.4 mL; Number Of Runs: 6 to afford:

[000761] First eluting isomer: Enantiopure N-(5[6]-cyano-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2[5]-yl)-2-hydroxyethane-1-sulfonamide (32.1 mg, 32.2% yield), LCMS (ESI-MS) m/z = 514.2 $[M+H]^+$.

[000762] Second eluting isomer: Enantiopure N-(5[6]-cyano-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2[5]-yl)-2-hydroxyethane-1-sulfonamide (28.2 mg, 28.5% yield), LCMS (ESI-MS) m/z = 514.2 $[M+H]^+$.

Table 28. KIF18A Biochemical data (2h assay) for Examples 203 and 204

Compound	**KIF18A ADP-Glo IC50, nM (2h)**
First eluting isomer	+
Second eluting isomer	+++++

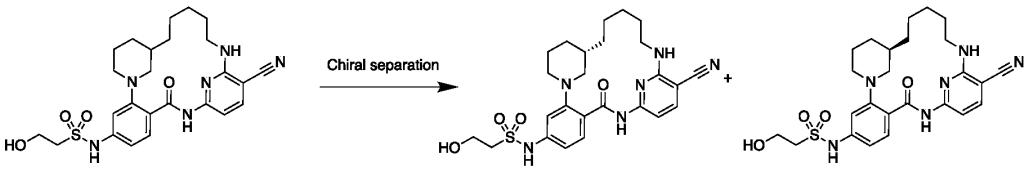
IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Table 28A. KIF18A Biochemical data (24h assay) for Examples 203 and 204

Compound	**KIF18A ADP-Glo IC50, nM (24h)**
First eluting isomer	+
Second eluting isomer	+++++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Examples 205 and 206. *N*-((13*R*)-5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide and *N*-((13*S*)-5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide benzenacyclodecaphan-3-one were prepared by Chiral separation of Example 196 as described below (Compound 205 and compound 206 respectively)



Example 196 Example 205 Example 206

[000763] *N*-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide (30 mg, 0.059 mmol) was dissolved with MeOH and purified by Chiral-prep-HPLC with the following conditions: Column: CHIRALPAKIG3; Mobile Phase A: Hex(0.2%FA): (EtOH: DCM=1: 1)=40: 60; Flow rate: 1mL/min mL/min; Gradient: isocratic ; Injection Volume: 1µl mL to afford the two products:

[000764] First eluting isomer: Enantiopure *N*-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide (10.9 mg, 36.3% yield), LCMS (ESI-MS) m/z = 513.6 $[M+H]^+$.

[000765] Second eluting isomer: Enantiopure *N*-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide (13.3 mg, 44.3% yield) LCMS (ESI-MS) m/z = 513.6 [M+H].

Table 29. KIF18A Biochemical data (2h assay) for Examples 205 and 206

Compound	KIF18A ADP-Glo IC50, nM (2h)
First eluting isomer	+++++
Second eluting isomer	+

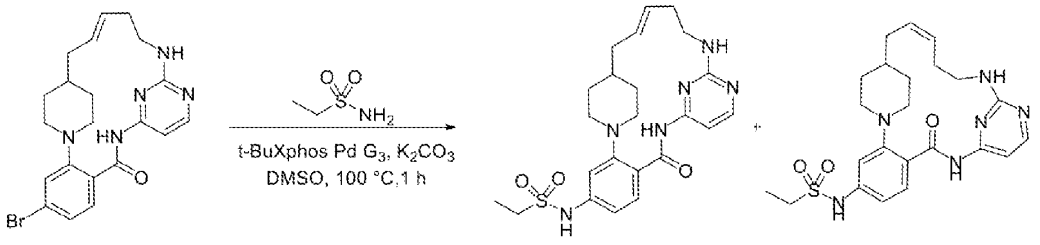
IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Table 29A. KIF18A Biochemical data (24h assay) for Examples 205 and 206

Compound	KIF18A ADP-Glo IC50, nM (24h)
First eluting isomer	+++++
Second eluting isomer	NA

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Examples 207 and 209. (E)-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide and (Z)-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide were synthesized from Intermediate AA and Intermediate R via General synthetic route 7A (Steps 1-4) following same procedures as described in Example 114. E- and Z- isomers of the final product were separated as described below. (Compound 207 and compound 209 respectively).



Example 207 **Example 209**

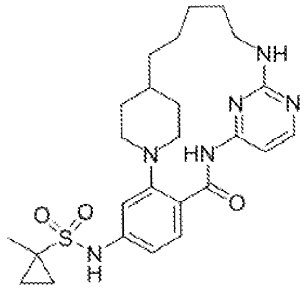
[000766] t-BuXPhos Pd G3 (17 mg, 0.023 mmol, 0.10 equiv) was added to a mixture of 2^5-bromo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (100 mg, 0.226 mmol) and K_2CO_3 (93 mg, 0.67 mmol) in DMSO (2 mL) under nitrogen atmosphere. The mixture was stirred at 100°C for 1 hour. The mixture was allowed to cool

down to room temperature. The reaction mixture was purified by Prep-HPLC with the following conditions: Column: X-Bridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 36% B to 66% B in 8min; Wave Length: 254nm/220nm nm; RT1(min): 6.92 to afford the mixture product. The mixture was purified by Prep-Chiral HPLC with the following conditions: Column: (R, R)-WHELK-O1-Kromasil, 2.12*25 cm, 5 μm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 40; Wave Length: 254/220nm nm; RT1(min): 10.576; RT2(min): 14.466; Sample Solvent: EtOH--HPLC; Injection Volume: 0.8 mL; Number of Runs: 4 to afford to products:

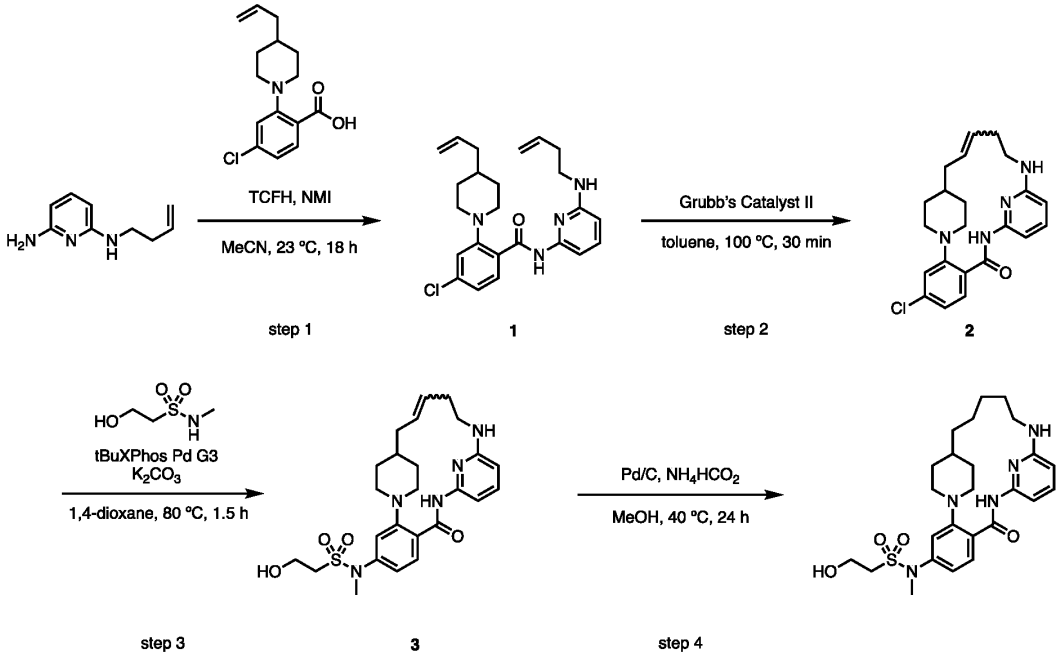
[000767] First eluting isomer: (E)-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl) ethanesulfonamide, LCMS (ESI-MS) m/z = 471.1 [M+H]+.

[000768] Second eluting isomer: (Z)-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl) ethanesulfonamide, LCMS (ESI-MS) m/z = 489.2 [M+H]+.

Example 208. 1-methyl-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzena-cyclounde-caphane-25-yl)cyclopropane-1-sulfonamide was synthesized from Example 247 as described in the procedure for Example 199 (Compound 208).



Example 210. 2-hydroxy-*N*-methyl-*N*-(3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide (Compound 210)



Step 1. 2-(4-allylpiperidin-1-yl)-*N*-(6-(but-3-en-1-ylamino)pyridin-2-yl)-4-chlorobenzamide

[000769] To a vial was added 2-(4-allylpiperidin-1-yl)-4-chlorobenzoic acid (663 mg, 2.37 mmol), *N*^{2}-(but-3-en-1-yl)pyridine-2,6-diamine (464 mg, 2.84 mmol), *N*-(chloro(dimethylamino)methylene)-*N*-methylmethanaminium hexafluorophosphate(V) (997 mg, 3.55 mmol), 1-Methylimidazole (681 mg, 8.29 mmol), and MeCN (10 mL). The reaction mixture was then stirred at rt. After 18 hour the reaction mixture was quenched with water and diluted with EtOAc. The organic layer was separated and washed with brine, dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-10% EtOAc on heptane) provided 2-(4-allylpiperidin-1-yl)-*N*-(6-(but-3-en-1-ylamino)pyridin-2-yl)-4-chlorobenzamide (599 mg, 59.5 %).

Step 2. 2^5-chloro-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one

[000770] A solution of 2-(4-allylpiperidin-1-yl)-*N*-(6-(but-3-en-1-ylamino)pyridin-2-yl)-4-chlorobenzamide (600 mg, 1.41 mmol) and Benzylidene(dichloro)(1,3-dimesityl-2-imidazolidinylidene)ruthenium - tricyclohexylphosphine (1:1) (240 mg, 282 μmol) in toluene (10.0 mL) was slowly added dropwise to toluene (40.0 mL) preheated to 100 °C under N_2 atmosphere. After 30 min the reaction mixture was diluted with EtOAc and washed with water,

brine, dried over MgSO4, and concentrated. Purification via Isco column chromatography (0-20% EtOAc on heptane) provided 2^5-chloro-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (179 mg, 31.9 %)

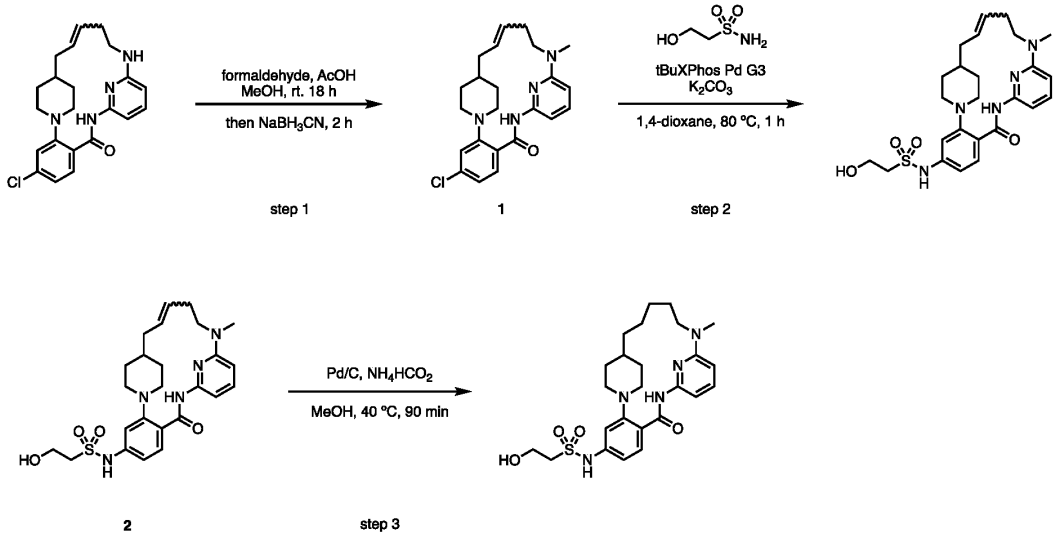
Step 3. 2-hydroxy-*N*-methyl-*N*-(3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide

[000771] To a vial was added 2^5-chloro-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (60 mg, 0.15 mmol), tBuXPhos Pd G3 (12 mg, 15 μmol), 2-hydroxy-N-methylethane-1-sulfonamide (0.16 g, 1.1 mmol), and K_2CO_3 (63 mg, 0.45 mmol). The reaction was placed under a N_2 atmosphere and 1,4-Dioxane (1.50 mL) was added. The reaction mixture was then heated to 80 °C. After 90 min, the reaction mixture was diluted with EtOAc, washed with sat. aq. $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated. The crude material was used for the next step without further purification. LCMS (ESI-MS) m/z = 500.1 $[M+H]^+$.

Step 4. 2-hydroxy-*N*-methyl-*N*-(3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide

[000772] To a vial was added 2-hydroxy-*N*-methyl-*N*-(3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide (76 mg, 0.15 mmol), Pd/C (40 mg, 10% Wt, 38 μmol), ammonium formate (0.38 g, 6.1 mmol), and MeOH (4.0 mL). The reaction mixture was then heated to 40 °C. After 24 hour, the reaction mixture was cooled to rt, diluted with EtOAc, filtered through celite, and concentrated. Purification by prepHPLC (10-100% MeCN in 0.1% TFA water) followed by Isco column chromatography (0-100% EtOAc in heptane) provided 2-hydroxy-*N*-methyl-*N*-(3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide (34.1 mg, 44 %). LCMS (ESI-MS) m/z = 502.2 $[M+H]^+$.

Example 211. 2-hydroxy-*N*-(6-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide (Compound 211)



Step 1. 2^5-chloro-6-methyl-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one

[000773] A solution of 2^5-chloro-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (120 mg, 302 μmol), acetic acid (36.3 mg, 34.6 μL, 605 μmol), and formaldehyde (491 mg, 450 μL, 37% Wt, 6.05 mmol) in MeOH (2.0 mL) was stirred at rt. After 18 hour sodium cyanoborohydride (95.0 mg, 1.51 mmol) was added. After 2 hour, the reaction mixture was quenched with 1.0 M aq. NaOH and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-10% EtOAc in heptane) provided 2^5-chloro-6-methyl-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (21 mg, 17 %). LCMS (ESI-MS) m/z = 411.1 $[M+H]^+$.

Step 2. 2-hydroxy-*N*-(6-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide

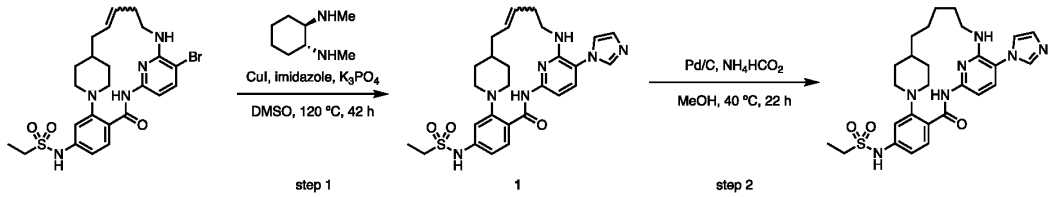
[000774] To a vial was added 2^5-chloro-6-methyl-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (21 mg, 51 μmol), tBuXPhos Pd G3 (4.1 mg, 5.1 μmol), 2-hydroxyethane-1-sulfonamide (48 mg, 0.38 mmol), and K_2CO_3 (21 mg, 0.15 mmol). The reaction vial was placed under a N_2 atmosphere and 1,4-Dioxane (2.0 mL) was added. The reaction mixture was then heated to 80 °C. After 1 hour, the reaction mixture was cooled to rt, diluted with EtOAc, filtered through celite, and concentrated. Purification via prepHPLC (10-100% MeCN in H_2O with 0.1% TFA) followed by neutralization and extraction provided 2-hydroxy-N-(6-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-

benzenacycloundecaphan-9-en-25-yl)ethane-1-sulfonamide (9 mg, 40 %). LCMS (ESI-MS) m/z = 500.2 $[M+H]^+$.

Step 3. 2-hydroxy-*N*-(6-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide

[000775] To a vial was added 2-hydroxy-*N*-(6-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide (9.0 mg, 18 μmol), Pd/C (9.6 mg, 10% Wt, 9.0 μmol), ammonium formate (45 mg, 0.72 mmol), and MeOH (1.0 mL). The reaction mixture was then heated to 40 °C. After 90 min, the reaction mixture was cooled to rt, diluted with EtOAc, filtered through celite, and concentrated. Purification by prepHPLC (10-100% MeCN in 0.1% TFA water) followed by Isco column chromatography (0-100% EtOAc in heptane) provided 2-hydroxy-*N*-(6-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide (8.6 mg, 91 %). LCMS (ESI-MS) m/z = 502.2 $[M+H]^+$.

Example 212. *N*-(5^5-(1*H*-imidazol-1-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethanesulfonamide. (Compound 212)



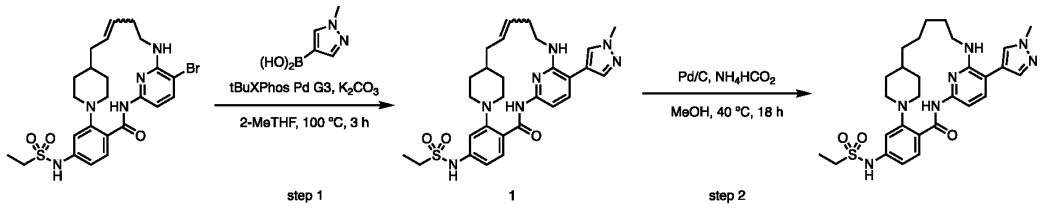
Step 1. *N*-(5^5-(1H-imidazol-1-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide

[000776] To a vial was added *N*-(5^5-bromo-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (36 mg, 66 μmol), CuI (12 mg, 66 μmol), trans-(1*R*,2*R*)-*N*,*N*'-Bismethyl-1,2-cyclohexanediamine HCl (12 mg, 66 μmol), K_3PO_4 (42 mg, 16 μL, 0.20 mmol), and DMSO (1.0 mL) under a N_2 atmosphere. The reaction mixture was then heated to 100 °C. After 18 hour, the reaction mixture was diluted with water and extracted with DCM (3 x). The combined organic layers were washed with brine (3 x), dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-40% EtOAc in heptane) provided *N*-(5^5-(1*H*-imidazol-1-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (12 mg, 34 %). LCMS (ESI-MS) m/z = 536.2 $[M+H]^+$.

Step 2. *N*-(5^5-(1*H*-imidazol-1-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethanesulfonamide

[000777] To a vial was added *N*-(5^5-(1*H*-imidazol-1-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (11 mg, 21 μmol), Pd/C (5.5 mg, 10% Wt, 5.1 μmol), ammonium formate (52 mg, 0.82 mmol), and MeOH (2.0 mL). The reaction mixture was then heated to 40 °C. After 22 hour, the reaction mixture was filtered through a syringe filter and purified directly via prepHPLC (10-100% MeCN in water with 0.1% TFA) followed by lyophilization to provide *N*-(5^5-(1*H*-imidazol-1-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethanesulfonamide 2,2,2-trifluoroacetate (4.0 mg, 29 %). LCMS (ESI-MS) m/z = 538.2 $[M+H]^+$.

Example 213. *N*-(5^5-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethanesulfonamide. (Compound 213)



Step 1. *N*-(5^5-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide

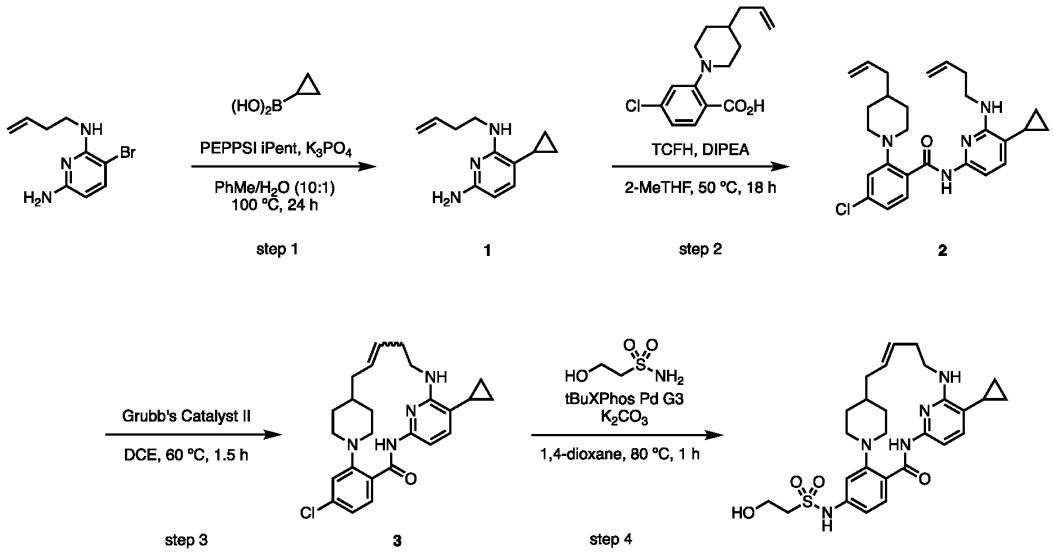
[000778] To a vial was added *N*-(5^5-bromo-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (20.0 mg, 36.5 μmol), tBuXPhos Pd G3 (2.90 mg, 65 μmol), 1-methylpyrazole-4-boronic acid (13.8 mg, 109 μmol), and 2-MeTHF (1.0 mL) under N_2 atmosphere. K_3PO_4 (1.0 M aq. solution) (23.2 mg, 109 μL, 109 μmol) was added via syringe through the septum. The reaction mixture was then heated to 100 °C. After 3 h, the reaction mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The crude residue was used for the next step without further purification. LCMS (ESI-MS) m/z = 550.2 $[M+H]^+$.

Step 2. *N*-(5^5-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethanesulfonamide

[000779] To a vial was added *N*-(5^5-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (20 mg, 36 μmol), Pd/C (9.7 mg, 10% Wt, 9.1 μmol), ammonium formate (92 mg, 1.5 mmol), and MeOH (2.0 mL). The reaction mixture was then heated to 40 °C. After 18 hour, the reaction mixture was cooled to rt, diluted with sat. aq. $NaHCO_3$ and extracted with EtOAc (3 x). The

combined organic layers were washed with brine, filtered through celite, and concentrated. Purification via prepHPLC (10-100% MeCN in water with 0.1% TFA) followed by lyophilization provided *N*-(5^5-(1-methyl-1*H*-pyrazol-4-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethanesulfonamide 2,2,2-trifluoroacetate (8.9 mg, 36 %). LCMS (ESI-MS) m/z = 552.2 $[M+H]^+$.

Example 214. (*E*)-*N*-(5^5-cyclopropyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide. (Compound 214)



Step 1. *N*^{2}-(but-3-en-1-yl)-3-cyclopropylpyridine-2,6-diamine

[000780] To a vial was added 3-bromo-*N*^{2}-(but-3-en-1-yl)pyridine-2,6-diamine (500 mg, 2.07 mmol), PEPPSI iPent (81.7 mg, 103 μmol), cyclopropylboronic acid (532 mg, 6.20 mmol), and K_3PO_4 (1.32 g, 6.20 mmol). The vial was placed under a N_2 atmosphere and degassed toluene/water (22.0 mL, 10:1 ratio) was added via syringe. The reaction was then heated to 100 °C. After 24 hour, the reaction mixture was diluted with aq. $NaHCO_3$ and extracted with EtOAc (3 x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-50% EtOAc on heptane) provided *N*^{2}-(but-3-en-1-yl)-3-cyclopropylpyridine-2,6-diamine (234 mg, 55.7 %). LCMS (ESI-MS) m/z = 204.2 $[M+H]^+$.

Step 2. 2-(4-allylpiperidin-1-yl)-*N*-(6-(but-3-en-1-ylamino)-5-cyclopropylpyridin-2-yl)-4-chlorobenzamide

[000781] To a vial was added 2-(4-allylpiperidin-1-yl)-4-chlorobenzoic acid (293 mg, 1.05 mmol), *N*^{2}-(but-3-en-1-yl)-3-cyclopropylpyridine-2,6-diamine (234 mg, 1.15 mmol), *N*-

(chloro(dimethylamino)methylene)-*N*-methylmethanaminium hexafluorophosphate(V) (382 mg, 1.36 mmol), DIPEA (271 mg, 365 µL, 2.09 mmol), and 2-MeTHF (8.0 mL). The reaction mixture was then stirred at 50 °C. After 18 hour the reaction mixture was quenched with 1 M aq. NaOH, diluted with water, and extracted with EtOAc (3 x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-50% EtOAc on heptane) provided 2-(4-allylpiperidin-1-yl)-*N*-(6-(but-3-en-1-ylamino)-5-cyclopropylpyridin-2-yl)-4-chlorobenzamide (95 mg, 20 %). LCMS (ESI-MS) m/z = 465.2 $[M+H]^+$.

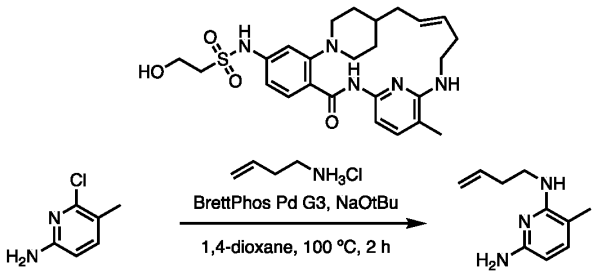
Step 3. 2^5-chloro-5^5-cyclopropyl-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one

[000782] To a vial was added 2-(4-allylpiperidin-1-yl)-*N*-(6-(but-3-en-1-ylamino)-5-cyclopropylpyridin-2-yl)-4-chlorobenzamide (95 mg, 0.20 mmol) and Benzylidene(dichloro)(1,3-dimesityl-2-imidazolidinylidene)ruthenium - tricyclohexylphosphine (1:1) (17 mg, 20 µmol). The reaction vial was placed under a N_2 atmosphere and DCE (14.0 mL) was added. The reaction mixture was then heated to 60 °C. After 1.5 hour, reaction was cooled to rt and washed with aq. $NaHCO_3$, then brine, dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-50% EtOAc on heptane) provided 2^5-chloro-5^5-cyclopropyl-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (45.9 mg, 51 %). LCMS (ESI-MS) m/z = 437.2 $[M+H]^+$.

Step 4. (*E*)-*N*-(5^5-cyclopropyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide

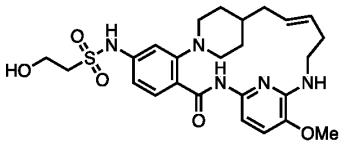
[000783] To a vial was added 2^5-chloro-5^5-cyclopropyl-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (46 mg, 0.11 mmol), tBuXPhos Pd G3 (8.4 mg, 11 µmol), 2-hydroxyethane-1-sulfonamide (99 mg, 0.79 mmol), and K_2CO_3 (44 mg, 0.32 mmol). The reaction was placed under a N_2 atmosphere and 1,4-Dioxane (2.0 mL) was added. The reaction mixture was then heated to 80 °C. After 1 hour, the reaction mixture was cooled to rt, diluted with EtOAc, filtered through celite, and concentrated. Purification via prepHPLC (10-100% MeCN in H_2O with 0.1% TFA) followed lyophilization provided (*E*)-*N*-(5^5-cyclopropyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide (15.1 mg, 27 %). LCMS (ESI-MS) m/z = 526.2 $[M+H]^+$.

Example 215 was synthesized using the same procedure as Example 214 with N^2-(but-3-en-1-yl)-3-methylpyridine-2,6-diamine for step 2, whose synthesis as step 1 is described below. (Compound 215)

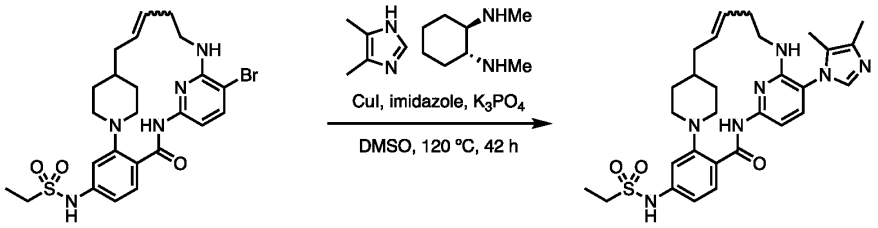


[000784] To a vial was added 3-Buten-1-amine, hydrochloride (453 mg, 4.21 mmol), 6-chloro-5-methyl-pyridin-2-amine (400 mg, 2.81 mmol), BrettPhos-Pd-G3 (127 mg, 140 µmol), and sodium tertbutoxide (809 mg, 8.42 mmol). The reaction mixture was placed under a N_2 atmosphere and 1,4-Dioxane (15 mL) was added. The reaction mixture was then heated to 100 °C. After 2 hour, the reaction mixture was quenched with aq. $NaHCO_3$ and extracted with EtOAc (3 x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-60% EtOAc in heptane) provided N^2-(but-3-en-1-yl)-3-methylpyridine-2,6-diamine (58 mg, 12 %). LCMS (ESI-MS) m/z = 178.1 $[M+H]^+$.

Example 216 was synthesized using the same procedure as Example 215 with 6-chloro-5-methoxypyridin-2-amine for step 1 and N^2-(but-3-en-1-yl)-3-methoxypyridine-2,6-diamine for step 2. (Compound 216)

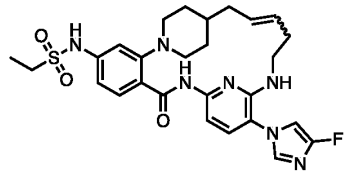


Example 217. *N*-(5^5-(4,5-dimethyl-1*H*-imidazol-1-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (Compound 217)

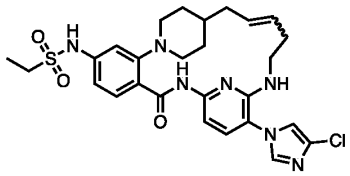


[000785] To a vial was added *N*-(5^5-bromo-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (23 mg, 42 μmol), 4,5-dimethyl-1*H*-imidazole (12 mg, 0.13 mmol), CuI (8.0 mg, 42 μmol), trans-(1*R*,2*R*)-*N*,*N*'-Bismethyl-1,2-cyclohexanediamine (6.0 mg, 42 μmol), and DMSO (0.20 mL). The reaction mixture was then heated to 120 °C. After 64 h, the reaction mixture was cooled to rt, filtered, and purified via prepHPLC (10-100% MeCN in H_2O with 0.1% TFA) followed by lyophilization to provide *N*-(5^5-(4,5-dimethyl-*1H*-imidazol-1-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (0.73 mg, 3.1 %). LCMS (ESI-MS) m/z = 564.3 $[M+H]^+$.

Example 218. *N*-(5^5-(4-fluoro-1*H*-imidazol-1-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide was synthesized following the same procedure as Example 217 with 4-fluoro-1*H*-imidazole. (Compound 218)

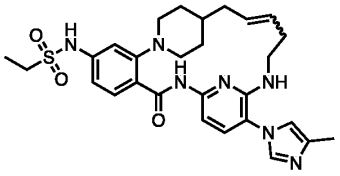


Example 219. *N*-(5^5-(4-chloro-1*H*-imidazol-1-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide was synthesized following the same procedure as Example 217 with 4-chloro-1*H*-imidazole. (Compound 219)

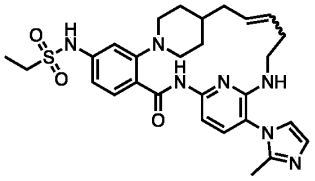


Example 220. *N*-(5^5-(4-methyl-1*H*-imidazol-1-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide was

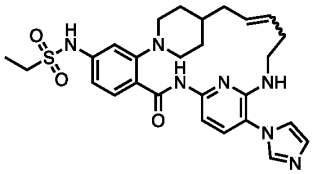
synthesized following the same procedure as Example 217 with 4-methyl-1*H*-imidazole. (Compound 220)



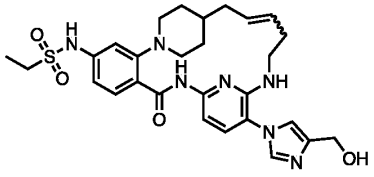
Example 221. *N*-(5^5-(2-methyl-1*H*-imidazol-1-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide was synthesized following the same procedure as Example 217 with 2-methyl-1*H*-imidazole. (Compound 221)



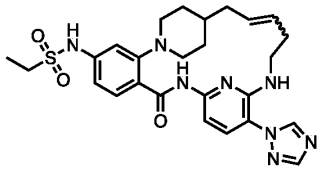
Example 222. *N*-(5^5-(1*H*-imidazol-1-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide was synthesized following the same procedure as Example 217 with 1*H*-imidazole. (Compound 222)



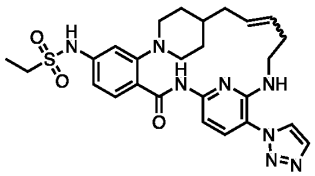
Example 223. *N*-(5^5-(4-(hydroxymethyl)-1*H*-imidazol-1-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide was synthesized following the same procedure as Example 217 with (1*H*-imidazol-4-yl)methanol. (Compound 223)



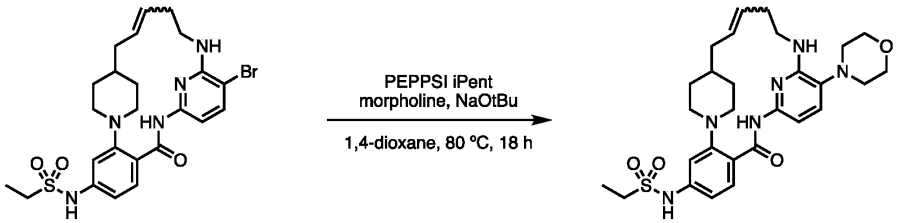
Example 224 ***N*****-(3-oxo-5^5-(1*H*-1,2,4-triazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide was synthesized following the same procedure as Example 217 with 1*H*-1,2,4-triazole. (Compound 224)**



Example 225. ***N*****-(3-oxo-5^5-(1*H*-1,2,3-triazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide was synthesized following the same procedure as Example 217 with 1*H*-1,2,3-triazole. (Compound 225)**



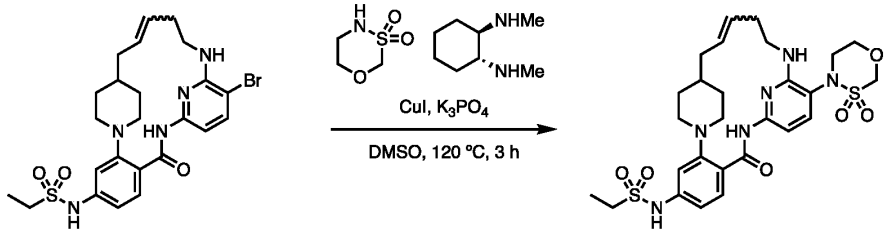
Example 226. ***N*****-(5^5-morpholino-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (Compound 226)**



[000786] To a vial was added *N*-(5^5-bromo-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (50 mg, 91 μmol), PEPPSI IPent (14 mg, 18 μmol), and NaOtBu (35 mg 0.36 mmol). The vial was placed under a N_2 atmosphere then 1,4-Dioxane (1.0 mL) and morpholine (16 μL, 0.18 mmol) were added. The reaction mixture was then heated to 80 °C. After 18 hour, the reaction mixture was diluted with water and extracted with DCM (3 x). The combined organic layers were washed with brine and concentrated. Purification via Isco column chromatography (0-60% EtOAc in heptane) then purification via prepHPLC (10-100% MeCN in H_2O with 0.1% TFA) followed by neutralization and extraction provided *N*-(5^5-morpholino-3-oxo-4,6-diaza-5(2,6)-pyridina-

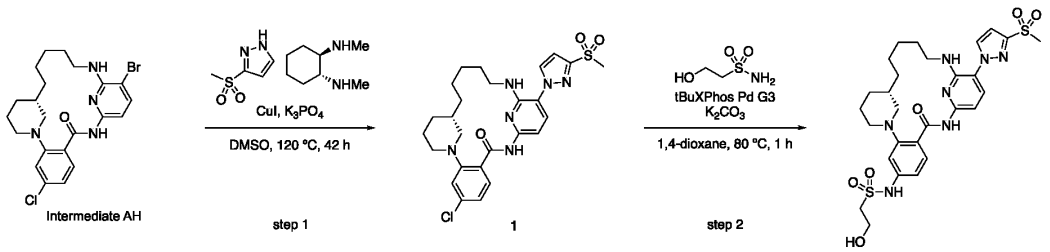
1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (11 mg, 22 %). LCMS (ESI-MS) m/z = 555.2 $[M+H]^+$.

Example 227. *N*-(5^5-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (Compound 227)



[000787] To a vial was added *N*-(5^5-bromo-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (60 mg, 0.11 mmol), CuI (31 mg, 0.16 mmol), trans-(1*R*,2*R*)-*N*,*N*'-Bismethyl-1,2-cyclohexanediamine (23 mg, 26 μL, 0.16 mmol), 1,3,4-Oxathiazinane 3,3-dioxide (60 mg, 0.44 mmol), and K_3PO_4 (70 mg, 0.33 mmol). The vial was placed under a N_2 atmosphere and DMSO (1.2 mL) was added. The reaction was then heated to 120 °C. After 3 hour, the reaction mixture was diluted with water and extracted with DCM (3 x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification via prepHPLC (10-100% MeCN in H_2O with 0.1% TFA) followed by neutralization and extraction provided *N*-(5^5-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (30 mg, 45 %). LCMS (ESI-MS) m/z = 605.2 $[M+H]^+$.

Example 228. 2-hydroxy-*N*-((1^3*R*)-5^5-(3-(methylsulfonyl)-1*H*-pyrazol-1-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide (Compound 228)



Step 1. (1^3*R*)-2^5-chloro-5^5-(3-(methylsulfonyl)-1*H*-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-3-one

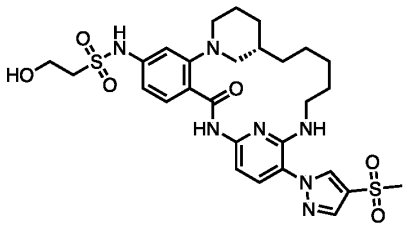
[000788] To a vial was added (1^3R)-5^5-bromo-2^5-chloro-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-3-one, Intermediate AH (50 mg, 0.10 mmol), 3-(methylsulfonyl)-1*H*-pyrazole (31 mg, 0.21 mmol), CuI (20 mg, 0.10 mmol), trans-(1*R*,2*R*)-*N*,*N*'-Bismethyl-1,2-cyclohexanediamine (15 mg, 17 µL, 0.10 mmol), K_3PO_4 (89 mg, 0.42 mmol), and DMSO (1.0 mL) under a N_2 atmosphere. The reaction was then heated to 120 °C. After 18 hour, the reaction mixture was diluted with water and extracted with DCM (3 x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-100% EtOAc in heptane) provided (1^3R)-2^5-chloro-5^5-(3-(methylsulfonyl)-1H-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-3-one (16.9 mg, 30 %). LCMS (ESI-MS) m/z = 543.2 $[M+H]^+$.

Step 2. 2-hydroxy-*N*-((1^3R)-5^5-(3-(methylsulfonyl)-1*H*-pyrazol-1-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-25-yl)ethane-1-sulfonamide

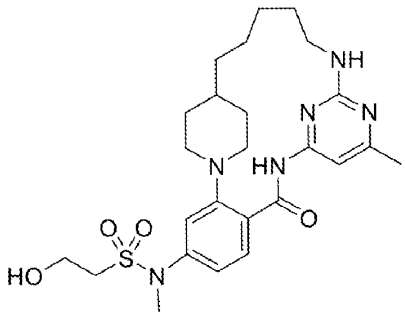
[000789] To a vial was added (1^3R)-2^5-chloro-5^5-(3-(methylsulfonyl)-1*H*-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-3-one (16.5 mg, 30.4 µmol), tBuXPhos Pd G3 (2.41 mg, 3.04 µmol), 2-hydroxyethane-1-sulfonamide (28.5 mg, 228 µmol), and K_2CO_3 (12.6 mg, 91.1 µmol). The reaction vial was placed under a N_2 atmosphere and 1,4-Dioxane (2.0 mL) was added. The reaction mixture was then heated to 80 °C. After 1 hour, the reaction mixture was cooled to rt, diluted with EtOAc, filtered through celite, and concentrated. Purification via prepHPLC (10-100% MeCN in H_2O with 0.1% TFA) followed by lyophilization provided 2-hydroxy-*N*-((1^3R)-5^5-(3-(methylsulfonyl)-1*H*-pyrazol-1-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide 2,2,2-trifluoroacetate (12.8 mg, 55.3 %). LCMS (ESI-MS) m/z = 632.2 $[M+H]^+$.

Example 229. 2-hydroxy-*N*-((1^3R)-5^5-(4-(methylsulfonyl)-1*H*-pyrazol-1-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-

1-sulfonamide was synthesized following the same procedure as Example 228 using 4-(methylsulfonyl)-1*H*-pyrazole in step 1. (Compound 229)

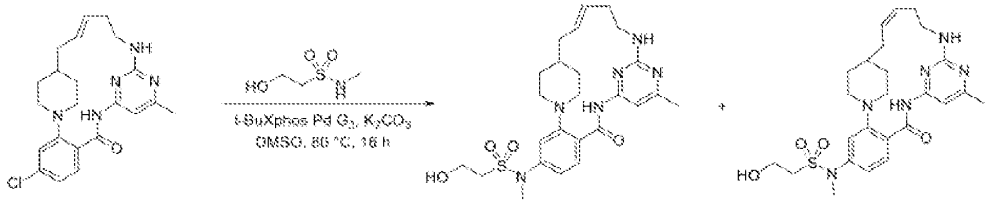


Example 230. 2-hydroxy-N-methyl-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide was synthesized from Example 231 via hydrogenation as described in the procedure for Example 199 (Compound 230).



Examples 231 and 289. (E)-2-hydroxy-N-methyl-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide and (Z)-2-hydroxy-N-methyl-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide were synthesized from Intermediate AD and Intermediate Q following General synthetic route 7B, following steps 1-3 procedure described for example 140.

Step 4 and isomer separation are described below (Compound 231 and compound 289 respectively).



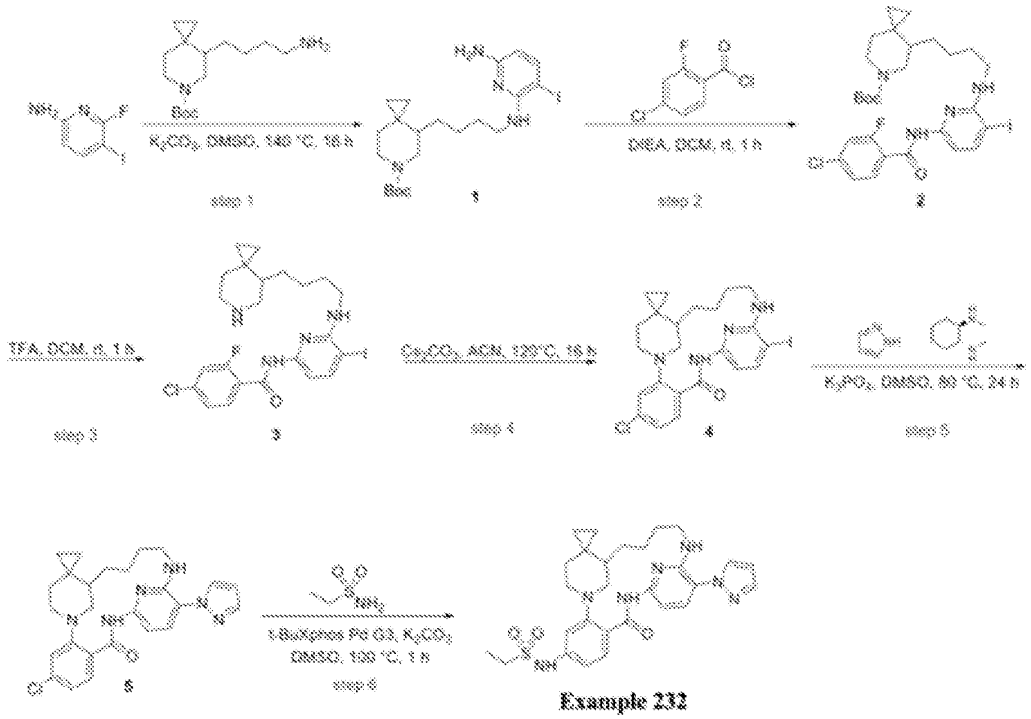
Example 231 Example 289

[000790] Into a solution of (E)-2^5-chloro-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (150 mg, 0.36 mmol) in DMSO (5 mL) was added 2-hydroxy-N-methylethane-1-sulfonamide (101 mg, 0.72 mmol), t-BuXphos Pd G3 (76.8 mg, 0.07 mmol) and K_2CO_3 (151 mg, 1.09 mmol) under nitrogen atmosphere. The resulting solution was heated to 80 °C and stirred for 16 hour. After cooling to room temperature, the reaction mixture was diluted with water (5 mL) and extracted with EA (2 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by reversed-phase flash chromatography with the following conditions: Column: XBridge Prep Shield RP18 OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 13% B to 43 % B in 15 min; Wave Length: 254nm/220nm nm; RT1(min): 13.5; 14.5 to afford two products:

[000791] First eluting isomer: (E)-2-hydroxy-N-methyl-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide (17.2 mg, 9.12% yield), LCMS = 515.2 $[M+H]^+$.

[000792] Second eluting isomer: (Z)-2-hydroxy-N-methyl-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide (12.2 mg, 6.25% yield), LCMS = 515.2 $[M+H]^+$.

Example 232. ***N*-(3'-oxo-5'-(1H-pyrazol-1-yl)spiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethanesulfonamide was prepared as described below (Compound 232).**



Step 1.*tert*-butyl 4-(4-((6-amino-3-iodopyridin-2-yl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate

[000793] K_2CO_3 (2.94 g, 21.2 mmol) was added to a *tert*-butyl 4-(4-aminobutyl)-6-azaspiro[2.5]octane-6-carboxylate (2 g, 7.08 mmol) and 6-fluoro-5-iodopyridin-2-amine (1.69 g, 7.08 mmol) in DMSO (20 mL). The resulting mixture was heated to 140 °C and stirred for 16 hours. After cooling to room temperature, the reaction mixture was diluted with water (20 mL) and extracted with EA (2 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with PE / EA 2 : 1 to afford *tert*-butyl 4-(4-((6-amino-3-iodopyridin-2-yl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate (600 mg, 62.9% yield), LCMS (ESI-MS) m/z = 500.4 $[M+H]^+$.

Step 2.*tert*-butyl 4-(4-((6-(4-chloro-2-fluorobenzamido)-3-iodopyridin-2-

yl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate

[000794] *tert*-butyl 4-(4-((6-amino-3-iodopyridin-2-yl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate (600 mg, 1.20 mmol) was added to a mixture of 4-chloro-2-fluorobenzoyl chloride (254 mg, 1.32 mmol) and DIEA (464 mg, 3.60 mmol) in DCM (10 mL). The resulting mixture was stirred for 1 hour at room temperature. The reaction mixture was diluted with water (20 mL) and extracted with EA (2 x 20 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with PE / EA 2 : 1 to afford *tert*-butyl 4-(4-((6-(4-chloro-2-fluorobenzamido)-3-iodopyridin-2-yl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate (450 mg, 57.1% yield), LCMS (ESI-MS) m/z = 657.0 $[M+H]^+$.

Step 3.*N*-(6-((4-(6-azaspiro[2.5]octan-4-yl)butyl)amino)-5-iodopyridin-2-yl)-4-chloro-2-fluorobenzamide

[000795] TFA (1 mL) was added to a stirred mixture of *tert*-butyl 4-(4-((6-(4-chloro-2-fluorobenzamido)-3-iodopyridin-2-yl)amino)butyl)-6-azaspiro[2.5]octane-6-carboxylate (450 mg, 0.695 mmol) in DCM (10 mL). The resulting mixture was stirred at room temperature for 1 hour and concentrated to afford the crude product *N*-(6-((4-(6-azaspiro[2.5]octan-4-yl)butyl)amino)-5-iodopyridin-2-yl)-4-chloro-2-fluorobenzamide (300 mg crude), LCMS (ESI-MS) m/z = 557.8 $[M+H]^+$.

Step 4.5'-chloro-5'-iodospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one

[000796] A solution of Cs_2CO_3 (526 mg, 1.62 mmol) and *N*-(6-((4-(6-azaspiro[2.5]octan-4-yl)butyl)amino)-5-iodopyridin-2-yl)-4-chloro-2-fluorobenzamide (300 mg, 0.539 mmol) in MeCN (5 mL) was stirred at 120 °C for 16 hours under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was diluted with water (5 mL) and extracted with EA (2 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product 5'-chloro-5'-iodospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one (200 mg, crude), LCMS (ESI-MS) m/z = 536.8 $[M+H]^+$.

Step 5.5'-chloro-5'-(1H-pyrazol-1-yl)spiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one

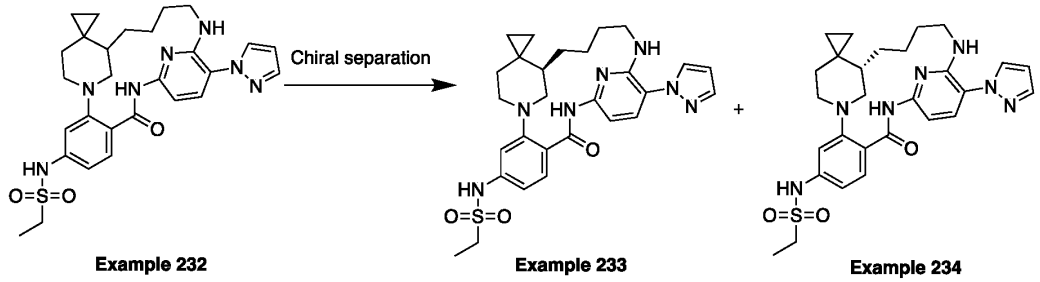
[000797] A solution of 5'-chloro-5'-iodospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one (200 mg, 0.373 mmol), pyrazole (76.1 mg, 1.12 mmol) , CuI (213 mg, 1.12 mmol) , (1R,2R)-1-N,2-N-dimethylcyclohexane-1,2-

diamine (159 mg, 1.11 mmol) and K_3PO_4 (237 mg, 1.11 mmol) in DMSO (5 ml) was stirred at 80 °C for 24 hours under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was diluted with water (5 mL) and extracted with EA (2 x 5 mL). The combined organic layers were washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified with silica gel column, eluted with PE / EA 6 : 1 to afford 5'-chloro-5'-(1H-pyrazol-1-yl)spiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one (80 mg, 45.1% yield), LCMS (ESI-MS) m/z = 477.0 $[M+H]^+$.

Step 6. *N*-(3'-oxo-5'-(1H-pyrazol-1-yl)spiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethanesulfonamide

[000798] 5'-chloro-5'-(1H-pyrazol-1-yl)spiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one (80 mg, 0.210 mmol) was added to a stirred mixture of tBuXPhos Pd G3 (16.6 mg, 0.021 mmol), ethanesulfonamide (68.6 mg, 0.630 mmol) and K_2CO_3 (86.9 mg, 0.630 mmol) in DMSO (2 mL). The resulting mixture was stirred for 16 hour at 80 °C . After cooling to room temperature, the reaction mixture was diluted with H_2O (2 mL) and extracted with EA (2 x 2 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with PE / EA 1:1 to afford *N*-(3'-oxo-5'-(1H-pyrazol-1-yl)spiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethanesulfonamide (6 mg, 10.4 % yield), LCMS (ESI-MS) m/z = 550.2 $[M+H]^+$.

Examples 233 and 234. *N*-((3'R)-3'-oxo-5'-(1H-pyrazol-1-yl)spiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethanesulfonamide & *N*-((3'S)-3'-oxo-5'-(1H-pyrazol-1-yl)spiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethanesulfonamide were prepared from Example 232 via chiral separation described below (Compound 233 and compound 234 respectively).



[000799] *N*-(3'-oxo-5'-(1H-pyrazol-1-yl)spiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethanesulfonamide (5 mg, 0.009 mmol) was separated by Prep-HPLC with the following conditions: Column: CHIRAL ART Cellulose-SC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient (B%): isocratic 30; Wave Length: 254/220nm nm; RT1(min): 10.777; RT2(min): 13.564; Sample Solvent: EtOH--HPLC; Injection Volume: 1.5 mL; Number Of Runs: 1 afford two products

[000800] First eluting isomer: enantiopure *N*-(3'-oxo-5'-(1H-pyrazol-1-yl)spiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethanesulfonamide (1.5 mg, 30.0 % yield), LCMS (ESI-MS) m/z = 550.2 $[M+H]^+$.

[000801] Second eluting isomer: enantiopure *N*-(3'-oxo-5'-(1H-pyrazol-1-yl)spiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethanesulfonamide (2.4 mg, 48.0 % yield) LCMS (ESI-MS) m/z = 550.2 $[M+H]^+$.

Table 30. KIF18A Biochemical data (2h assay) for Examples 233 and 234

Compound	**KIF18A ADP-Glo IC50, nM (2h)**
First eluting isomer	+
Second eluting isomer	++++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

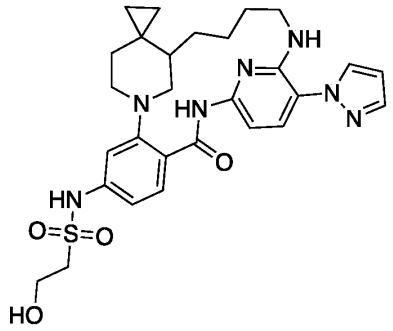
Table 30A KIF18A Biochemical data (24h assay) for Examples 233 and 234

Compound	**KIF18A ADP-Glo IC50, nM (24h)**
First eluting isomer	+
Second eluting isomer	+++++

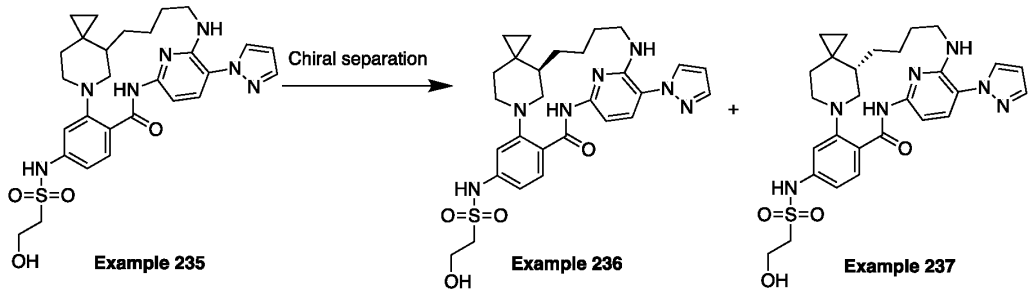
IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 235. 2-hydroxy-*N*-(3'-oxo-5'-(1*H*-pyrazol-1-yl)spiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide as prepared following the same procedure as described in Example 232. In

step 6, 2-hydroxyethane-1-sulfonamide was used in place of ethanesulfonamide (Compound 235).



Examples 236 and 237. 2-hydroxy-*N*-((3'S)-3'-oxo-5'-(1H-pyrazol-1-yl)spiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide & 2-hydroxy-*N*-((3'R)-3'-oxo-5'-(1H-pyrazol-1-yl)spiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide were prepared from Example 235 via chiral separation described below (Compound 236 and compound 237 respectively).



[000802] 2-hydroxy-*N*-(3'-oxo-5'-(1H-pyrazol-1-yl)spiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (10 mg, 0.018 mmol) was purified by Prep-Chiral-HPLC with the following conditions: Column: CHIRALPAK IE, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.1% FA)--HPLC, Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient (B%): isocratic 35; Wave Length: 254/220nm nm; RT1(min): 13.014; RT2(min): 16.058; Sample Solvent: EtOH--HPLC; Injection Volume: 0.7 mL; Number Of Runs: 2 to afford two products:

[000803] First eluting isomer: enantiopure 2-hydroxy-*N*-(3'-oxo-5'-(1H-pyrazol-1-yl)spiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-

benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (1.0 mg, 9.37% yield), LCMS (ESI-MS) m/z = 566.2 $[M+H]^+$.

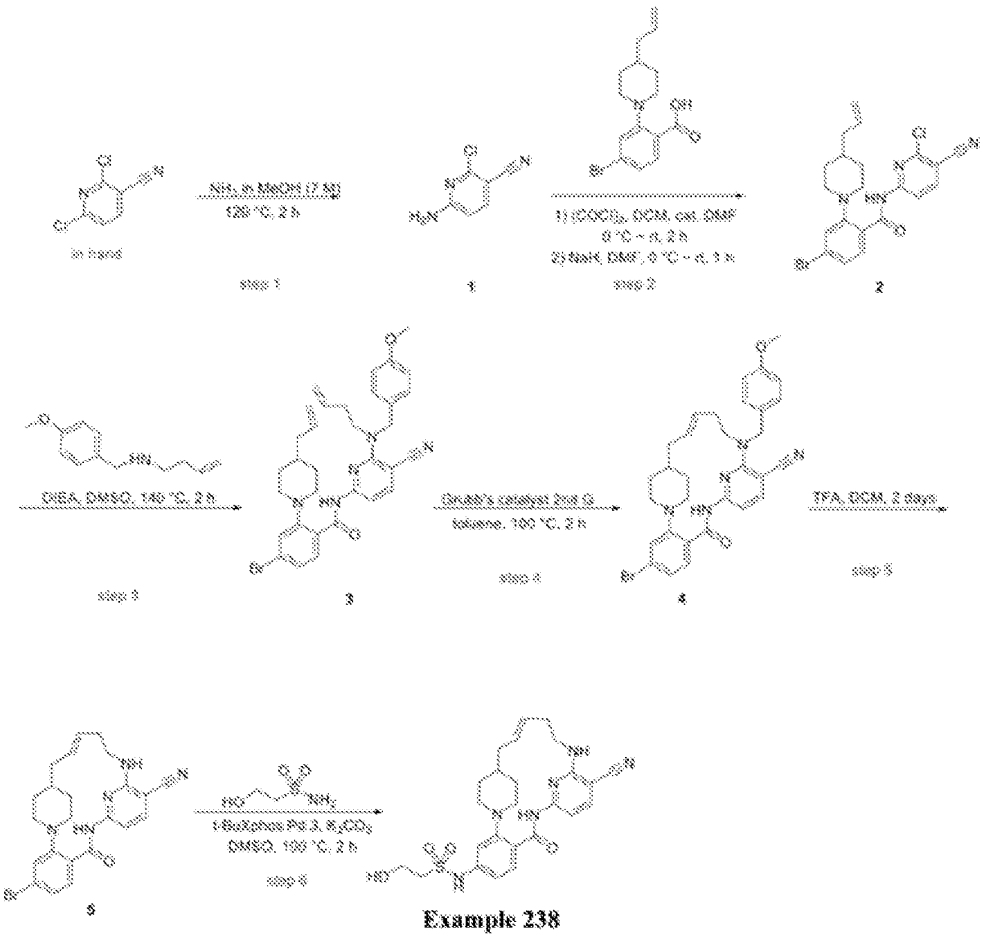
[000804] Second eluting isomer: enantiopure 2-hydroxy-*N*-(3'-oxo-5'-(1H-pyrazol-1-yl)spiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-5'-yl)ethane-1-sulfonamide (1.0 mg, 9.75% yield), LCMS (ESI-MS) m/z = 566.3 $[M+H]^+$.

Table 31A. KIF18A Biochemical data (24h assay) for Examples 236 and 237

Compound	**KIF18A ADP-Glo IC50, nM (24h)**
First eluting isomer	+++++
Second eluting isomer	+

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 238. (E)-2[5]-bromo-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-ene-5[5]-carbonitrile was synthesized from intermediate W as described below (Compound 238).



Example 238

Step 1. 6-amino-2-chloronicotinonitrile

[000805] 2,6-dichloronicotinonitrile (20 g, 116.3 mmol) was added to a solution of NH_3 in MeOH (7M, 180 mL). The resulting mixture was heated to 120 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was filtered and concentrated under vacuum to afford the crude product. The residue was purified with silica gel column, eluted with PE / EA 2 : 1 to afford the desired product 6-amino-2-chloronicotinonitrile (7 g, 39.3% yield). LCMS (ESI-MS) m/z = 154.0 $[M+H]^+$.

Step 2. 2-(4-allylpiperidin-1-yl)-4-bromo-N-(6-chloro-5-cyanopyridin-2-yl)benzamide

[000806] To a stirred solution of Intermediate W (285 mg, 1.30 mmol) in DCM (3 mL) was added $(COCl)_2$ (215 mg, 1.70 mmol) and DMF (3 mL) dropwise at 0 °C. Then the reaction

mixture was stirred for 2 hours. After completion of reaction, the reaction mixture was concentrated under reduced pressure to give crude product P1. To a stirred solution of 6-amino-2-chloronicotinonitrile (200 mg, 1.30 mmol) in anhydrous DMF (3 mL) was added NaH (94 mg, 3.90 mmol) at 0 °C and stirred for 1 hour. Then add dropwise the product P1 dissolved in DMF. The resulting mixture was stirred for 2 hours and monitored by LCMS. After completion of reaction, the reaction was quenched with water (10 mL) and the aqueous layer was extracted with EA (2 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with PE / EA 4 : 1 to afford 2-(4-allylpiperidin-1-yl)-4-bromo-N-(6-chloro-5-cyanopyridin-2-yl)benzamide (270 mg, 45.2% yield), LCMS (ESI-MS) m/z = 459.1 $[M+H]^+$.

Step 3. 2-(4-allylpiperidin-1-yl)-4-bromo-N-(6-(but-3-en-1-yl(4-methoxybenzyl)amino)-5-cyanopyridin-2-yl)benzamide

[000807] DIEA (151 mg, 1.09 mmol) was added to a mixture of 2-(4-allylpiperidin-1-yl)-4-bromo-N-(6-chloro-5-cyanopyridin-2-yl)benzamide (250 mg, 0.55 mmol) and N-(4-methoxybenzyl)but-3-en-1-amine (104 mg, 0.55 mmol) in DMSO (2 mL). The resulting mixture was heated to 140 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was diluted with water (10 mL) and extracted with EA (2 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with PE : EA = 2 : 1 to afford 2-(4-allylpiperidin-1-yl)-4-bromo-N-(6-(but-3-en-1-yl(4-methoxybenzyl)amino)-5-cyanopyridin-2-yl)benzamide (80 mg, 23.9% yield), LCMS (ESI-MS) m/z = 614.2 $[M+H]^+$.

Step 4. (E)-2^5-bromo-6-(4-methoxybenzyl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-ene-5^5-carbonitrile

[000808] To a stirred solution of 2-(4-allylpiperidin-1-yl)-4-bromo-N-(6-(but-3-en-1-yl(4-methoxybenzyl)amino)-5-cyanopyridin-2-yl)benzamide (70 mg, 0.11 mmol) in anhydrous toluene (0.5 mL) was added Grubb's catalyst 2nd G (18 mg, 0.022 mmol). The resulting mixture was heated to 100 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was diluted with water (5 mL) and extracted with EA (2 x 5 mL). The combined organic layers were washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified with silica gel column, eluted with PE / EA 4 : 1 to afford the desired product (E)-2^5-bromo-6-(4-methoxybenzyl)-3-oxo-4,6-diaza-

5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-ene-5^5-carbonitrile (30 mg, 44.9% yield), LCMS (ESI-MS) m/z = 586.2 $[M+H]^+$.

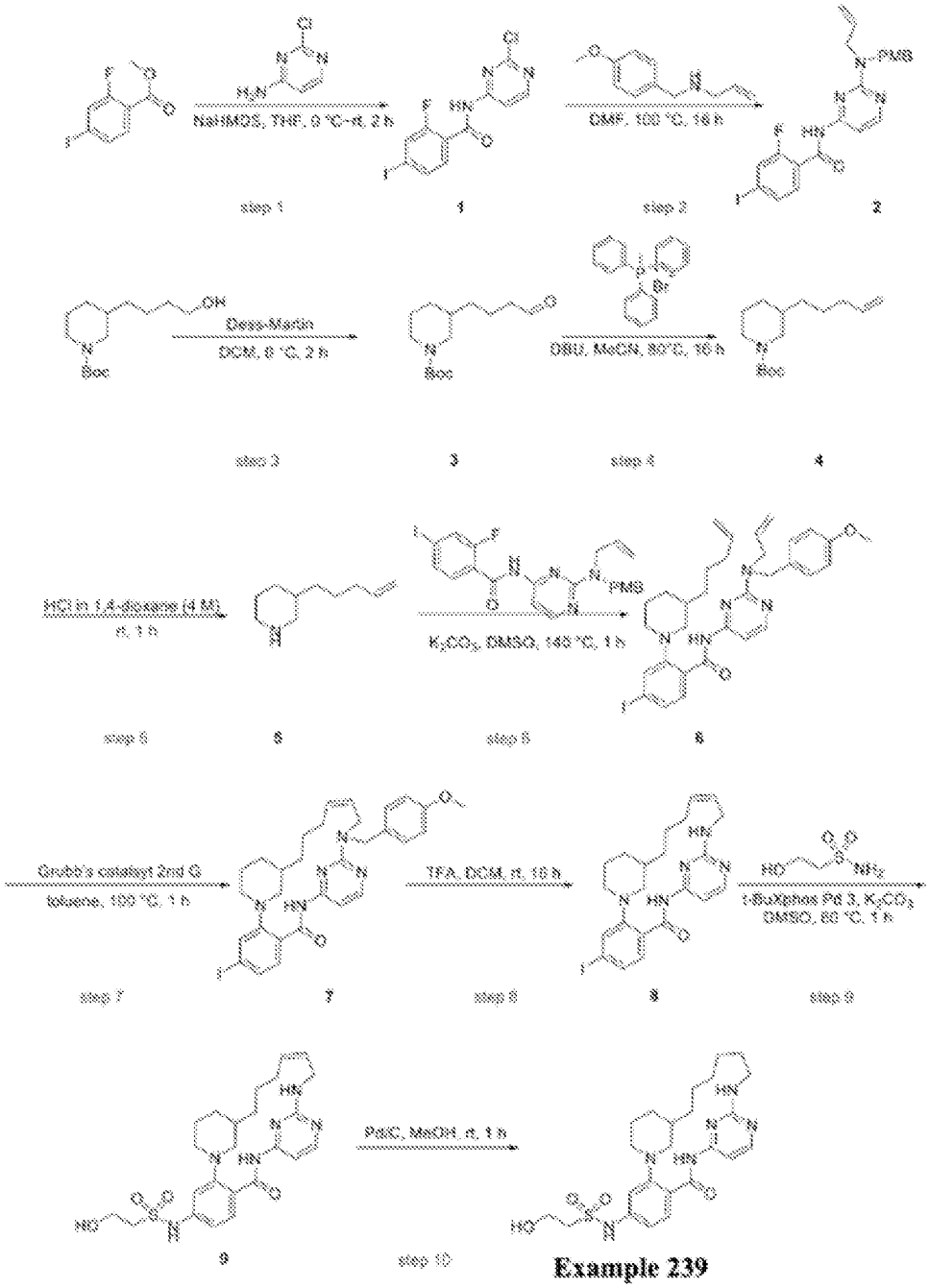
Step 5. (E)-2^5-bromo-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-ene-5^5-carbonitrile

[000809] TFA (10 mL) was added to a stirred mixture of (E)-2^5-bromo-6-(4-methoxybenzyl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-ene-5^5-carbonitrile (30 mg, 0.05 mmol) in DCM (1 mL). The resulting mixture was stirred at room temperature for 2 days and concentrated to afford the crude product (E)-2^5-bromo-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-ene-5^5-carbonitrile (20 mg crude) as yellow oil. LCMS (ESI-MS) m/z = 466.2 $[M+H]^+$.

Step 6. (E)-2^5-bromo-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-ene-5^5-carbonitrile

[000810] Into a solution of (E)-2^5-bromo-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-ene-5^5-carbonitrile (18 mg, 0.039 mmol) in DMSO (0.5 mL) was added 2-hydroxyethanesulfonamide (10 mg, 0.078 mmol), t-BuXPhos Pd G3 catalyst (6 mg, 0.0078 mmol) and K_2CO_3 (17 mg, 0.12 mmol) under nitrogen atmosphere. The resulting solution was heated to 100 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was diluted with water (2 mL) and extracted with EA (2 x 2 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by reversed-phase flash chromatography with the following conditions: Column: XBridge Prep Shield RP18 OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10nmol/LNH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 39% B to 69 % B in 10 min; Wave Length: 254nm/220nm nm; RT1(min): 8.65 to afford the desired product (E)-2^5-bromo-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-ene-5^5-carbonitrile (6.4 mg, 32.4% yield), LCMS (ESI-MS) m/z = 511.2 $[M+H]^+$.

Example 239. 2-hydroxy-*N*-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclododecaphane-2^5-yl)ethane-1-sulfonamide was synthesized as described below (Compound 239).



Step 1.*N*-(2-chloropyrimidin-4-yl)-2-fluoro-4-iodobenzamide

[000811] Methyl 2-fluoro-4-iodobenzoate (10 g, 35.7 mmol) was added to a stirred mixture of 2-chloropyrimidin-4-amine (5.55 g, 42.9 mmol) and NaHMDS (44.6 mL, 89.3 mmol) in

THF (100 mL). The resulting mixture was stirred for 3 hours at 0 °C under nitrogen atmosphere. The reaction was quenched by the addition of Water (100 mL) at 0°C. The aqueous layer was extracted with EA (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with DCM : PE= 1:1 to afford *N*-(2-chloropyrimidin-4-yl)-2-fluoro-4-iodobenzamide (5 g, 32.8% yield), LCMS (ESI-MS) m/z = 378.5 $[M+H]^+$.

Step 2.*N*-(2-(allyl(4-methoxybenzyl)amino)pyrimidin-4-yl)-2-fluoro-4-iodobenzamide

[000812] *N*-(2-chloropyrimidin-4-yl)-2-fluoro-4-iodobenzamide (2.13 g, 5.64 mmol) was added to a mixture of *N*-(4-methoxybenzyl)prop-2-en-1-amine (1 g, 5.64 mmol) in DMF (10 mL). The resulting mixture was stirred for 16 hours at 100 °C. The reaction was quenched with water at room temperature. The aqueous layer was extracted with EA (2 x 10 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with PE / EA 5:1 to afford *N*-(2-(allyl(4-methoxybenzyl)amino)pyrimidin-4-yl)-2-fluoro-4-iodobenzamide (1.2 g, 39.7% yield),LCMS (ESI-MS) m/z =519.3 $[M+H]^+$.

Step 3.*tert*-butyl 3-(4-oxobutyl)piperidine-1-carboxylate

[000813] Dess-Martin reagent (20.6 g, 48.6 mmol) was added to a stirred mixture of *tert*-butyl 3-(4-hydroxybutyl)piperidine-1-carboxylate (5 g, 19.4 mmol,) in DCM (50 mL) . The resulting mixture was stirred for 2 hours at 0 °C. The reaction was quenched with water at 0 °C. The aqueous layer was extracted with EA (2 x 50 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with PE / EA 5:1 to afford *tert*-butyl 3-(4-oxobutyl)piperidine-1-carboxylate (3 g, 57.4% yield), LCMS (ESI-MS) m/z = 226.3$[M+H]^+$.

Step 4.*tert*-butyl 3-(pent-4-en-1-yl)piperidine-1-carboxylate

[000814] DBU (5.37 g, 35.2 mmol) was added to a stirred mixture of *tert*-butyl 3-(4-oxobutyl)piperidine-1-carboxylate (3 g, 11.7 mmol) and methyltriphenylphosphonium bromide (10.5 g, 29.3 mmol) in MeCN (50 mL) . The resulting mixture was stirred for 16 hours at 80 °C. The resulting mixture was concentrated under reduced pressure. The resulting mixture was washed with water (2 x 100 mL). The aqueous layer was extracted with EA (2 x 100 mL).

The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with PE / EA 9:1 to afford *tert*-butyl 3-(pent-4-en-1-yl)piperidine-1-carboxylate (2 g, 63.8% yield), LCMS (ESI-MS) m/z =254.2 $[M+H]^+$.

Step 5. 3-(pent-4-en-1-yl)piperidine

[000815] To a stirred solution of *tert*-butyl 3-(pent-4-en-1-yl)piperidine-1-carboxylate (2 g, 7.89 mmol) in HCl in 1,4-dioxane (4 M) (20 mL). The resulting mixture was stirred at room temperature for 1 hour and concentrated to afford the crude product 3-(pent-4-en-1-yl)piperidine (1.2 g, crude), LCMS (ESI-MS) m/z = 154.2 $[M+H]^+$.

Step 6. *N*-(2-(allyl(4-methoxybenzyl)amino)pyrimidin-4-yl)-4-iodo-2-(3-(pent-4-en-1-yl)piperidin-1-yl)benzamide

[000816] K_2CO_3 (1.62 g, 11.7 mmol) was added to a mixture of 3-(pent-4-en-1-yl)piperidine (600 mg, 3.92 mmol) and *N*-(2-(allyl(4-methoxybenzyl)amino)pyrimidin-4-yl)-2-fluoro-4-iodobenzamide (2.03 g, 3.92 mmol) in DMSO (10 mL). The resulting mixture was heated to 140 °C and stirred for 1 hour. After cooling to room temperature, the reaction mixture was diluted with water (20 mL) and extracted with EA (2 x 20 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with PE / EA 6 : 1 to afford N-(2-(allyl(4-methoxybenzyl)amino)pyrimidin-4-yl)-4-iodo-2-(3-(pent-4-en-1-yl)piperidin-1-yl)benzamide (800 mg, 29.8% yield), LCMS (ESI-MS) m/z = 652.5 $[M+H]^+$.

Step 7. (*Z*)-2^5-iodo-6-(4-methoxybenzyl)-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclododecaphan-8-en-3-one

[000817] Grubb's catalyst 2nd G (52.2 mg, 0.061 mmol) was added to a stirred mixture of N-(2-(allyl(4-methoxybenzyl)amino)pyrimidin-4-yl)-4-iodo-2-(3-(pent-4-en-1-yl)piperidin-1-yl)benzamide (400 mg, 0.614 mmol) in toluene (10 mL) . The resulting mixture was stirred for 1 hour at 100 °C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / THF 9:1 to afford (*Z*)-2^5-iodo-6-(4-methoxybenzyl)-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclododecaphan-8-en-3-one (100 mg, 22.2% yield), LCMS (ESI-MS) m/z = 624.5 $[M+H]^+$.

Step 8.5'-chloro-5'-iodospiro[cyclopropane-1,4'-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacyclodecaphan]-3'-one

[000818] To a stirred solution of (*Z*)-2^5-iodo-6-(4-methoxybenzyl)-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclododecaphan-8-en-3-one (100 mg, 7.89 mmol) in TFA (2 mL). The resulting mixture was stirred at room temperature for 16 hours and concentrated to afford the crude product (*Z*)-2^5-iodo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclododecaphan-8-en-3-one (70 mg, crude), LCMS (ESI-MS) m/z = 504.3 $[M+H]^+$.

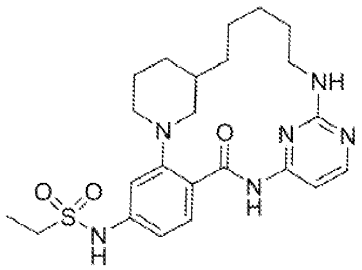
Step 9. (*Z*)-2-hydroxy-*N*-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclododecaphan-8-en-2^5-yl)ethane-1-sulfonamide

[000819] (*Z*)-2^5-iodo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclododecaphan-8-en-3-one (50 mg, 0.099 mmol) was added to a stirred mixture of tBuXPhos Pd G3 (7.89 mg, 0.010 mmol), 2-hydroxyethane-1-sulfonamide (37.3 mg, 0.297 mmol) and K_2CO_3 (82.3 mg, 0.594 mmol) in DMSO (2 mL) .The resulting mixture was stirred for 1 hour at 100 °C . After cooling to room temperature, the reaction mixture was diluted with H_2O (2 mL) and extracted with EA (2 x 2 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford (*Z*)-2-hydroxy-*N*-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclododecaphan-8-en-2^5-yl)ethane-1-sulfonamide (20 mg, 22.1 % yield), LCMS (ESI-MS) m/z = 501.2 $[M+H]^+$.

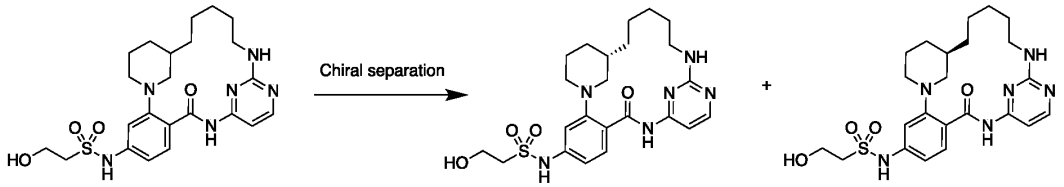
Step 10. 2-hydroxy-*N*-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclododecaphane-2^5-yl)ethane-1-sulfonamide

[000820] Pd/C (15 mg, 0.141 mmol)was added to a stirred mixture of (*Z*)-2-hydroxy-*N*-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclododecaphan-8-en-2^5-yl)ethane-1-sulfonamide (20 mg, 060 mmol) in MeOH (1 mL) under hydrogen atmosphere. The mixture was stirred for 1 hour at room temperature. The reaction mixture was filtered, the filter cake was washed with MeOH (3 x 1 mL). The filtrate was concentrated under reduced pressure to afford the crude product 2-hydroxy-*N*-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclododecaphane-2^5-yl)ethane-1-sulfonamide (2.6 mg , 97.1%purity, 8.38% yield),L CMS (ESI-MS) m/z = 503.1 $[M+H]^+$.

Example 240. 2^5-bromo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-3-one was synthesized via General synthetic route 4A as described in procedure from Example 18 using tert-butyl 3-(5-aminopentyl)piperidine-1-carboxylate and Intermediate H in Step 1; ethanesulfonamide was used in Step 4 (Compound 240).



Examples 241 and 242. *N*-((13*R*)-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethanesulfonamide & *N*-((13*S*)-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethanesulfonamide were prepared via chiral separation of Example 240 as described below (Compound 241 and compound 242 respectively).



Example 240 Example 241 Example 242

[000821] *N*-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethanesulfonamide (20 mg, 0.042 mmol) was purified by Prep-Chiral-HPLC with the following conditions: Column: CHIRALPAKIG3; Mobile Phase A: Hex(0.2%FA): (EtOH: DCM=1: 1)=60: 40; Flow rate: 1mL/min mL/min; Gradient: isocratic ; Injection Volume: 1μl mL to two products:

[000822] first eluting isomer: enantiopure *N*-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethanesulfonamide (7.0 mg, 35.0% yield), LCMS (ESI-MS) m/z = 473.2 $[M+H]^+$.

[000823] second eluting isomer: enantiopure N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethanesulfonamide (7.7 mg, 38.5% yield), LCMS (ESI-MS) m/z = 473.1 $[M+H]^+$.

Table 32. KIF18A Biochemical data (2h assay) for Examples 241 and 242

Compound	**KIF18A ADP-Glo IC50, nM (2h)**
First eluting isomer	+++++
Second eluting isomer	+

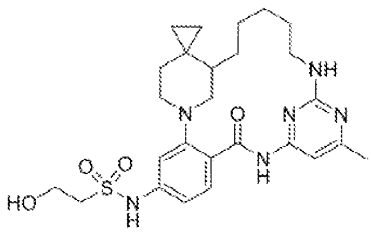
IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Table 32A. KIF18A Biochemical data (24h assay) for Examples 241 and 242

Compound	**KIF18A ADP-Glo IC50, nM (24h)**
First eluting isomer	+++++
Second eluting isomer	++

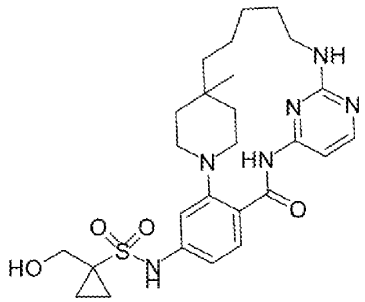
IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 243. 2-hydroxy-N-(6'-methyl-3'-oxospiro[cyclopropane-1,4'-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan]-5'-yl)ethane-1-sulfonamide was prepared starting from Intermediate AL and Intermediate G, following General synthetic route 4A as described in procedure in Example 62 (Compound 243).

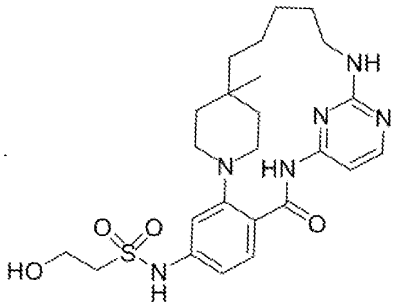


Example 244. 1-(hydroxymethyl)-N-(14-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)cyclopropane-1-sulfonamide

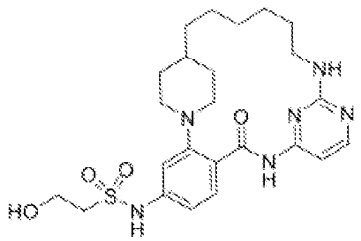
was prepared from Example 257 via hydrogenation as described in the procedure for Example 199 (Compound 244).



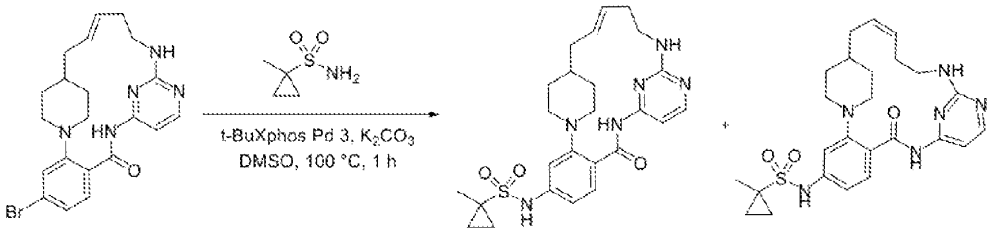
Example 245. 2-hydroxy-N-(14-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide was prepared from Example 255 via hydrogenation as described in the procedure for Example 199 (Compound 245).



Example 246. 2-hydroxy-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacyclododecaphane-25-yl)ethane-1-sulfonamide was prepared following the same procedures as steps 1-2 and 6-10 in Example 239 except in step 2 *N*-(4-methoxybenzyl)but-3-en-1-amine was used in place of *N*-(4-methoxybenzyl)prop-2-en-1-amine and in step 6 4-(but-3-en-1-yl)piperidine was used in place of 3-(pent-4-en-1-yl)piperidine (Compound 246).



Examples 247 and 249. (E)-1-methyl-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacyclounde-caphan-9-en-2^5-yl)cyclopropane-1-sulfonamide and (Z)-1-methyl-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)cyclopropane-1-sulfonamide were synthesized from Intermediate AA and Intermediate W following General synthetic route 7B, steps 1-3 procedure described for example 140. Step 4 and isomer separation are described below (Compound 247 and compound 249 respectively).



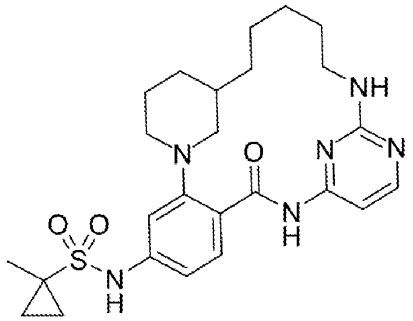
Example 247 **Example 249**

[000824] t-BuXPhos Pd G3 (17mg, 0.023 mmol) was added to a mixture of 2^5-bromo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (100 mg, 0.226 mmol), (1R,2R)-cyclohexane-1,2-diamine (38 mg, 0.34mmol) and K_2CO_3 (93 mg, 0.67 mmol) in DMSO (2 mL) under nitrogen atmosphere. The mixture was stirred at 100 °C for 1 hour. The mixture was allowed to cool down to room temperature. The reaction mixture was purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10nmol/LNH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 40% B to70 % B in 10 min; Wave Length: 254nm/220nm nm; RT1(min): 8.35 to afford the mixture product. The mixture was purified by Prep-Chiral HPLC with the following conditions: Column: (R, R)-WHELK-O1-Kromasil, 2.12*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 35; Wave Length: 254/220nmnm; RT1(min): 10.321; RT2(min): 13.724; Sample Solvent: EtOH-HPLC; Injection Volume: 1.2 mL; Number Of Runs: 2 to afford :

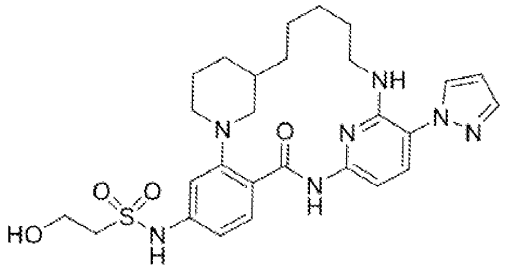
[000825] first eluting isomer: (E)-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl) ethanesulfonamide, LCMS (ESI-MS) m/z = 497.1[M+H]+.

[000826] second eluting isomer: (Z)-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl) ethanesulfonamide, LCMS (ESI-MS) m/z = 497.1 [M+H]+.

Example 248. 1-methyl-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)cyclopropane-1-sulfonamide was prepared via General synthetic route 4A as described in procedure from Example 18 using tert-butyl 3-(5-aminopentyl)piperidine-1-carboxylate and Intermediate H in Step 1. 1-methylcyclopropane-1-sulfonamide and CuI-coupling conditions as in step 4 of Example 86 were used in Step 4 (Compound 248).



Example 250. 2-hydroxy-N-(3-oxo-5^5-(1H-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-25-yl)ethane-1-sulfonamide was synthesized following the same route/procedure as for Example 232 except for tert-butyl 3-(5-aminopentyl)piperidine-1-carboxylate was used in place of *tert*-butyl 4-(4-aminobutyl)-6-azaspiro[2.5]octane-6-carboxylate in step 1 (Compound 250).



Examples 251 and 252. Enantiopure 2-hydroxy-N-(3-oxo-5^5-(1H-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-

sulfonamide was synthesized from enantiopure Intermediate AH (or AH-1 for Example 252) following the same procedure as Example 228 using 1*H*-pyrazole and Cs_2CO_3 in place of K_3PO_4 in step 1. (Compound 251 and compound 252).

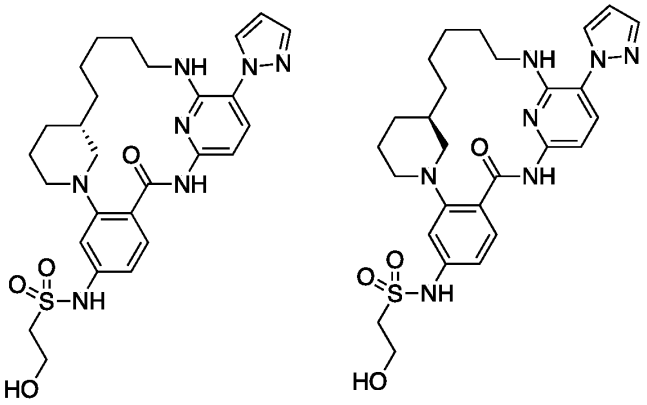


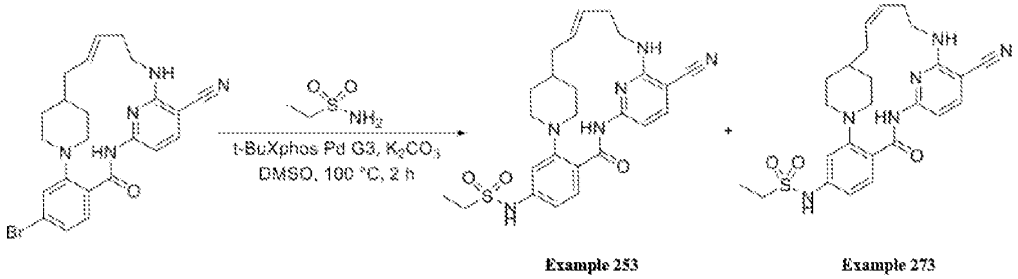
Table 33A. KIF18A Biochemical data (24h assay) for Examples 251 and 252

Compound	**KIF18A ADP-Glo IC50, nM (24h)**
Product from Intermediate AH	+++++
Product from Intermediate AH-1	++++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 253 and 273. (E)-N-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide and (Z)-N-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide were synthesized from Intermediate W and intermediate AK following General synthetic route 8 as described

in Examples 201/267. The last step and separation of isomers is described below (Compound 253 and Compound 273 respectively).



Example 253 Example 273

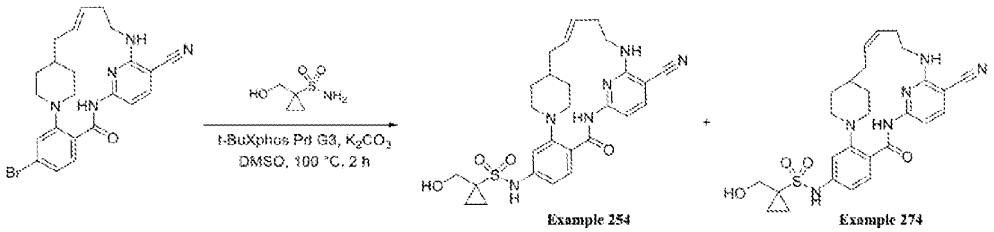
[000827] To a solution of 2-(4-allylpiperidin-1-yl)-4-bromo-N-(6-chloro-5-cyanopyridin-2-yl)benzamide (40 mg, 0.086 mmol) and ethanesulfonamide (28 mg, 0.258 mmol) in DMSO (5 mL) was added t-BuXphos Pd G3 (14 mg, 0.017 mmol) and K_2CO_3 (36 mg, 0.258 mmol). The resulting mixture was stirred for 2 hours at 100 °C. After cooling to room temperature, the reaction mixture was diluted with water (10 mL) and extracted with EA (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified with silica gel column, eluted with PE /EA = 1 : 1 to afford a mixture of isomers. The mixture was dissolved with MeOH and purified by Chiral-Prep-HPLC with the following conditions: Column: (R, R)-WHELK-O1-Kromasil, 2.12*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient (B%): isocratic 40; Wave Length: 254/220nm nm; RT1(min): 9.669; RT2(min): 14.798; Sample Solvent: EtOH--HPLC; Injection Volume: 1.2 mL; Number Of Runs: 1 to afford

[000828] first eluting isomer: (E)-N-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (5.5 mg, 13% yield), LCMS (ESI-MS) m/z = 495.2 $[M+H]^+$.

[000829] second eluting isomer: (Z)-N-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (1.1 mg, 2.5% yield), LCMS (ESI-MS) m/z = 495.2 $[M+H]^+$.

Example 254 and 274. (E)-N-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-1-(hydroxymethyl)cyclopropane-1-sulfonamide and (Z)-N-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-1-(hydroxymethyl)cyclopropane-1-sulfonamide were synthesized from Intermediate W and intermediate AK following General synthetic route 8 as described in Examples 201/267. The last step and

separation of isomers is described below (Compound 254 and Compound 274 respectively).



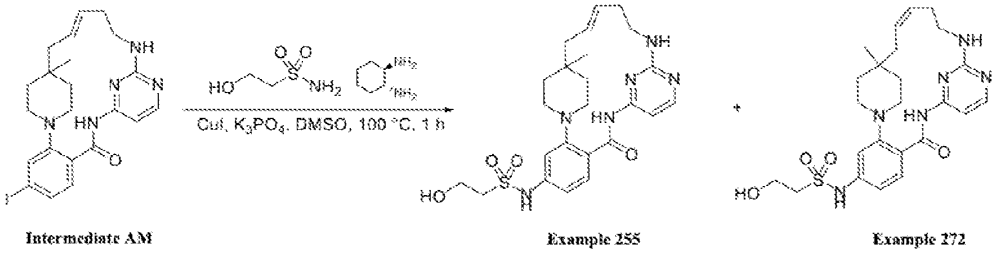
[000830] To a solution of (E)-2[5]-bromo-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-ene-5[5]-carbonitrile (40 mg, 0.086 mmol) and 1-(hydroxymethyl)cyclopropane-1-sulfonamide (39 mg, 0.26 mmol) in DMSO (2 mL) was added t-BuXphos Pd G3 (14 mg, 0.017 mmol) and K_2CO_3 (36 mg, 0.26 mmol). The resulting mixture was stirred for 2 hours at 100°C. After cooling to room temperature, the reaction mixture was diluted with water (10 mL) and extracted with EA (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified with silica gel column, eluted with PE : EA = 1 : 1 to afford mixture product. The mixture product was dissolved with MeOH and purified by Chiral-Prep-HPLC with the following conditions: Column: (R, R)-WHELK-O1-Kromasil, 2.12*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient (B%): isocratic 40; Wave Length: 254/220nm nm; RT1(min): 9.233; RT2(min): 13.436; Sample Solvent: EtOH--HPLC; Injection Volume: 1.2 mL; Number Of Runs: 1 to afford:

[000831] first eluting isomer: (E)-N-(5[5]-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2[5]-yl)-1-(hydroxymethyl)cyclopropane-1-sulfonamide (5.6 mg, 12.1% yield), LCMS (ESI-MS) m/z = 537.3 $[M+H]^+$.

[000832] second eluting isomer: (Z)-N-(5[5]-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2[5]-yl)-1-(hydroxymethyl)cyclopropane-1-sulfonamide (0.9 mg, 1.8% yield), LCMS (ESI-MS) m/z = 537.3 $[M+H]^+$.

Examples 255 and 272. (E)-2-hydroxy-N-(14-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2[5]-yl)ethane-1-sulfonamide & (Z)-2-hydroxy-N-(14-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2[5]-yl)ethane-1-sulfonamide were synthesized from

intermediate AM. E- and Z- isomers of the final product were prepared and separated as described below (Compound 255 and compound 272 respectively).



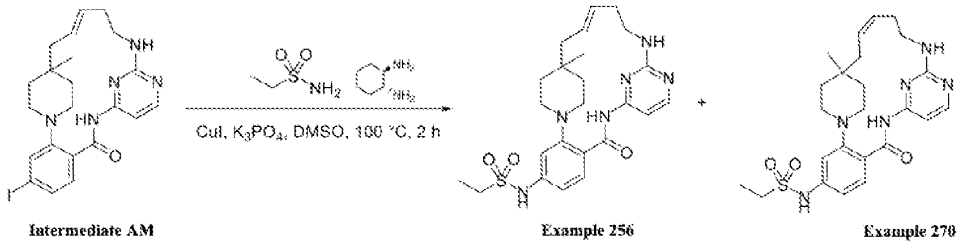
[000833] Into a solution of (E)-2^5-iodo-14-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one, Intermediate AM (110 mg, 0.22 mmol) in DMSO (2 mL) was added 2-hydroxyethane-1-sulfonamide (82 mg, 0.66 mmol), (1R,2R)-cyclohexane-1,2-diamine (74.86 mg, 0.66 mmol), CuI (124.8 mg, 0.66 mmol) and K_3PO_4 (139.2 mg, 0.66 mmol). The resulting mixture was heated to 100 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was filtered off and the filtrate was concentrated under vacuum and the crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep Shield RP18 OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10nmol/LNH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 26% B to56 % B in 10 min; Wave Length: 254nm/220nm nm; RT1(min): 9.07) to afford a mixture product 40 mg. 25 mg of the mixture was separated by Prep-CHIRAL-HPLC with the following conditions (Column: (R, R)-WHELK-O1-Kromasil, 2.12*25 cm, 5 μm; Mobile Phase A: Hex--HPLC, Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 40; Wave Length: 254/220nm nm; RT1(min): 9.042; RT2(min): 12.277; Sample Solvent: EtOH--HPLC; Injection Volume: 1.2 mL; Number Of Runs: 2) to afford the two products:

[000834] First eluting isomer:(E)-2-hydroxy-N-(14-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide (6 mg, 5.5% yield), LCMS (ESI-MS) m/z = 501.1 $[M+H]^+$.

[000835] second eluting isomer: (Z)-2-hydroxy-N-(14-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide (2 mg, 1.83%yield), LCMS (ESI-MS) m/z = 501.1 $[M+H]^+$.

Examples 256 and 270. (E)-N-(14-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide & (Z)-N-(14-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide were prepared from

intermediate AM. E- and Z- isomers of the final product were prepared and separated as described below (Compound 256 and compound 270 respectively).



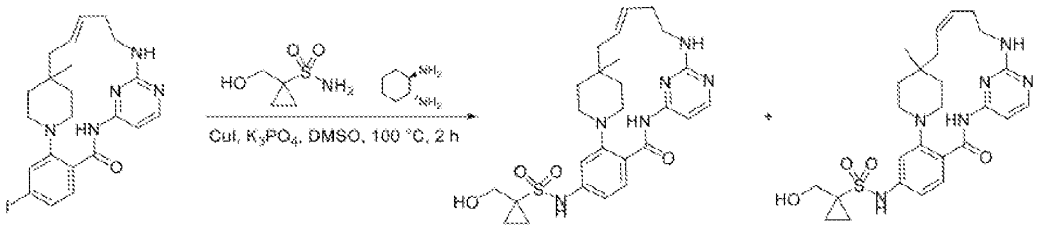
[000836] A solution of AM (70 mg, 0.14 mmol) in DMSO (1.5 mL) was added ethanesulfonamide (45.5 mg, 0.42 mmol), (1R,2R)-cyclohexane-1,2-diamine (47.6 mg, 0.42 mmol), CuI (79.5 mg, 0.42 mmol) and K_3PO_4 (88.55 mg, 0.42 mmol). The resulting mixture was heated to 100 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was filtered off and the filtrate was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep Shield RP18 OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10nmol/LNH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 36% B to66 % B in 10 min; Wave Length: 254nm/220nm nm; RT1(min): 8.77) to afford a pure mixture. The mixture was separated by Prep-CHIRAL-HPLC with the following conditions (Column: (R, R)-WHELK-O1-Kromasil, 2.12*25 cm, 5 μm; Mobile Phase A: Hex--HPLC, Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 40; Wave Length: 254/220nm nm; RT1(min): 9.624; RT2(min): 13.066; Sample Solvent: EtOH--HPLC; Injection Volume: 1.2 mL; Number Of Runs: 2) to afford the two products:

[000837] First eluting isomer: (E)-N-(14-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (8.3 mg, 12.3%yield), LCMS (ESI-MS) m/z = 485.1 $[M+H]^+$..

[000838] Second eluting isomer: (Z)-N-(14-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (2.5 mg, 3.7%yield), LCMS (ESI-MS) m/z = 485.1 $[M+H]^+$.

Example 257 and 332. (E)-1-(hydroxymethyl)-N-(1^4-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)cyclopropane-1-sulfonamide & (Z)-1-(hydroxymethyl)-N-(1^4-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)cyclopropane-1-sulfonamide were prepared from intermediate AM. E- and Z- isomers of the final

product were prepared and separated as described below (Compound 257 and compound 332 respectively).



Intermediate AM **Example 257** **Example 332**

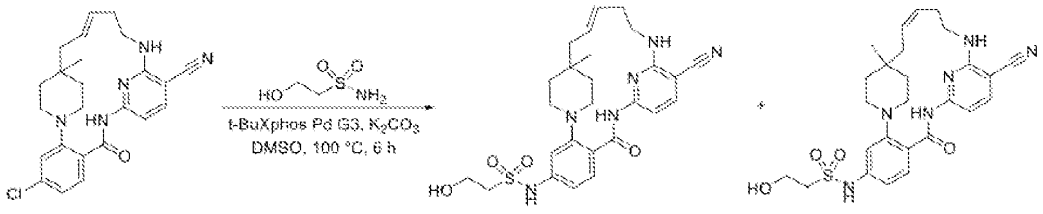
[000839] Into a solution of (E)-2^5-iodo-14-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (230 mg, 0.46 mmol) in DMSO (3 mL) was added 1-(hydroxymethyl)cyclopropane-1-sulfonamide (138.2 mg, 0.92 mmol), CuI (261.1 mg, 1.37 mmol), (1R,2R)-cyclohexane-1,2-diamine (156.5 mg, 1.37 mmol) and K_3PO_4 (290.95 mg, 1.37 mmol). The resulting mixture was heated to 100 °C and stirred for 2 hours. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (50 ml) and washed with brine (3 x 50 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60mL/min mL/min; Gradient: 33% B to 63 % B in 8min; Wave Length: 254nm/220nm nm; RT1(min): 6.52) to afford a pure mixture product 60 mg. 40 mg of the mixture was separated by Prep-chiral-HPLC with the following conditions (Column: (R, R)-WHELK-O1-Kromasil, 2.12*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 35; Wave Length: 254/220nm nm; RT1(min): 10.612; RT2(min): 14.772; Sample Solvent: EtOH--HPLC; Injection Volume: 0.8 mL; Number Of Runs: 6) to afford the two products:

[000840] First eluting isomer: (E)-1-(hydroxymethyl)-N-(14-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)cyclopropane-1-sulfonamide (11.3 mg, 4.7% yield), LCMS (ESI-MS) m/z = 527.0 $[M+H]^+$.

[000841] second eluting isomer: (Z)-1-(hydroxymethyl)-N-(14-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)cyclopropane-1-sulfonamide (4.3 mg, 1.8% yield), LCMS (ESI-MS) m/z = 527.0 $[M+H]^+$.

Examples 258 and 275. (E)-N-(5^5-cyano-1^4-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-

sulfonamide and (Z)-N-(5^5-cyano-14-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide were synthesized from Intermediate AN and intermediate AK following General synthetic route 8 similarly to procedure used in Example 201/267. E- and Z- isomers of the final product were prepared and separated as described below (Compound 258 and Compound 275 respectively).



Example 258 **Example 275**

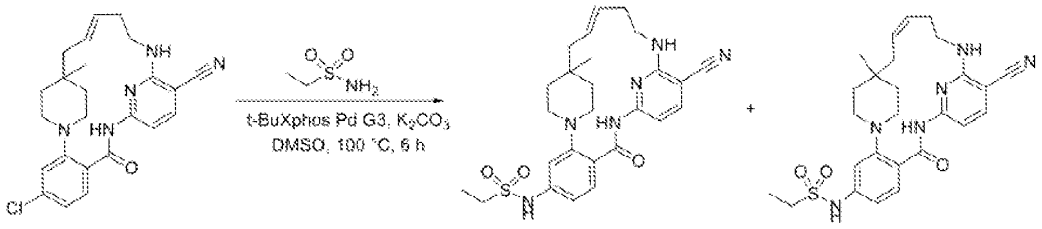
[000842] To a solution of (E)-2^5-chloro-1^4-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-ene-5^5-carbonitrile (60 mg, 0.12 mmol) in DMSO (5 mL) was added t-BuXphos Pd G3 (18 mg, 0.023 mmol) and K_2CO_3 (48 mg, 0.35 mmol). The resulting mixture was stirred for 6 hours at 100 °C. After cooling to room temperature, the reaction mixture was diluted with water (10 mL) and extracted with EA (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified with silica gel column, eluted with PE : EA = 1 : 1 to afford mixture product. The mixture product was dissolved with MeOH and purified by Chiral-Prep-HPLC with the following conditions: Column: (R, R)-WHELK-O1-Kromasil, 2.12*25 cm, 5 μm; Mobile Phase A: Hex--HPLC, Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient (B%): isocratic 40; Wave Length: 254/220nm nm; RT1(min): 10.073; RT2(min): 15.541; Sample Solvent: EtOH--HPLC; Injection Volume: 1.7 mL; Number Of Runs: 2 to afford

[000843] first eluting isomer: (E)-N-(5^5-cyano-1^4-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide (11.1 mg, 18.3% yield), LCMS (ESI-MS) m/z =525.3 $[M+H]^+$.

[000844] second eluting isomer: (Z)-N-(5^5-cyano-1^4-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide (4.8 mg, 7.9% yield), LCMS (ESI-MS) m/z = 525.3 $[M+H]^+$.

Example 259 and 271. (E)-N-(5^5-cyano-1^4-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide and (Z)-N-(5^5-

cyano-1^4-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide were synthesized from Intermediate AN and intermediate AK following General synthetic route 8 similarly to procedure used in Example 201/267. E- and Z- isomers of the final product were prepared and separated as described below (Compound 259 and Compound 271 respectively).



Example 259 Example 271

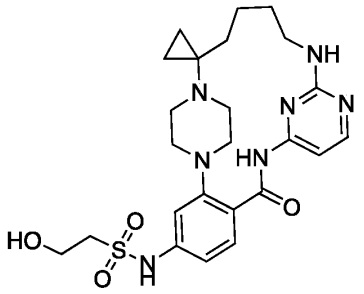
[000845] To a solution of (E/Z)-2^5-chloro-1^4-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-ene-5^5-carbonitrile (50 mg, 0.12 mmol) in DMSO (5 mL) was added t-BuXphos Pd G3 (18 mg, 0.023 mmol) and K_2CO_3 (48 mg, 0.35 mmol). The resulting mixture was stirred for 6 hours at 100 °C. After cooling to room temperature, the reaction mixture was diluted with water (10 mL) and extracted with EA (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified with silica gel column, eluted with PE /EA 1 : 1 to afford mixture product. The mixture product was dissolved with MeOH and purified by Chiral-Prep-HPLC with the following conditions: Column: (R, R)-WHELK-O1-Kromasil, 2.12*25 cm, 5 μm; Mobile Phase A: Hex--HPLC, Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient (B%): isocratic 50; Wave Length: 254/220nm nm; RT1(min): 6.578; RT2(min): 9.409; Sample Solvent: EtOH--HPLC; Injection Volume: 2.2 mL; Number Of Runs: 2 to afford

[000846] first eluting isomer: (E)-N-(5^5-cyano-14-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (11.9 mg, 20.1% yield), LCMS (ESI-MS) m/z =509.2 $[M+H]^+$.

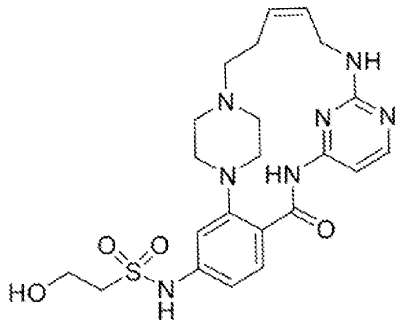
[000847] second eluting isomer: (Z)-N-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (6.4 mg, 10.9% yield), LCMS (ESI-MS) m/z = 509.2 $[M+H]^+$.

Example 260. 2-hydroxy-N-(3'-oxospiro[cyclopropane-1,11'-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperazina-2(1,2)-benzenacycloundecaphan]-5'-yl)ethane-1-

sulfonamide was synthesized from Intermediate AO and Intermediate S following General synthetic route 7B with TCFH, DIEA, THF at 50 °C used as a coupling agent in step 1 and the rest of the procedure was similar to as described for Example 140 (steps 2-4) and 199 (last step) (compound 260).

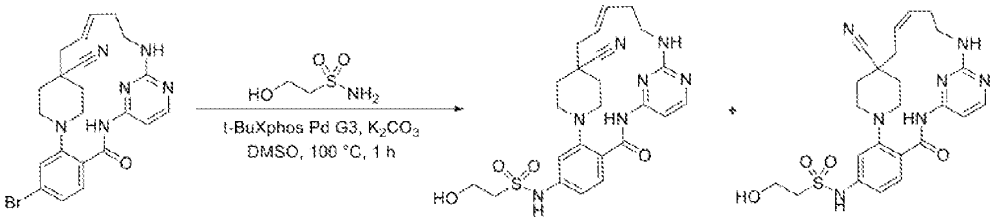


Example 261. (Z)-2-hydroxy-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperazina-2(1,2)-benzenacycloundecaphan-8-en-2^5-yl)ethane-1-sulfonamide was synthesized from Intermediate S and Intermediate AP via General synthetic route 7A utilizing NaHMDS in THF in Step 1 (Compound 261).



Examples 262 and 303. (*E*)-*N*-(1^4-cyano-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide & (*Z*)-*N*-(1^4-cyano-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide were prepared following the same procedures as steps 1-2 and 6-10 in Example 239 except in step 2 4-allylpiperidine-4-carbonitrile was used in place of *N*-(4-methoxybenzyl)prop-2-en-1-

amine. E- and Z- isomers of the final product were prepared and separated as described below (Compound 262 and Compound 303 respectively).



Example 262 Example 303

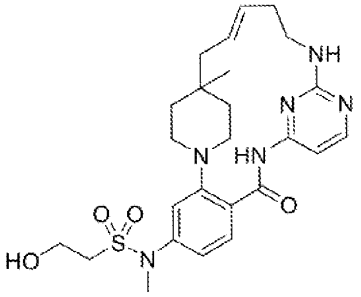
[000848] tBuXPhos Pd G3 (1.7 mg, 0.002 mmol) was added to a mixture of (*E*)-2^5-bromo-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-ene-1^4-carbonitrile (10 mg, 0.021 mmol), 2-hydroxyethane-1-sulfonamide (8.03 mg, 0.063 mmol) and K_2CO_3 (8.87 mg, 0.063 mmol) in DMSO (2 mL) under nitrogen atmosphere. The resulting solution was heated to 100 °C and stirred for 1 hour. The reaction was quenched by the addition of water (5mL) at room temperature. The crude product was purified by Prep-HPLC with the following conditions Column: Xselect CSH Prep C18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water(0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient (B%): 3% B to 33% B in 10 min; Wave Length: 254nm/220nm nm; RT1(min): 9.3, 10.1(min): to afford two products:

[000849] first eluting isomer: (*E*)-*N*-(1^4-cyano-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide (1.77 mg, 16.1% yield), LCMS (ESI-MS) m/z = 512.2 $[M+H]^+$.

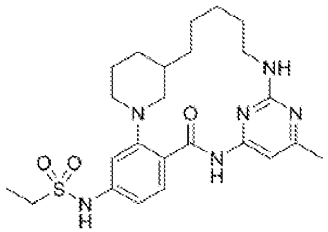
[000850] second eluting isomer: (*Z*)-*N*-(1^4-cyano-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide (0.3 mg, 2.57% yield) LCMS (ESI-MS) m/z = 512.2 $[M+H]^+$.

Example 263. (E)-2-hydroxy-N-methyl-N-(14-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)ethane-1-sulfonamide as

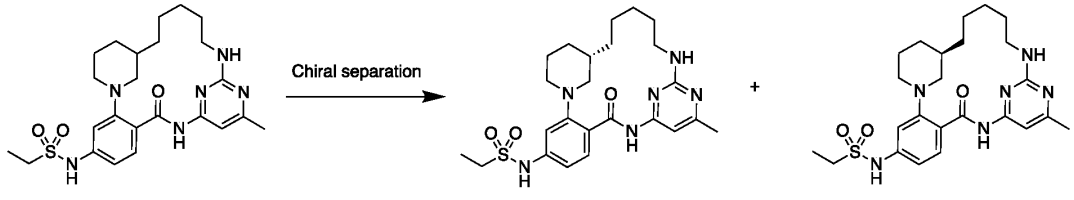
prepared from Intermediate Am following the same Cu-catalyzed coupling procedure as described for Example 255 (Compound 263).



Example 264. *N*-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethanesulfonamide was synthesized via General synthetic route 4A as described in procedure from Example 18 using tert-butyl 3-(5-aminopentyl)piperidine-1-carboxylate and Intermediate G in Step 1 (Compound 264).



Example 265 and 266. *N*-((13*R*)-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethanesulfonamide & *N*-((13*S*)-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethanesulfonamide were prepared via chiral separation of Example 264 as described below (Compound 265 and compound 266 respectively).



Example 264 Example 265 Example 266

[000851] *N*-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-25-yl)ethanesulfonamide (40 mg, 0.082 mmol) was purified by Prep-Chiral-HPLC with the following conditions: Column: CHIRALPAK IE, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient (B%): isocratic 35; Wave Length: 254/220nm nm; RT1(min): 17.394; RT2(min): 20.134; Sample Solvent: EtOH--HPLC; Injection Volume: 0.4 mL; Number Of Runs: 6 to afford two products:

[000852] first eluting isomer: enantiopure *N*-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-25-yl)ethanesulfonamide (7.5 mg, 18.7% yield), LCMS (ESI-MS) m/z = 487.3 $[M+H]^+$.

[000853] second eluting isomer: enantiopure *N*-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-25-yl)ethanesulfonamide (14.8 mg, 36.9% yield), LCMS (ESI-MS) m/z = 487.2$[M+H]^+$.

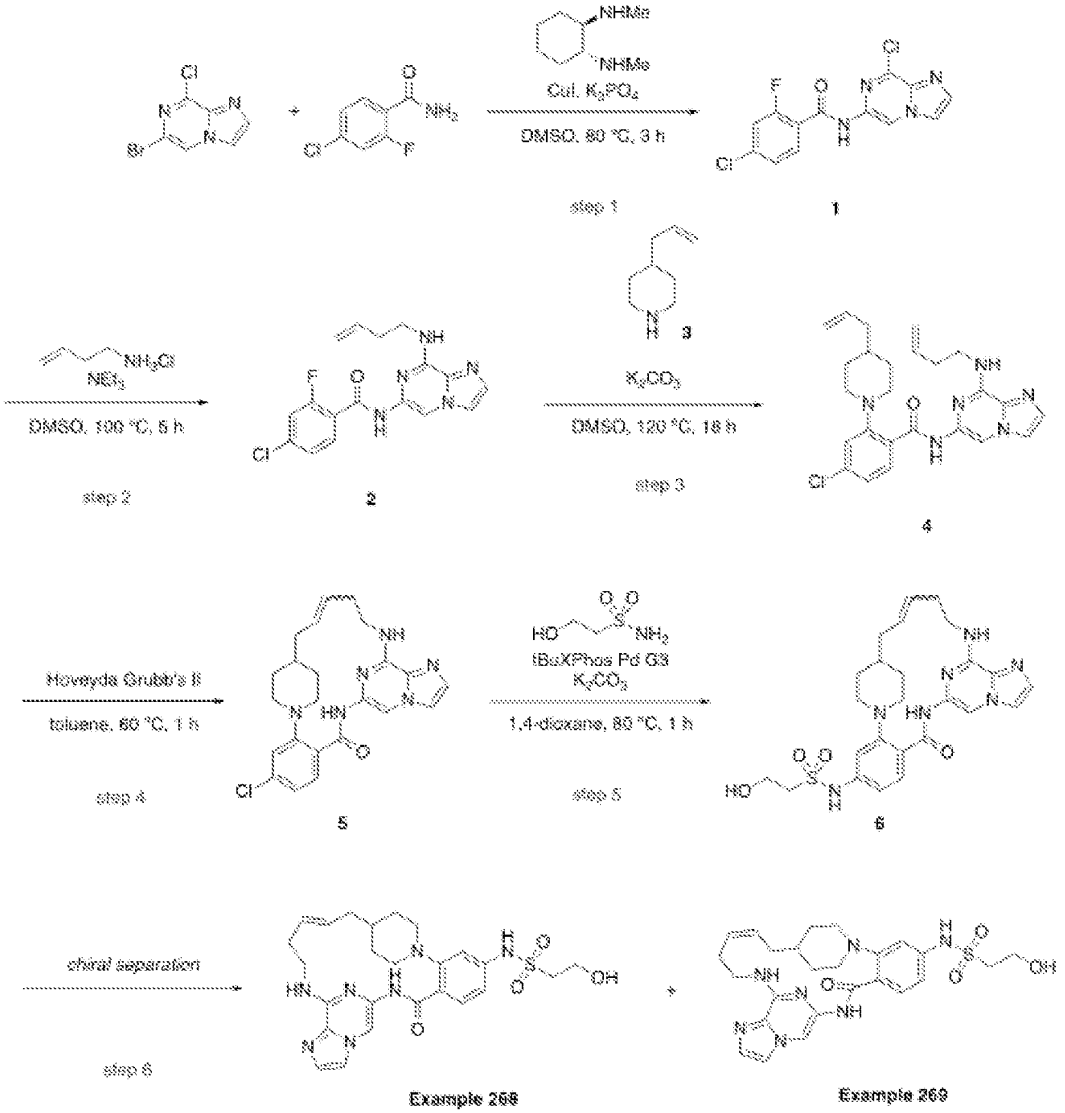
Table 34A. KIF18A Biochemical data (24h assay) for Examples 265 and 266

Compound	**KIF18A ADP-Glo IC50, nM (24h)**
First eluting isomer	+++++
Second eluting isomer	++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 268 and 269. 2-hydroxy-N-((5^{7}E,9E)-3-oxo-4,6-diaza-5(6,8)-imidazo[1,2-a]pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide & 2-hydroxy-N-((5^{7}E,9Z)-3-oxo-4,6-diaza-5(6,8)-imidazo[1,2-a]pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide were

synthesized following the procedure described below (Compound 268 and Compound 269 respectively).



1. 4-chloro-*N*-(8-chloroimidazo[1,2-*a*]pyrazin-6-yl)-2-fluorobenzamide

[000854] To a vial was added 6-bromo-8-chloro-imidazo[1,2-a]pyrazine (400 mg, 1.72 mmol), CuI (328 mg, 1.72 mmol), 4-Chloro-2-fluorobenzamide (747 mg, 2.5 Eq, 4.30 mmol), trans-(1R,2R)-N,N'-Bismethyl-1,2-cyclohexanediamine HCl (307 mg, 1.72 mmol), and K_3PO_4 (1.46 g, 6.88 mmol). The reaction vial was placed under a nitrogen atmosphere and DMSO (12 mL) was added. The reaction mixture was then heated to 80 °C. After 3 hour, the reaction mixture was diluted with EtOAc and washed with water, then brine (5 x), dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-40% EtOAc in heptane)

provided 4-chloro-*N*-(8-chloroimidazo[1,2-a]pyrazin-6-yl)-2-fluorobenzamide (113 mg, 20.2% yield). LCMS (ESI-MS) m/z = 324.9 $[M+H]^+$.

2. *N*-(8-(but-3-en-1-ylamino)imidazo[1,2-*a*]pyrazin-6-yl)-4-chloro-2-fluorobenzamide

[000855] To a vial was added 3-Buten-1-amine, hydrochloride (72.8 mg, 677 μmol) and 4-chloro-*N*-(8-chloroimidazo[1,2-a]pyrazin-6-yl)-2-fluorobenzamide (110 mg, 338 μmol). The vial was placed under a nitrogen atmosphere and DMSO (2.0 mL) and triethylamine (137 mg, 189 μL, 1.35 mmol) were added. The reaction mixture was then heated to 100 °C. After 5 hour, the reaction mixture was diluted aq. $NaHCO_3$ and extracted with DCM (3 x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-60% EtOAc in heptane) provided *N*-(8-(but-3-en-1-ylamino)imidazo[1,2-a]pyrazin-6-yl)-4-chloro-2-fluorobenzamide (79 mg, 65 % yield). LCMS (ESI-MS) m/z = 360.0 $[M+H]^+$.

3. 2-(4-allylpiperidin-1-yl)-*N*-(8-(but-3-en-1-ylamino)imidazo[1,2-*a*]pyrazin-6-yl)-4-chlorobenzamide

[000856] To the crude residue from the previous step was added N-(8-(but-3-en-1-ylamino)imidazo[1,2-a]pyrazin-6-yl)-4-chloro-2-fluorobenzamide (79 mg, 0.22 mmol) and cesium carbonate (0.29 g, 0.88 mmol). The reaction vial was placed under a nitrogen atmosphere and DMSO (2.0 mL) was added. The reaction mixture was then heated to 120 °C. After 18 hour, the reaction mixture was diluted with water and extracted with EtOAc (3 x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-100% EtOAc in heptane) provided 2-(4-allylpiperidin-1-yl)-*N*-(8-(but-3-en-1-ylamino)imidazo[1,2-a]pyrazin-6-yl)-4-chlorobenzamide (87 mg, 65% yield). LCMS (ESI-MS) m/z = 465.1 $[M+H]^+$.

4. (5^7E)-2^5-chloro-4,6-diaza-5(6,8)-imidazo[1,2-*a*]pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one

[000857] To a vial was added 2-(4-allylpiperidin-1-yl)-*N*-(8-(but-3-en-1-ylamino)imidazo[1,2-a]pyrazin-6-yl)-4-chlorobenzamide (100 mg, 215 μmol) and Dichloro(1,3-dimesityl-2-imidazolidinylidene)(2-isopropoxybenzylidene)ruthenium (6.74 mg, 10.8 μmol). The reaction vial was placed under a nitrogen atmosphere and toluene (11 mL) was added. The reaction mixture was then heated to 60 °C. After 60 min the reaction mixture was quenched with aq. $NaHCO_3$ and diluted with EtOAc. The organic layer was separated and washed with brine, dried over $MgSO_4$, and concentrated. Purification via Isco column chromatography (0-20% EtOAc on heptane) provided (5^7E)-2^5-chloro-4,6-diaza-5(6,8)-

imidazo[1,2-a]pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (27 mg, 29% yield). LCMS (ESI-MS) m/z = 437.1 $[M+H]^+$.

5. 2-hydroxy-*N*-((5^7*E*)-3-oxo-4,6-diaza-5(6,8)-imidazo[1,2-*a*]pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide

[000858] To a vial was added (5^7*E*)-25-chloro-4,6-diaza-5(6,8)-imidazo[1,2-a]pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (27 mg, 62 μmol), tBuXPhos Pd G3 (4.9 mg, 6.2 μmol), 2-hydroxyethane-1-sulfonamide (58 mg, 0.46 mmol), and K_2CO_3 (26 mg, 0.19 mmol). The vial was placed under a nitrogen atmosphere and 1,4-dioxane (1.5 mL) was added. The reaction mixture was then heated to 80 °C. After 1 hour, the reaction mixture was cooled to rt and concentrated. The resultant crude material was washed with water, EtOAc, and DCM. The filtrate was discarded and the solid material was dissolved in DMSO, filtered through a syringe filter, and purified via prepHPLC (10-100% MeCN in H_2O with 0.1% TFA) and lyophilized to provide 2-hydroxy-*N*-((5^7*E*)-3-oxo-4,6-diaza-5(6,8)-imidazo[1,2-*a*]pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide (20.9 mg, 64% yield). LCMS (ESI-MS) m/z = 526.1 $[M+H]^+$.

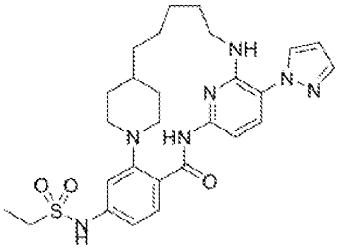
6. 2-hydroxy-*N*-((5^7*E*,9*E*)-3-oxo-4,6-diaza-5(6,8)-imidazo[1,2-*a*]pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide and 2-hydroxy-*N*-((5^7*E*,9*Z*)-3-oxo-4,6-diaza-5(6,8)-imidazo[1,2-*a*]pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide

[000859] 2-hydroxy-*N*-((5^7*E*)-3-oxo-4,6-diaza-5(6,8)-imidazo[1,2-*a*]pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide (20.4 mg, 0.04 mmol) was separated by Prep-Chiral-HPLC with the condition: (Column: (R, R)-WHELK-O1-Kromasil, 2.12*25 cm, 5 μm; Mobile Phase A: Hex--HPLC, Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 50; Wave Length: 254/220nm nm; RT1(min): 6.7; RT2(min): 13.902; Sample Solvent: EtOH--HPLC; Injection Volume: 1.4 mL; Number Of Runs: 1). The desired fraction was combined and lyophilized to afford the two products:

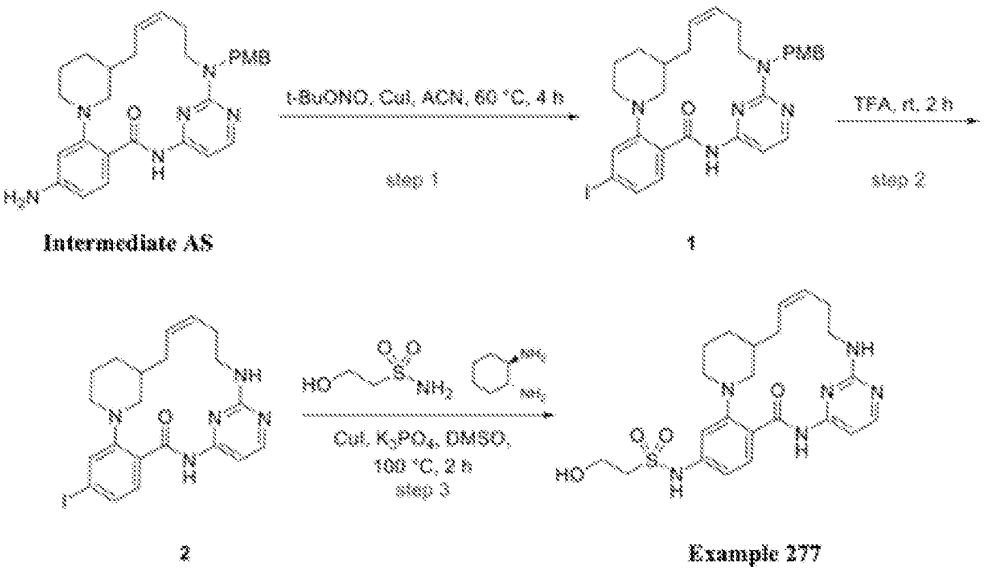
[000860] first eluting isomer: 2-hydroxy-*N*-((5^{7}E,9E)-3-oxo-4,6-diaza-5(6,8)-imidazo[1,2-a]pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide (2.3 mg, 11% yield). LCMS (ESI-MS) m/z = 526.1 $[M+H]^+$.

[000861] second eluting isomer: 2-hydroxy-N-((5^{7}E,9Z)-3-oxo-4,6-diaza-5(6,8)-imidazo[1,2-a]pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide (0.5 mg, 2.4% yield). LCMS (ESI-MS) m/z = 526.0 $[M+H]^+$.

Example 276. ***N*-(3-oxo-5^5-(1*H*-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethanesulfonamide was prepared from Intermediate AE following the procedure described for Example 192. Ethanesulfonamide was used in step 2 (Compound 276).**



Example 277. (Z)-2-hydroxy-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide was synthesized from Intermediate AS following the procedure described below (Compound 277).



1. **(Z)-2^5-iodo-6-(4-methoxybenzyl)-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one**

[000862] Into a solution of (Z)-2^5-amino-6-(4-methoxybenzyl)-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (150 mg, 301 μmol) in ACN (5 mL) was added tert-Butyl nitrite (62 mg, 602 μmol). After stirring for a few minutes, add CuI

(115 mg, 602 μmol) and the resulting mixture was heated to 60 °C and stirred for 4 hour. After cooling to room temperature, the reaction mixture was filtered and concentrated under vacuum. The residue was purified with silica gel column, eluted with PE / EA 1 : 1 to afford desired product (Z)-2^5-iodo-6-(4-methoxybenzyl)-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (120 mg, 65.4% yield). LCMS (ESI-MS) m/z = 610.2 $[M+H]^+$.

2. (Z)-2^5-iodo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one

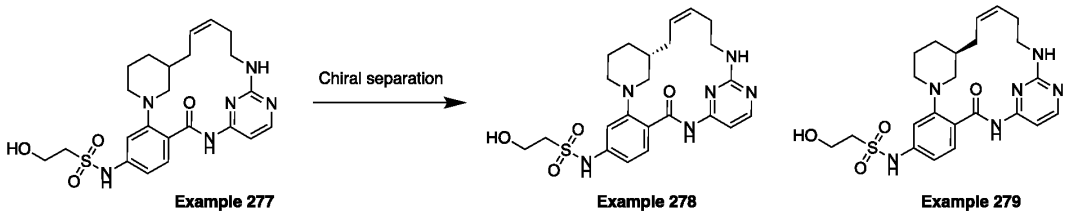
[000863] TFA (10 mL, 94.2 mmol) was added to (Z)-2^5-iodo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (115 mg, 0.19 mmol) in DCM (1 mL) and stirred at room temperature for 2 hours. Then, the reaction mixture was filtered and concentrated under vacuum to afford (Z)-2^5-iodo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (90 mg, crude). LCMS (ESI-MS) m/z = 490.1 $[M+H]^+$.

3. (Z)-2-hydroxy-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide

[000864] Into a solution of (Z)-2^5-iodo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (100 mg, 204 μmol) in DMSO (10 mL) was added 2-hydroxyethane-1-sulfonamide (76.7 mg, 613 μmol), CuI (117 mg, 613 μmol), Potassium phosphate tribasic (130 mg, 613 μmol) and 1,2-cyclohexanediamine, (1r,2r)- (70.0 mg, 613 μmol). The resulting mixture was heated to 100 °C and stirred for 2 hour. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10nmol/LNH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 25% B to 55 % B in 10 min; Wave Length: 254nm/220nm nm; RT1(min): 8.11 to afford (Z)-2-hydroxy-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)ethane-1-sulfonamide (15 mg, 15% yield). LCMS (ESI-MS) m/z = 487.2 $[M+H]^+$.

Examples 278 and 279. 2-hydroxy-N-((13S,Z)-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide and 2-hydroxy-N-((13R,Z)-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-

benzenacycloundecaphan-9-en-2[5]-yl)ethane-1-sulfonamide were prepared via chiral separation of Example 277 as described below (Compound 278 and compound 279 respectively).



[000865] (Z)-2-hydroxy-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)ethane-1-sulfonamide (12 mg, 25 μmol) was dissolved with MeOH and purified by Chiral-Prep-HPLC with the following conditions: Column: CHIRALPAKIH3, Mobile Phase A: Hex(0.1%DEA) : (EtOH: DCM=1: 1)=40: 60; Flow rate: 1 mL/min; Gradient: isocratic ; Injection Volume: 2 μl to afford

[000866] First eluting isomer: enantiopure (Z)-2-hydroxy-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)ethane-1-sulfonamide (2.9 mg, 23% yield), LCMS (ESI-MS) m/z = 487.2 $[M+H]^+$.

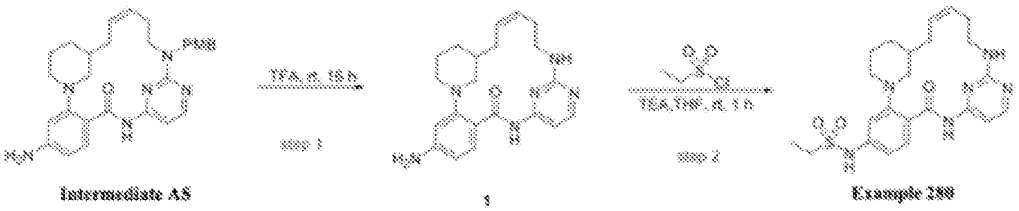
[000867] Second eluting isomer: enantiopure (Z)-2-hydroxy-N-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)ethane-1-sulfonamide (1.6 mg, 13% yield), LCMS (ESI-MS) m/z = 487.2 $[M+H]^+$.

Table 35A. KIF18A Biochemical data (24h assay) for Examples 278 and 279

Compound	**KIF18A ADP-Glo IC50, nM (24h)**
First eluting isomer	+++++
Second eluting isomer	++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 280. (*Z*)-*N*-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide was synthesized from Intermediate AS following the procedure described below (Compound 280).



Step 1.(*Z*)-2^5-amino-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one

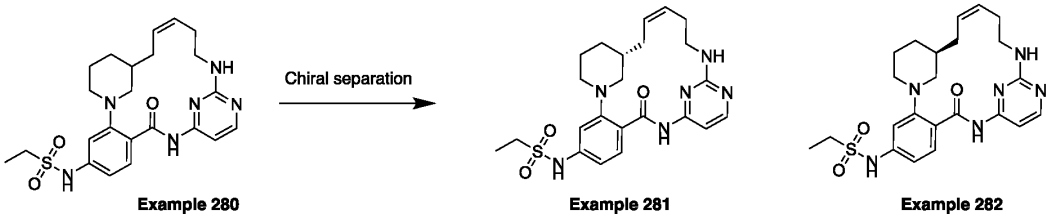
[000868] To a stirred solution of (*Z*)-2^5-amino-6-(4-methoxybenzyl)-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (100 mg, 0.201 mmol) in TFA (5 mL). The resulting mixture was stirred at room temperature for 16 hours and concentrated to afford the crude product (*Z*)-2^5-amino-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (60 mg, crude), LCMS (ESI-MS) m/z = 379.2 $[M+H]^+$.

Step 2. (*Z*)-2^5-amino-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one

[000869] Et_3N (40.11 mg, 0.396 mmol) was added to a stirred mixture of(*Z*)-2^5-amino-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (50 mg, 0.132 mmol) and ethanesulfonyl chloride (25.48 mg, 0.198 mmol) in THF (2 mL). The resulting mixture was stirred for 1 hour at room temperature. The reaction was quenched with Water at room temperature. The aqueous layer was extracted with EA (2x2 mL) dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA 1:1 to afford(*Z*)-2^5-amino-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (11 mg, 16.8 % yield), LCMS (ESI-MS) m/z = 471.2 $[M+H]^+$.

Examples 281 and 282. *N*-((13*S*,*Z*)-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide & *N*-((13*R*,*Z*)-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-

yl)ethanesulfonamide were prepared via chiral separation of Example 280 as described below (Compound 281 and compound 282 respectively).



[000870] (Z)-*N*-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (10 mg, 0.021 mmol) was purified by Prep-Chiral-HPLC with the following conditions Column: CHIRALPAKIH3; Mobile Phase A: Hex(0.1%DEA): (IPA: DCM=1: 1)=70: 30; Flow rate: 1 mL/min; Gradient: isocratic ; Injection Volume: 2μl mL afford:

[000871] first eluting isomer: enantiopure (Z)-*N*-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (2.49 mg, 24.8 % yield). LCMS (ESI-MS) m/z = 471.2[M+H]$^+$.

[000872] second eluting isomer: enantiopure (Z)-*N*-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (2.49 mg, 24.8 % yield). LCMS (ESI-MS) m/z = 471.2[M+H]$^+$,

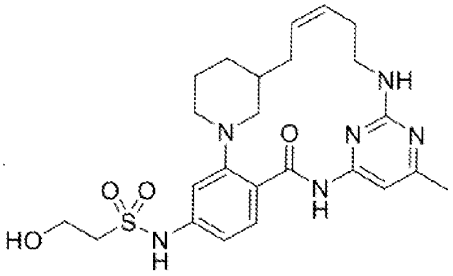
Table 36A. KIF18A Biochemical data (24h assay) for Examples 281 and 282

Compound	**KIF18A ADP-Glo IC50, nM (24h)**
First eluting isomer	+++++
Second eluting isomer	++

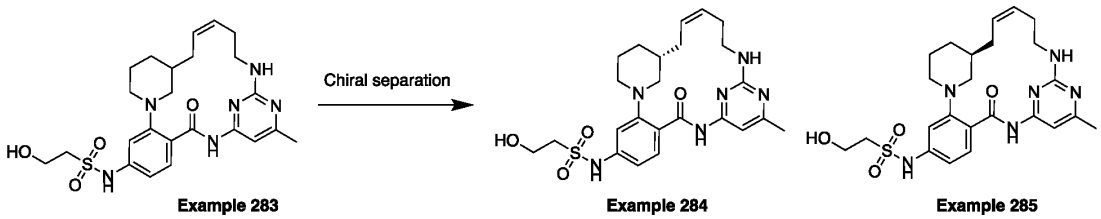
IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 283. (Z)-2-hydroxy-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide was

synthesized from Intermediate AT following the procedure for Example 277 (Compound 283).



Example 284 and 285. 2-hydroxy-N-((13S,Z)-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide and 2-hydroxy-N-((13R,Z)-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide were prepared via chiral separation of Example 283 as described below (Compound 284 and compound 285 respectively).



[000873] (Z)-2-hydroxy-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide (27 mg, 54 μmol) was dissolved with MeOH and purified by Chiral-Prep-HPLC with the following conditions: Column: CHIRALPAKIH3, Mobile Phase A: Hex(0.1%DEA): (MeOH: DCM=1: 1)=40: 60; Flow rate: 1 mL/min; Gradient: isocratic to afford

[000874] First eluting isomer: enantiopure (Z)-2-hydroxy-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide (7.4 mg, 27% yield), LCMS (ESI-MS) m/z = 501.2 $[M+H]^+$.

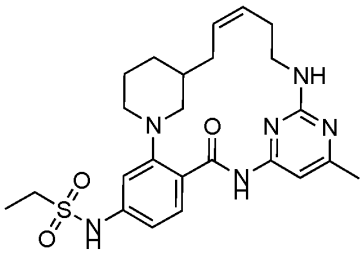
[000875] Second eluting isomer: enantiopure (Z)-2-hydroxy-N-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethane-1-sulfonamide (5.8 mg, 21% yield), LCMS (ESI-MS) m/z = 501.2 $[M+H]^+$.

Table 37A. KIF18A Biochemical data (24h assay) for Examples 284 and 285

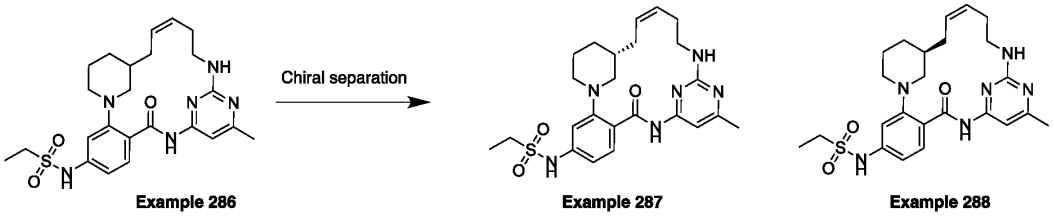
Compound	KIF18A ADP-Glo IC50, nM (24h)
First eluting isomer	+++++
Second eluting isomer	+++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 286. (*Z*)-2^5-amino-5^6-methyl-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one was synthesized from Intermediate AT following the procedure for Example 280 (Compound 286).



Example 287 and 288. *N*-((13*S*,*Z*)-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide & *N*-((13*R*,*Z*)-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide were prepared via chiral separation of Example 286 as described below (Compound 287 and compound 288 respectively).



[000876] (*Z*)-*N*-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (10 mg, 0.021 mmol) was purified by Prep-Chiral-HPLC with the following conditions Column: CHIRALPAKIH3; Mobile Phase A: Hex(0.1%DEA): (IPA: DCM=1: 1)=70: 30; Flow rate: 1 mL/min; Gradient: isocratic ; Injection Volume: 2μl mL afford to *N*-((13*S*,*Z*)-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-

1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (2.2 mg, 99.4%purity, 21.9 % yield) as a white solid and *N*-((13*R*,*Z*)-5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (2.4 mg, 23.9 % yield) as a white solid.

[000877] first eluting isomer: enantiopure (*Z*)-*N*-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (2.2 mg, 21.9 % yield), LCMS (ESI-MS) m/z = 471.2[M+H]$^+$.

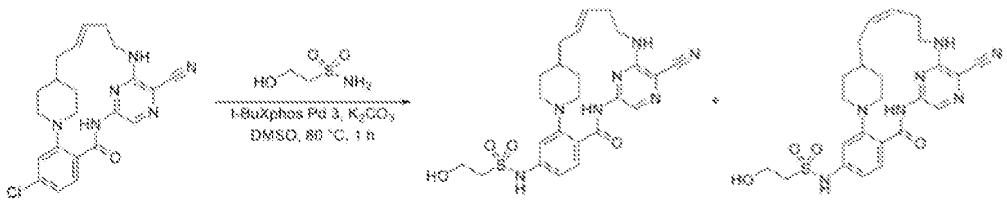
[000878] second eluting isomer: enantiopure (*Z*)-*N*-(5^6-methyl-3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide (2.4 mg, 23.9 % yield), LCMS (ESI-MS) m/z = 471.2[M+H]$^+$.

Table 38A. KIF18A Biochemical data (24h assay) for Examples 287 and 288

Compound	**KIF18A ADP-Glo IC50, nM (24h)**
First eluting isomer	+++++
Second eluting isomer	++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Examples 290 and 291. (*E*)-*N*-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide & (*Z*)-*N*-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide were synthesized from Intermediate AU and Intermediate AD following general synthetic route 8. E- and Z- isomers of the final product were prepared and separated as described below (Compound 290 and Compound 291 respectively).



Example 290 Example 291

[000879] (*E*)-2^5-chloro-3-oxo-4,6-diaza-5(2,6)-pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-ene-55-carbonitrile (90 mg, 0.21 mmol) was added to a stirred mixture of Reactant II (22 mg, 21 μmol) ,2-hydroxyethane-1-sulfonamide (80 mg, 0.64 mmol)

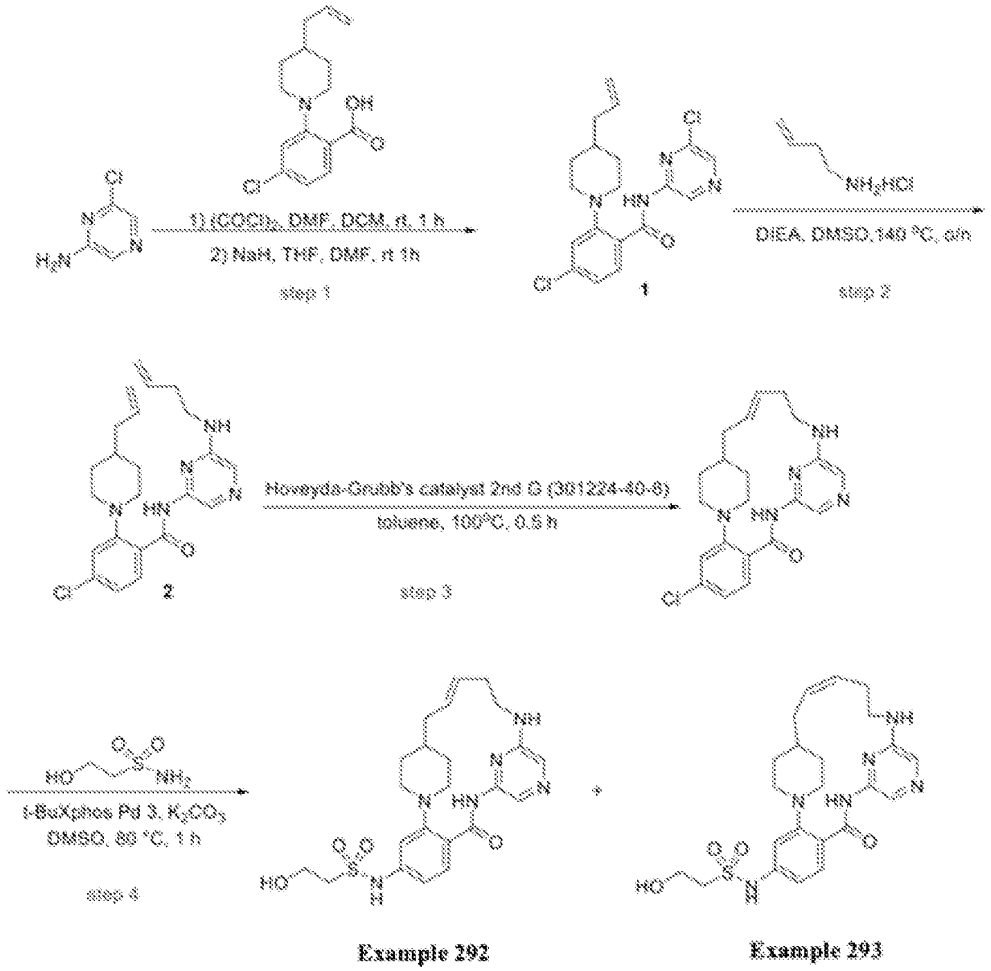
and K_2CO_3 (88 mg, 0.64 mmol) in DMSO (5 mL) .The resulting mixture was stirred for 1 hour at 80 °C. After cooling to room temperature, the reaction mixture was diluted with H_2O (5 mL) and extracted with EA (2 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The crude product was purified by Prep-HPLC with the following conditions: Column: X Bridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 35% B to 50% B in 8 min; Wave Length: 254nm/220nm nm; RT1(min): 7.67 afford to the mixture of K-325 & K-326 . The crude product was purified by Prep-Chiral-HPLC with the following conditions: Column: CHIRALARTCellulose Z; Mobile Phase A: Hex(0.1%DEA): (MeOH : DCM=1: 1)=70: 30; Flow rate: 1 mL/min; Gradient: isocratic ; Injection Volume: 2μl mL afford:

[000880] first eluting isomer: (*E*)-*N*-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide (2.2 mg, 2.5 % yield), LCMS (ESI-MS) m/z = 512.1 $[M+H]^+$.

[000881] second eluting isomer: (*Z*)-*N*-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide (0.9 mg, 4 % yield), LCMS (ESI-MS) m/z = 512.2 $[M+H]^+$.

Example 292 and 293. (E)-2-hydroxy-N-(3-oxo-4,6-diaza-5(2,6)-pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)ethane-1-sulfonamide and (Z)-2-hydroxy-N-(3-oxo-4,6-diaza-5(2,6)-pyrazina-1(1,4)-piperidina-2(1,2)-

benzenacycloundecaphan-9-en-25-yl)ethane-1-sulfonamide were synthesized as described below (Compound 292 and compound 293 respectively).



1. **2-(4-allylpiperidin-1-yl)-N-(6-(but-3-en-1-ylamino)-5-cyanopyridin-2-yl)-4-chlorobenzamide**

[000882] $(COCl)_2$ (544 mg, 4.29 mmol) was added to the mixture of 2-(4-allylpiperidin-1-yl)-4-chlorobenzoic acid (800 mg, 2.86 mmol) and two drops DMF in DCM (10 mL). The mixture was stirred at room temperature for 1 hour. The resulting mixture was concentrated under vacuum to remove $(COCl)_2$. The residue was dissolved in THF (1 mL) as solution A. NaH (103 mg, 4.29 mmol) was added to the mixture of 6-chloropyrazin-2-amine (370 mg, 2.86 mmol) in THF (9 mL) and DMF (1 mL). the mixture was stirred at room temperature for 1 hour. Then solution A was added to the reaction mixture dropwise at 0 °C and stirred at room temperature for 1 hour. The reaction mixture was diluted with water (30 mL). The resulting

mixture was extracted with EA (3 x 30 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA / PE = (1:4) to afford 2-(4-allylpiperidin-1-yl)-4-chloro-N-(6-chloropyrazin-2-yl)benzamide (500 mg, 44.7 % yield), LCMS (ESI-MS) m/z =391.1 $[M+H]^+$.

2. **2-(4-allylpiperidin-1-yl)-N-(6-(but-3-en-1-ylamino)pyrazin-2-yl)-4-chlorobenzamide**

[000883] DIEA (20 mg, 0.15 mmol) was added to the mixture of but-3-en-1-amine hydrochloride (500 mg, 4.65 mmol) and 2-(4-allylpiperidin-1-yl)-4-chloro-N-(6-chloropyrazin-2-yl)benzamide(500 mg, 1.28 mmol) in DMSO (5 mL). The mixture was stirred at 140°C overnight. The reaction mixture was diluted with water (30 mL). The resulting mixture was extracted with EA (3 x 30 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA /PE (1 : 4) to afford 2-(4-allylpiperidin-1-yl)-N-(6-(but-3-en-1-ylamino)pyrazin-2-yl)-4-chlorobenzamide (200 mg, 36.7 % yield), LCMS (ESI-MS) m/z =426.2 $[M+H]^+$.

3. **2^5-chloro-4,6-diaza-5(2,6)-pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one**

[000884] Dichloro(1,3-dimesityl-2-imidazolidinylidene)(2-isopropoxybenzylidene)ruthenium (60 mg, 96 μmol) was added to 2-(4-allylpiperidin-1-yl)-N-(6-(but-3-en-1-ylamino)pyrazin-2-yl)-4-chlorobenzamide (150 mg, 0.35 mmol) in toluene (4 mL) under nitrogen atmosphere. The mixture was stirred at 100 °C for 30 mins. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC, eluted with EA/PE (5:1) to afford the product 2^5-chloro-4,6-diaza-5(2,6)-pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (70 mg, 50 % yield), LCMS (ESI-MS) m/z =398.2 $[M+H]^+$.

4. **(E)-2-hydroxy-N-(3-oxo-4,6-diaza-5(2,6)-pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)ethane-1-sulfonamide and (Z)-2-hydroxy-N-(3-oxo-4,6-diaza-5(2,6)-pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)ethane-1-sulfonamide**

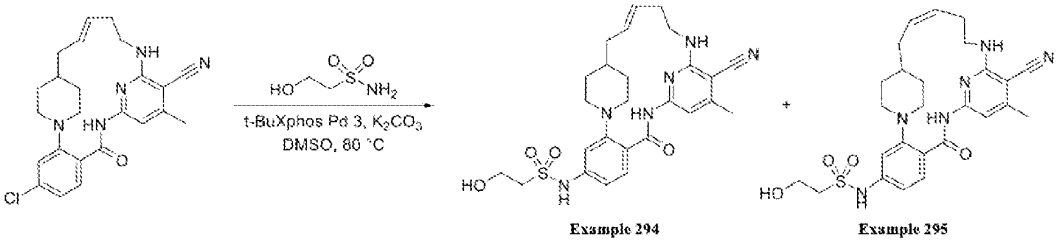
[000885] tBuXPhos-Pd-G3 (16 mg, 15 μmol) was added to the mixture of 2^5-chloro-4,6-diaza-5(2,6)-pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-3-one (60 mg, 0.15 mmol), 2-hydroxyethane-1-sulfonamide (57 mg, 0.45 mmol) and K_2CO_3 (63 mg, 0.45

mmol) in DMSO (2 mL) under nitrogen atmosphere. The mixture was stirred at 80 °C for 16 hours. The mixture was purified by Prep-Chiral-HPLC with following condition with Column: CHIRAL ART Cellulose-SC, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient (B%): isocratic 50; Wave Length: 254/220nm nm; RT1(min): 7.649; RT2(min): 10.858; Sample Solvent: EtOH--HPLC; Injection Volume: 1.2 mL; Number Of Runs: 3 to afford

[000886] first eluting isomer: (Z)-2-hydroxy-N-(3-oxo-4,6-diaza-5(2,6)-pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)ethane-1-sulfonamide (18.2 mg, 25 % yield), LCMS (ESI-MS) m/z =487.20 $[M+H]^+$.

[000887] second eluting isomer: (E)-2-hydroxy-N-(3-oxo-4,6-diaza-5(2,6)-pyrazina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)ethane-1-sulfonamide (2 mg, 3 % yield), LCMS (ESI-MS) m/z =487.20 $[M+H]^+$.

Examples 294 and 295. were synthesized using the same procedure as described in Example 292/293 steps 1-3 except in Step 1, 6-amino-2-chloro-4-methylnicotinonitrile was used in place of 6-chloropyrazin-2-amine. Step 4 and chiral separation are described below (Compound 294 and compound 295 respectively).



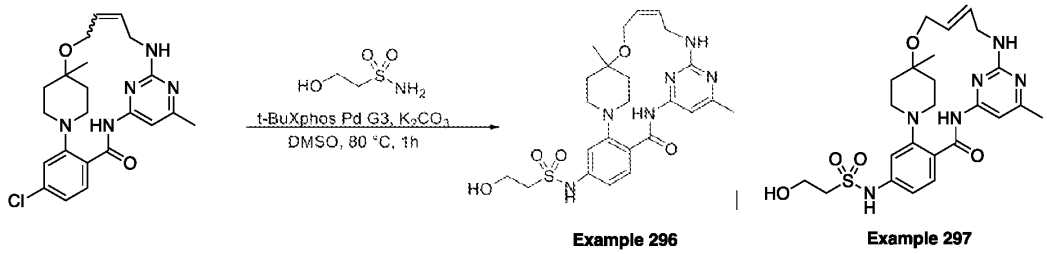
Example 294 Example 295

[000888] 2^5-chloro-5^4-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-ene-5^5-carbonitrile (60 mg, 0.14 mmol) was added to a stirred mixture of tBuXPhos Pd G3 (15 mg, 0.014 mmol), 2-hydroxyethane-1-sulfonamide (52 mg, 0.41 mmol) and K_2CO_3 (57 mg, 0.41 mmol) in DMSO (5 mL) .The resulting mixture was stirred for 1 hour at 100 °C . After cooling to room temperature, the reaction mixture was diluted with H_2O (5 mL) and extracted with EA (2 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. The crude product was purified by Prep-Chiral-HPLC with the following conditions: Column: Column: (R, R)hel1; Mobile Phase A: Hex(0.1%DEA): (MeOH: DCM=1: 1)=65: 35; Flow rate: 1 mL/min; Gradient: isocratic ; Injection Volume: 1μl mL afford:

[000889] first eluting isomer: (*E*)-*N*-(5^5-cyano-5^4-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide (11.8 mg, 20.4 % yield), LCMS (ESI-MS) m/z = 525.2 $[M+H]^+$.

[000890] second eluting isomer: (*Z*)-*N*-(5^5-cyano-5^4-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxyethane-1-sulfonamide (1.0 mg, 6.9 % yield), LCMS (ESI-MS) m/z = 525.2 $[M+H]^+$.

Examples 296 and 297. (*Z*)-N-(14,5^6-dimethyl-3-oxo-11-oxa-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-8-en-2^5-yl)-2-hydroxyethane-1-sulfonamide and (*E*)-N-(14,5^6-dimethyl-3-oxo-11-oxa-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-8-en-2^5-yl)-2-hydroxyethane-1-sulfonamide were synthesized from Intermediate AV and Intermediate AW following general synthetic route 7A steps 1-4. The last step and chiral separation are described below. (Compound 296 and compound 297 respectively).



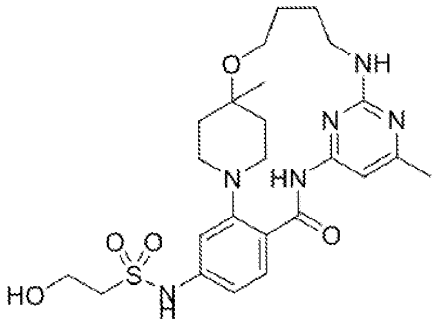
Example 296 Example 297

[000891] t-BuXphos Pd G3 (12 mg, 12 μmol) was added to the mixture of 2^5-chloro-1^4,5^6-dimethyl-11-oxa-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-8-en-3-one (50 mg, 0.12 mmol), 2-hydroxyethane-1-sulfonamide (44 mg, 0.35 mmol) and K_2CO_3 (48 mg, 0.35 mmol) in DMSO (1 mL) under nitrogen atmosphere. The mixture was stirred at 80 °C for 1 hour. The reaction mixture was purified by Prep-HPLC with the following conditions (Column: Xbridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 18% B to39 % B in 10 min; Wave Length: 254nm/220nm nm; RT1(min): 8.68) to afford

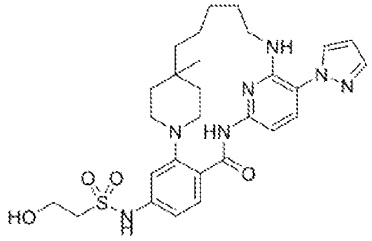
[000892] first eluting isomer: (Z)-N-(14,5^6-dimethyl-3-oxo-11-oxa-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-8-en-2^5-yl)-2-hydroxyethane-1-sulfonamide (5.6 mg, 9.2 % yield), LCMS (ESI-MS) m/z =517.2 $[M+H]^+$.

[000893] second eluting isomer: (E)-N-(14,5^6-dimethyl-3-oxo-11-oxa-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-8-en-2^5-yl)-2-hydroxyethane-1-sulfonamide (2.1 mg, 3.2 % yield), LCMS (ESI-MS) m/z =517.2 $[M+H]^+$.

Example 298. N-(1^4,5^6-dimethyl-3-oxo-11-oxa-4,6-diaza-5(4,2)-pyrimidina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)-2-hydroxyethane-1-sulfonamide was synthesized from a mixture of Example 296/297 using hydrogenation procedure described in Example 199 (Compound 298).

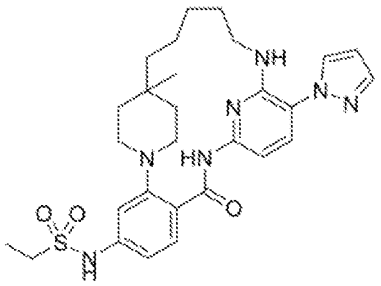


Example 299. 2-hydroxy-*N*-(1^4-methyl-3-oxo-5^5-(1H-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide was synthesized from Intermediate AX following the same procedure as steps 2 and 3 in Example 192 (Compound 299).

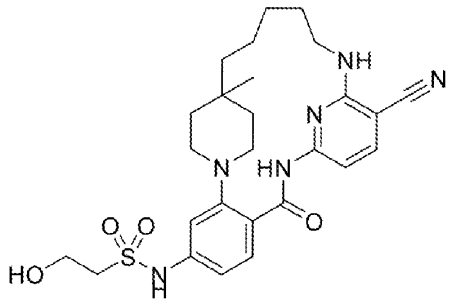


Example 300. *N*-(1^4-methyl-3-oxo-5^5-(1H-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethanesulfonamide was synthesized

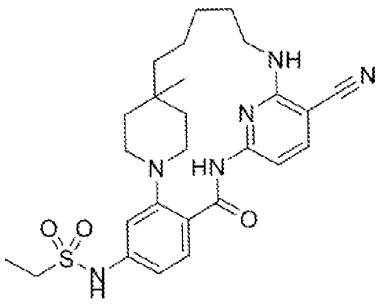
from Intermediate AX following the same procedure as steps 2 and 3 in Example 192. Ethanesulfonamide was used in Pd-catalyzed coupling (Compound 300).



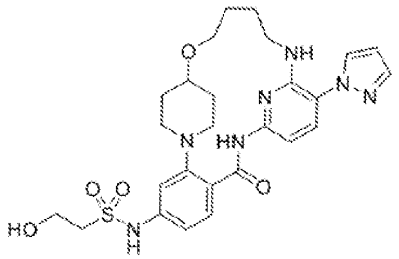
Example 301. (*E*)-2^5-chloro-1^4-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-**9-ene-5^5-carbonitrile was synthesized from a mixture of Example 258/275 using hydrogenation procedure described in Example 202 (Compound 301).**



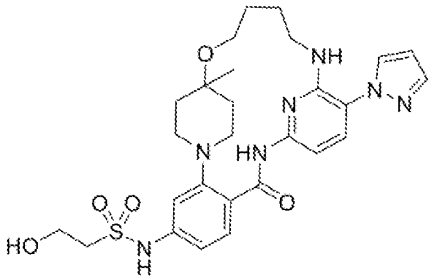
Example 302. *N*-(5^5-cyano-14-methyl-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethanesulfonamide was synthesized from a mixture of Example 259/271 using hydrogenation procedure described in Example 202 (Compound 302).



Example 304. 2-hydroxy-N-(3-oxo-5^5-(1H-pyrazol-1-yl)-11-oxa-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide was prepared from Intermediate AZ and intermediate AR following General synthetic route 8 as described in Examples 201/267. The last hydrogenation step was following procedure from Example 199 (Compound 304).

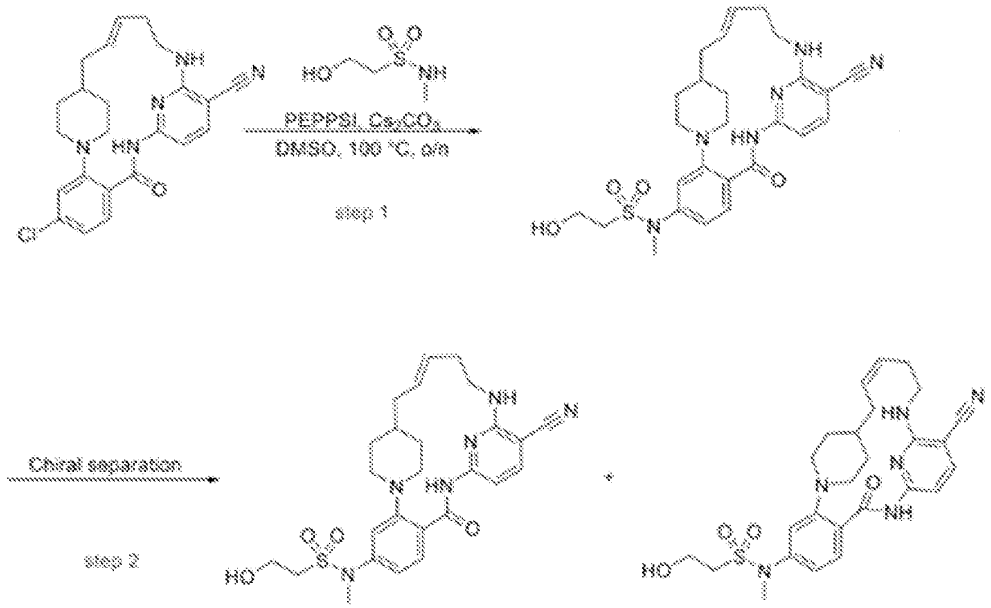


Example 305. 2-hydroxy-*N*-(1^4-methyl-3-oxo-5^5-(1H-pyrazol-1-yl)-11-oxa-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide was prepared from Intermediate AZ and intermediate AW-1 following General synthetic route 8 as described in Examples 201/267. The last hydrogenation step was following procedure from Example 199 (Compound 305).



Example 306 and 307. (E)-N-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxy-N-methylethane-1-sulfonamide and (Z)-N-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxy-N-methylethane-1-sulfonamide were synthesized from Intermediate AD following the same reaction procedures as in Example

238 Steps 1-5. The final step – Pd-catalyzed coupling and E/Z – isomer separation is described below (Compound 306 and compound 307 respectively).



Example 306 **Example 307**

Step 11. N-(5[5]-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2[5]-yl)-2-hydroxy-N-methylethane-1-sulfonamide

[000894] (SP-4-1)-[1,3-Bis[2,6-bis(1-propylbutyl)phenyl]-4,5-dichloro-1,3-dihydro-2H-imidazol-2-ylidene]dichloro(3-chloropyridine-kappaN)-Palladium (2.3 mg, 2.4 μmol) was added to the mixture of 2[5]-chloro-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-ene-5[5]-carbonitrile (10 mg, 24 μmol), 2-hydroxy-N-methylethane-1-sulfonamide (9.9 mg, 71 μmol) and Cs_2CO_3 (23 mg, 71 μmol) in DMSO (1 mL) under nitrogen atmosphere. The mixture was stirred at 100 °C overnight. The mixture was purified by Prep-TLC (MeOH: DCM= 1:20) to afford the crude product. The crude product was purified by Prep-HPLC with following conditions: Column: Xbridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 44% B to 69 % B in 10 min; Wave Length: 254nm/220nm nm; RT1(min): 8.76 to afford the product (E)-N-(55-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)-2-hydroxy-N-methylethane-1-sulfonamide (6 mg, 50 %), LCMS (ESI-MS) m/z =525.2 $[M+H]^+$.

2. (E)-N-(5[5]-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-

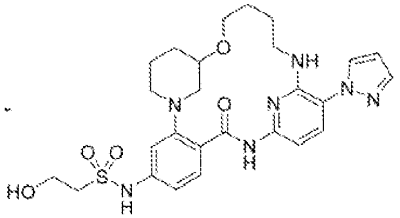
benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxy-N-methylethane-1-sulfonamide and (Z)-N-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxy-N-methylethane-1-sulfonamide

[000895] N-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxy-N-methylethane-1-sulfonamide (5 mg, 1 Eq, 0.01 mmol) was separated by Chiral-HOwith following conditions (Column: (R, R)-WHELK-O1-Kromasil, 2.12*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient: isocratic 50; Wave Length: 254/220nm nm; RT1(min): 7.743; RT2(min): 10.974; Sample Solvent: EtOH--HPLC; Injection Volume: 1.2 mL; Number Of Runs: 1) to afford

[000896] first eluting isomer: (E)-N-(5^5-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)-2-hydroxy-N-methylethane-1-sulfonamide (2.0 mg, 41.2 %yield), LCMS (ESI-MS) m/z =525.3 $[M+H]^+$.

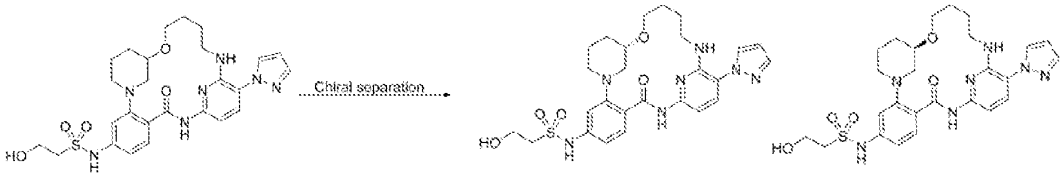
[000897] second eluting isomer: (Z)-N-(55-cyano-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-25-yl)-2-hydroxy-N-methylethane-1-sulfonamide (1.5 mg, 32.7 % yield), LCMS (ESI-MS) m/z =525.3 $[M+H]^+$.

Example 308. 2-hydroxy-*N*-(3-oxo-5^5-(1H-pyrazol-1-yl)-11-oxa-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide was prepared from Intermediate AZ and intermediate BA following General synthetic route 8 as described in Examples 201/267. The last hydrogenation step was following procedure from Example 199 (Compound 308).



Example 309 and 310. 2-hydroxy-*N*-((13*R*)-3-oxo-5^5-(1H-pyrazol-1-yl)-11-oxa-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide & 2-hydroxy-*N*-((13*S*)-3-oxo-5^5-(1H-pyrazol-1-yl)-11-oxa-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide

were prepared by chiral separation of Intermediate 308 as described below (Compound 309 and compound 310 respectively).



[000898] 2-hydroxy-*N*-(3-oxo-5^5-(1H-pyrazol-1-yl)-11-oxa-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide (20 mg, 0.036 mmol) was purified by Prep-Chiral-HPLC with the following conditions: Column: CHIRAL ART Cellulose Z; Mobile Phase A: Hex(0.1%DEA): (MeOH: DCM=1: 1)=75: 25; Flow rate: 1 mL/min; Gradient: isocratic ; Injection Volume: 2 μl to afford

[000899] first eluting isomer: enantiopure 2-hydroxy-*N*-(3-oxo-5^5-(1H-pyrazol-1-yl)-11-oxa-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide (6.83 mg, 66 % yield), LCMS (ESI-MS) m/z = 556.2 $[M+H]^+$.

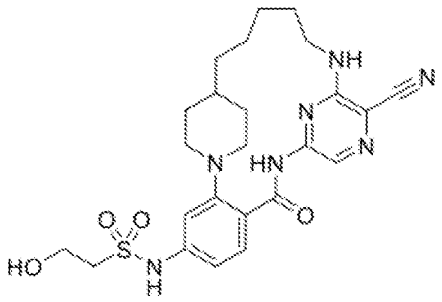
[000900] second eluting isomer: enantiopure 2-hydroxy-*N*-(3-oxo-5^5-(1H-pyrazol-1-yl)-11-oxa-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide (7.33 mg, 72 % yield), LCMS (ESI-MS) m/z = 556.2 $[M+H]^+$.

Table 39A. KIF18A Biochemical data (24h assay) for Examples 309 and 310

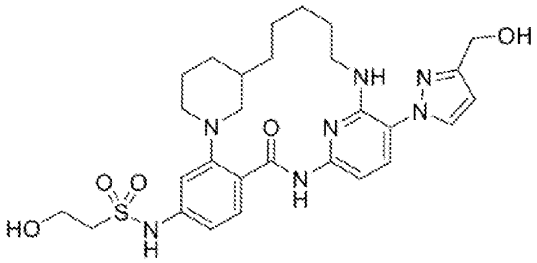
Compound	**KIF18A ADP-Glo IC50, nM (24h)**
First eluting isomer	+++++
Second eluting isomer	++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 317. 2-hydroxy-*N*-(3-oxo-4,6-diaza-5(4,2)-pyrimidina-1(1,3)-piperidina-2(1,2)-benzenacyclododecaphane-2^5-yl)ethane-1-sulfonamide was synthesized from Example 290 using hydrogenation procedure described in Example 202 (Compound 317).

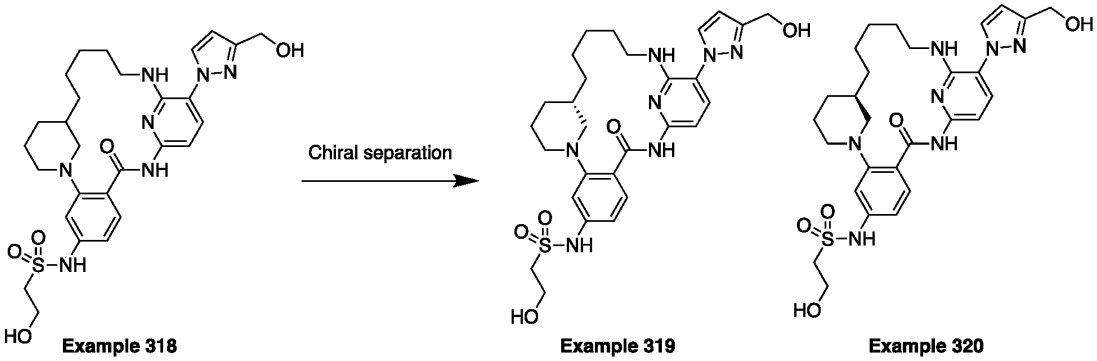


Example 318. 2^5-chloro-5^5-(3-(hydroxymethyl)-1H-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphan-3-one was prepared from Intermediate AH-ent as described in Example 228 using (1H-pyrazol-3-yl)methanol in Step 1 (Compound 318) .



Examples 319 and 320. 2-hydroxy-*N*-((13*R*)-5^5-(3-(hydroxymethyl)-1H-pyrazol-1-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide & 2-hydroxy-*N*-((13*S*)-5^5-(3-(hydroxymethyl)-1H-pyrazol-1-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-

yl)ethane-1-sulfonamide were prepared by chiral separation of Intermediate 318 as described below (Compound 319 and compound 320 respectively).



[000901] 2-hydroxy-*N*-(5^5-(3-(hydroxymethyl)-1H-pyrazol-1-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide (32 mg) was purified by Prep-Chiral-HPLC with the following conditions: Column: CHIRALPAK IG3; Mobile Phase A: Hex(0.2%FA): (EtOH: DCM=1: 1)=60: 40; Flow rate: 1 mL/min mL/min; Gradient: isocratic ; Injection Volume: 1 µl mL to afford

[000902] first eluting isomer: enantiopure 2-hydroxy-*N*-(5^5-(3-(hydroxymethyl)-1H-pyrazol-1-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide (15.3 mg, 91 % yield), LCMS (ESI-MS) m/z = 584.3 $[M+H]^+$.

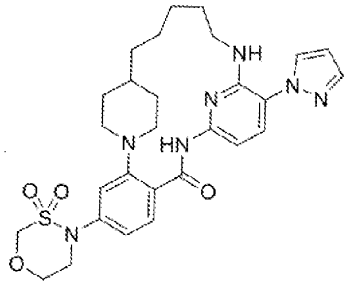
[000903] second eluting isomer: enantiopure 2-hydroxy-*N*-(5^5-(3-(hydroxymethyl)-1H-pyrazol-1-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide (14.3 mg, 86 % yield), LCMS (ESI-MS) m/z = 584.3 $[M+H]^+$.

Table 42A. KIF18A Biochemical data (24h assay) for Examples 319 and 320

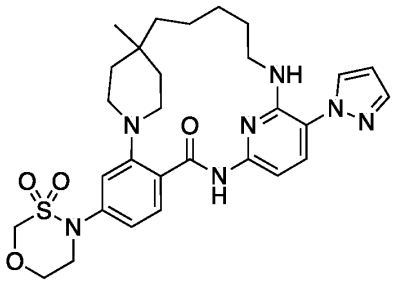
Compound	**KIF18A ADP-Glo IC50, nM (24h)**
First eluting isomer	+++++
Second eluting isomer	++++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

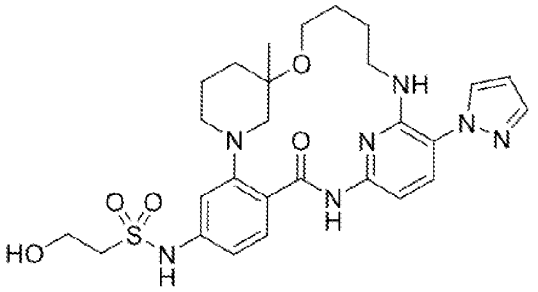
Example 321. 2^5-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)-5^5-(1H-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-3-one was prepared from Intermediate AE following the procedure described for Example 192. 1,3,4-oxathiazinane 3,3-dioxide was used in step 2 (Compound 321).



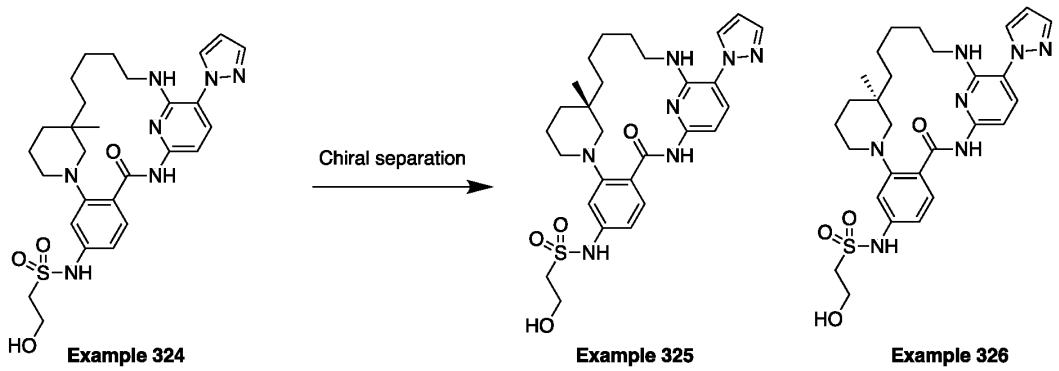
Example 322. 2^5-(3,3-dioxido-1,3,4-oxathiazinan-4-yl)-1^4-methyl-5^5-(1H-pyrazol-1-yl)-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-3-one was synthesized from Intermediate AX following the same procedure as steps 2 and 3 in Example 192. 1,3,4-oxathiazinane 3,3-dioxide was used in Pd-catalyzed coupling (Compound 322).



Example 324. was prepared from Intermediate AZ and intermediate BE following General synthetic route 8 as described in Examples 201/267. The last hydrogenation step was following procedure from Example 199 (Compound 324).



Examples 325 and 326. 2-hydroxy-N-((1^{3}S)-13-methyl-3-oxo-5^5-(1H-pyrazol-1-yl)-11-oxa-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide and 2-hydroxy-N-((1^{3}R)-13-methyl-3-oxo-5^5-(1H-pyrazol-1-yl)-11-oxa-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide were prepared by chiral separation of Intermediate 324 as described below (Compound 325 and compound 326 respectively).



[000904] 2-hydroxy-N-(1^3-methyl-3-oxo-5^5-(1H-pyrazol-1-yl)-11-oxa-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide (60 mg, 0.11 mmol) was separated by Prep-Chiral-HPLC with following condition(Column: CHIRALPAK IM, 2*25 cm, 5 μm; Mobile Phase A: Hex--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20ML/MIN mL/min; Gradient (B%): isocratic 30; Wave Length: 254/220nm nm; RT1(min): 11.967; RT2(min): 15.888; Sample Solvent: EtOH--HPLC; Injection Volume: 1.2 mL; Number Of Runs: 5) to afford

[000905] first eluting isomer: enantiopure 2-hydroxy-N-(1^3-methyl-3-oxo-5^5-(1H-pyrazol-1-yl)-11-oxa-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide (24.2 mg, 39.3 %yield), LCMS (ESI-MS) m/z = 570.2 $[M+H]^+$.

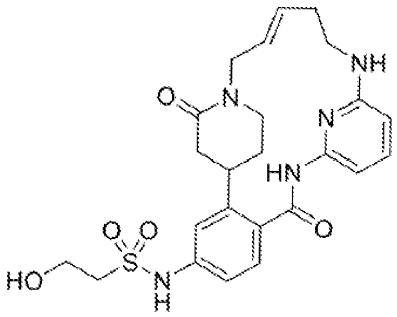
[000906] second eluting isomer: enantiopure 2-hydroxy-N-(1^3-methyl-3-oxo-5^5-(1H-pyrazol-1-yl)-11-oxa-4,6-diaza-5(2,6)-pyridina-1(1,3)-piperidina-2(1,2)-benzenacycloundecaphane-2^5-yl)ethane-1-sulfonamide (25.1 mg, 41.2 % yield), LCMS (ESI-MS) m/z = 570.2 $[M+H]^+$.

Table 43A. KIF18A Biochemical data (24h assay) for Examples 325 and 326

Compound	**KIF18A ADP-Glo IC50, nM (24h)**
First eluting isomer	+++++
Second eluting isomer	++

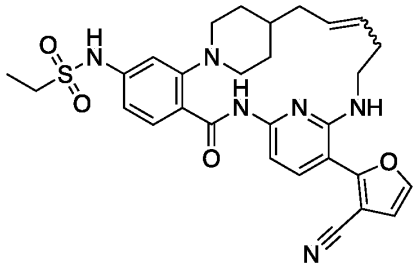
IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

Example 327. Was prepared from Intermediate BF and Intermediate X following General synthetic route 7B, steps 1-4 procedure described for example 140, except for step 1 where $POCl_3$, pyridine in toluene were used for amide coupling (Compound 327).



Example 331. *N*-(5^5-(3-cyanofuran-2-yl)-3-oxo-4,6-diaza-5(2,6)-pyridina-1(1,4)-piperidina-2(1,2)-benzenacycloundecaphan-9-en-2^5-yl)ethanesulfonamide was prepared

following the procedure from step 1 of Example 213 using (3-cyanofuran-2-yl)boronic acid (Compound 331)



Biological data

KIF18A ADP-Glo Assay – 2-hour

[000907] The purpose of KIF18A ADP-Glo assay is to evaluate the inhibition (% inhibition and IC50 values) of small molecule inhibitors by using a Luminescent based ADP-Glo assay. KIF18A catalyzes the production of ADP from ATP. ADP-Glo assay monitors ADP producing biochemical reactions. ADP-Glo is performed in 2 steps upon completion of ATPase reaction: a combined termination of ATPase reaction and depletion of remaining ATP in the first step, and conversion of generated ADP to ATP and the newly produced ATP to light output using luciferase/luciferin reaction in the second step. The luminescent signal generated is proportional to the ADP concentration produced and is correlated with the ATPase activity. KIF18A was purchased from Cytoskeleton (CS-KF18). Typical reaction solutions (5 uL final reaction volume) contained 1% DMSO (± inhibitor), 10 mM MgCI2, 4 uM Taxol, 250 uM ATP (ATP Km = 140.8 uM), 0.01% Pluronic F-68, 0.1 mg/ml pre-formed micro-tubules, and 12.5nM enzyme complex in 15 mM HEPES buffer at pH 7. 5. The assay was initiated with the addition of ATP solution, following a 30-minute pre-incubation of enzyme and inhibitor at room temperature in the reaction mixture. The reaction was stopped after 120 minutes at room temperature by the addition of 5 uL of ADP-GLO Reagent and 10 uL of Kinase Detection Reagent. A ClarioStar plate-reader (BMG) was used to read the luminescent signal. The IC50 determinations were made from a plot of the fractional velocity as a function of inhibitor concentration fit to the 4 parameters IC50 equation with the enzyme concentration as a variable using the GraphPad Prism (San Diego).

Table A. KIF18A Biochemical data, 2-hour assay

Example #	KIF18A ADP-Glo IC50
1	+
2	+
3	+

Example #	KIF18A ADP-Glo IC50
4	+++++
5	++++
8	++++

Example #	KIF18A ADP-Glo IC50
9	++
10	+++
11	+
12	++++
13	+++++
14	+
15	+++++
18	+++++
23	+++
24	++++
25	++
26	++++
27	+
28	++++
29	++
30	+
31	+
32	++
33	++++
34	+
35	+
36	+
37	+
38	+
39	++++
40	+
41	+
42	++++
43	++++
44	++
45	++++
46	++
47	+
48	+++++
49	+++++
50	++++
51	++++
52	+
53	+
54	+++
55	++++
56	+
57	+
58	+++++
59	+++++

Example #	KIF18A ADP-Glo IC50
60	++
61	+
62	+++++
65	+++++
66	+
71	+++
74	+
75	+
76	+
77	+
78	+
79	+
80	+
81	+
82	+
83	+++
84	+
85	+
86	+
87	++++
88	++++
89	++
90	++
91	+++
92	+++
93	+
94	+
95	+
96	+
97	+++
98	+++++
101	++
102	++
103	+++++
104	++++
105	++++
106	+++++
107	+++++
108	++++
111	++++
114	+++++
115	+
116	+++++
117	+
118	++++

Example #	KIF18A ADP-Glo IC50
119	+++++
124	++++
127	+++++
128	+++++
131	++++
134	+++++
135	+++++
136	++++
139	++++
140	+++++
141	+++++
142	+++++
143	++++
146	+++
147	++++
148	++++
151	+++++
152	+++++
155	+++++
156	++++
159	+++++
160	++++
161	+++++
162	+++++
163	++
164	+
165	+++++
166	+++++
167	+++++
168	+++++
171	+++++
172	+++++
173	+++++
174	+++++

Example #	KIF18A ADP-Glo IC50
175	+++++
176	+++++
177	+++++
180	+++++
183	+++++
184	++
185	++++
186	+++++
187	+++++
188	+++++
191	+++++
192	+++++
193	+++++
194	++++
195	+++++
196	++++
199	+++++
200	+++++
201	+++++
202	++++
207	+++++
208	+++++
209	+++++
210	+++++
211	+++++
232	++
238	+++++
240	+++++
245	+++++
246	++++
247	+++++
248	++++
249	+++++
250	++++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

KIF18A ADP-Glo Assay – 24-hour

[000908] The purpose of KIF18A ADP-Glo assay is to evaluate the inhibition (% inhibition and IC50 values) of small molecule inhibitors by using a Luminescent based ADP-Glo assay.

KIF18A catalyzes the production of ADP from ATP. ADP-Glo assay monitors ADP producing biochemical reactions. ADP-Glo is performed in 2 steps upon completion of ATPase reaction: a combined termination of ATPase reaction and depletion of remaining ATP in the first step, and conversion of generated ADP to ATP and the newly produced ATP to light output using luciferase/luciferin reaction in the second step. The luminescent signal generated is proportional to the ADP concentration produced and is correlated with the ATPase activity. KIF18A was purchased from Cytoskeleton (CS-KF18). Typical reaction solutions (5 uL final reaction volume) contained 1% DMSO (± inhibitor), 10 mM MgCI2, 4 uM Taxol, **1000 uM** ATP, 0.01% Pluronic F-68, 0.1 mg/ml pre-formed micro-tubules, and **1** nM enzyme complex in 15 mM HEPES buffer at pH 7. 5. The assay was initiated with the addition of ATP solution, following a 30-minute pre-incubation of enzyme and inhibitor at room temperature in the reaction mixture. The reaction was stopped after **24 hours** at room temperature by the addition of 5 uL of ADP-GLO Reagent and 10 uL of Kinase Detection Reagent. A ClarioStar plate-reader (BMG) was used to read the luminescent signal. The IC50 determinations were made from a plot of the fractional velocity as a function of inhibitor concentration fit to the 4 parameters IC50 equation with the enzyme concentration as a variable using the GraphPad Prism (San Diego).

Table B. KIF18A Biochemical data, 24-hour assay

Example #	KIF18A ADP-Glo IC50
57	+
58	+++++
59	++++
61	+
62	+++++
65	++++
66	+
68	+++
72	++++
73	+
74	+
75	+
77	++
78	+
79	+
80	+
81	+
83	+++
84	+
85	+
86	++
87	+++++
88	+++++
89	++
90	+++
91	+++
92	+++
93	+
94	+
95	+
96	+
97	++++
98	+++++
102	+++
103	+++++
104	+++++
105	++++
106	+++++

107	+++++
108	+++++
109	+++++
110	+++
111	++++
114	+++++
116	+++++
117	+
118	++++
119	+++++
124	+++++
127	+++++
128	+++++
131	+++++
134	+++++
135	+++++
136	+++++
137	+++++
139	+++++
140	+++++
141	+++++
142	+++++
143	++++
146	++++
147	++++
148	+++++
151	+++++
152	+++++
155	+++++
156	+++++
159	+++++
161	+++++
162	+++++
163	++
164	+
165	+++++
166	+++++
167	+++++
168	+++++
171	+++++
172	+++++
173	+++++
174	+++++
175	+++++
176	+++++
177	+++++

180	+++++
183	+++++
184	++++
185	++++
186	+++++
187	+++++
188	+++++
191	+++++
192	+++++
193	+++++
194	+++++
195	+++++
196	+++++
199	+++++
200	+++++
201	+++++
207	+++++
208	+++++
209	+++++
210	+++++
211	+++++
212	+++++
213	+++++
214	+++++
215	+++++
216	+++++
217	++++
218	+++++
219	+++++
220	+++++
221	+
222	+++++
223	+++++
224	+++++
225	+++++
226	++++
227	++
228	+++++
229	+++++
230	+++++
231	+++++
232	++++
235	+++++
238	+++++
239	+++++
240	+++++

243	+++++
244	+++++
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261	+
262	+++++
263	+++++
264	+++++
267	+++++
268	+++++
269	+++
270	+++++
271	+++++
272	+++++
273	+++++
274	+++++
275	+++++
276	+++++
277	+++++

280	+++++
283	+++++
286	+++++
289	+++++
290	+++++
291	+++++
292	+++++
293	++++
294	+++++
295	+++++
296	+++++
297	+++++
298	++++
299	+++++
300	+++++
301	+++++
302	+++++
303	++++
304	+++
305	+++++
306	+++++
307	++
308	+++++
317	+++++
318	+++++
321	+++++
322	+++++
324	+++++
327	+
331	+++
332	+++++

IC50 data in nM, values <100 are denoted at +++++; values from 100-499 are denoted as ++++; values from 500-999 are denoted as +++; values from 1000-4999 are denoted as ++; values of 5000 and greater are denoted as +

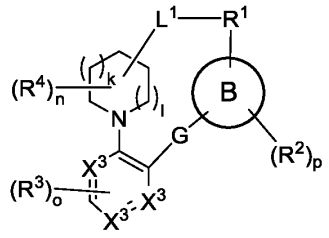
[000909] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope

of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

What is claimed is:

1. A compound having the structure of Formula (I-0), or a pharmaceutically acceptable salt or solvate thereof:



(I-0)

wherein:

each X^3 is independently CH or N;

ring B is a 5- or 6- membered heteroaryl or phenyl;

L^1 is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond, -O-, -NL^{1a1}-, -S-, or -SO_2-;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene;

G is -(C=O)-NH- or -NH-(C=O)-;

R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-Q-, -NR^{1a}-CO-, -CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a};

R^{1a} is hydrogen, -C(=O)R^{1a1}, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

R^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

Q is optionally substituted C_1-C_6alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene;

each R^2 is independently halogen, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl, or two R^2 are taken together to form an oxo, an optionally substituted C_3-C_8 cycloalkyl, an optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl;

each R^{2a} is independently hydrogen or optionally substituted C_1-C_6 alkyl;

each R^3 is independently halogen, -CN, -$(CH_2)_m$-$N(R^{3a})_2$-, -OR^{3a}, -$N(R^{3a})_2$, -$N(SO_2R^{3b})R^{3a}$, -SR^{3a}, -SO_2R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-R^{3a}, -NH-S(O)(NH)-R^{3a}, -

NH-S(O)(NH)-$(CH_2)_m$-R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-OR^{3b}, -NH-S(O)R^{3a}-$(CH_2)_m$-OR^{3b}, -NH-$S(O)_2$-R^{3c}, -$B(R^{3a})_3$, -$P(R^{3a})_3$, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl;

each R^{3a} is independently hydrogen, -C(O)OR^{3b}, optionally substituted C_1-C_6 alkyl, or -$N(R^{3b})_2$;

R^{3b} is hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_2-C_6 alkenyl;

R^{3c} is C_3-C_8 cycloalkyl or 3- to 8- membered heterocycle;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, two or more R^4 combine to form a C_3-C_8 cycloalkyl, or two R^4 combine to form a C_1-C_3 alkylene bridge;

k is 0 to 2;

l is 0 to 2 ;

m is 1 to 6;

n is 0 to 9;

o is 0 to 4;

p is 0 to 4; and

wherein when any one of variable G, L^1, R^1, R^2, R^3, or R^4 are present, the bond to variable G, L^1, R^1, R^2, R^3 or R^4 replaces a hydrogen on a carbon or nitrogen atom.

2. The compound of claim 1, wherein ring B is phenyl.

3. The compound of claim 1, wherein ring B is a 5-membered heteroaryl, 6-membered heteroaryl, or 9 membered bicyclic heteroaryl.

4. The compound of claim 1, wherein ring B is a 6-membered heteroaryl.

5. The compound of claim 4, wherein ring B is triazine, pyridine, pyrimidine, pyridazine, pyrazinone, pyrazine, or imidazopyrizine.

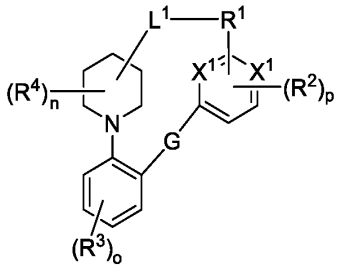
6. The compound of any one of claims 1 to 5, wherein k is 0 or 1.

7. The compound of any one of claims 1 to 6, wherein l is 0 or 1.

8. The compound of any one of claims 1 to 7, wherein each X^3 is CH.

9. The compound of any one of claims 1 to 8, wherein at least one of $X^3$is N.

10. The compound of claim 1, having the structure of Formula (I-0a), or a pharmaceutically acceptable salt or solvate thereof:

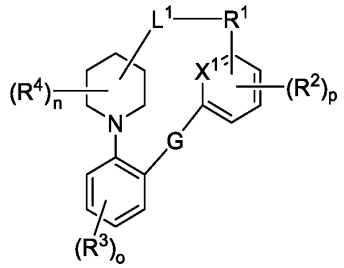


(I-0a)

wherein:

each X^1 is independently CH or N.

11. The compound of claim 1 or 2, having the structure of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



(I).

12. The compound of any one of claims 1 to 11, wherein o is 1.

13. The compound of any one of claims 1 to 12, wherein p is 0 to 2.

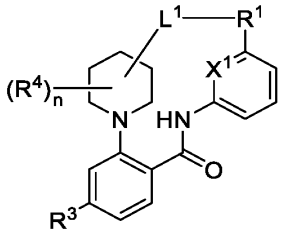
14. The compound of claim 13, wherein p is 0 or 1.

15. The compound of claim 14, wherein p is 0.

16. The compound of any one of claims 1 to 15, wherein G is -NH-(C=O)-.

17. The compound of any one of claims 1 to 15, wherein G is -(C=O)-NH-.

18. The compound of claim 17, wherein the compound has the structure of Formula (II), or a pharmaceutical salt or solvate thereof:



(II)

wherein:

X^1 is CH or N;

$L^1$is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond, -O-, or -NL^{1a1}-;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

L^{1b} is optionally substituted C_1-C_8 alkylene;

R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-C_1-C_6alkylene-, -NR^{1a}-CO-,-CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a};

R^{1a} is hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

R^3 is halogen, -CN, -OR^{3a}, -$N(R^{3a})_2$, -$N(SO_2R^{3b})R^{3a}$, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-OR^{3b}, -NH-$S(O)_2$-R^{3c}, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl;

each R^{3a} is independently hydrogen or C_1-C_6 alkyl;

R^{3b} is hydrogen or C_1-C_6 alkyl;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, two or more R^4 combine to form a C_3-C_8 cycloalkyl, or two R^4 combine to form a C_1-C_3 alkylene bridge;

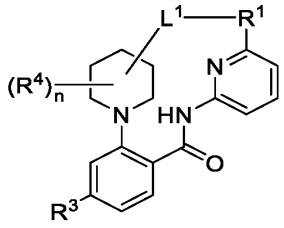
m is 1 to 3; and

n is 1 or 2.

19. The compound of any one of claims 10 to 18, wherein X^1 is N.

20. The compound of any one of claims 10 to 18, wherein X^1 is CH.

21. The compound of claim 19, wherein the compound has the structure of Formula (III-A), or a pharmaceutical salt or solvate thereof:



(III-A)

wherein:

L^1 is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond or -O-;

L^{1b} is optionally substituted C_1-C_8 alkylene;

R^1 is a bond, -O-, -NR^{1a}-, or -NR^{1a}-C_1-C_3 alkylene-;

R^{1a} is hydrogen, -C(=O)H, optionally substituted C_1-C_6 alkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl;

R^3 is halogen, -$N(R^{3a})_2$, -$N(SO_2R^{3b})R^{3a}$, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-OR^{3b}, -NH-$S(O)_2$-R^{3c}, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl;

R^{3a} is C_1-C_6 alkyl;

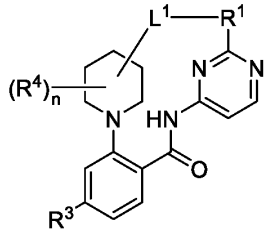
R^{3b} is hydrogen or C_1-C_6 alkyl;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, or two or more R^4 combine to form a C_3-C_8 cycloalkyl;

m is 1 to 3; and

n is 0 to 2.

22. The compound of claim 10, wherein the compound has the structure of Formula (III-B), or a pharmaceutical salt or solvate thereof:



(III-B)

wherein:

L^1 is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond or -O-;

L^{1b} is optionally substituted C_1-C_8 alkylene;

R^1 is a bond, -O-, -NR^{1a}-, or -NR^{1a}-C_1-C_3 alkylene-

R^{1a} is hydrogen, -C(=O)H, optionally substituted C_1-C_6 alkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl;

R^3 is halogen, -$N(R^{3a})_2$, -$N(SO_2R^{3b})R^{3a}$, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-OR^{3b}, -NH-$S(O)_2$-R^{3c}, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl;

R^{3a} is C_1-C_6 alkyl;

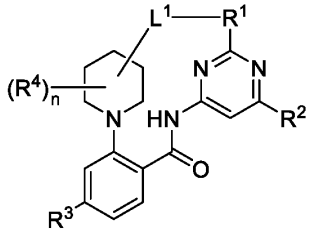
R^{3b} is hydrogen or C_1-C_6 alkyl;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, or two or more R^4 combine to form a C_3-C_8 cycloalkyl;

m is 1 to 3; and

n is 0 to 2.

23. The compound of claim 10, wherein the compound has the structure of Formula (III-C), or a pharmaceutical salt or solvate thereof:



(III-C)

wherein:

L^1 is a linker comprising the structure $-L^{1a}-L^{1b}-$;

L^{1a} is a bond, -O-, or $-NL^{1a1}-$;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or $-SO_2$-C_1-C_6 alkyl;

L^{1b} is optionally substituted C_1-C_8 alkylene;

R^1 is a bond, -O-, $-NR^{1a}-$, $-NR^{1a}$-C_1-C_6alkylene-, $-NR^{1a}$-CO-,-CO-$NR^{1a}-$, $-NR^{1a}$-SO_2-, -S-, $-SO_2-$, or $-SO_2$-NR^{1a};

R^{1a} is hydrogen, -C(=O)H, C_1-C_6 alkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl;

R^2 is halogen, $-OR^{2a}$, $-N(R^{2a})_2$, $-S(O)_2N(R^{2a})_2$, $-SO_2$-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl;

each R^{2a} is independently hydrogen or C_1-C_6 alkyl;

R^3 is halogen, -CN, $-OR^{3a}$, $-N(R^{3a})_2$, $-N(SO_2R^{3b})R^{3a}$, $-NR^{3a}$-$S(O)_2$-$(CH_2)_m$-R^{3a}, $-NR^{3a}$-$S(O)_2$-$(CH_2)_m$-OR^{3b}, -NH-$S(O)_2$-R^{3c}, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl;

R^{3a} is hydrogen or C_1-C_6 alkyl;

R^{3b} is hydrogen or C_1-C_6 alkyl;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, or two or more R^4 combine to form a C_3-C_8 cycloalkyl;

m is 1 to 3; and

n is 0, 1, or 2.

24. The compound of any one of claims 1 to 23, wherein R^2 is halogen, $-OR^{2a}$, $-N(R^{2a})_2$, optionally substituted C_1-C_6 alkyl, or $-S(O)_2N(R^{2a})_2$.

25. The compound of claim 23 or 24, wherein R^2 is C_1-C_6 alkyl.

26. The compound of any one of claims 1 to 25, wherein R^2 is methyl.

27. The compound of any one of claims claim 1 to 24, wherein each R^{2a} is independently optionally substituted C_1-C_4 alkyl.

28. The compound of claim 27, wherein each R^{2a} is independently methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, or tert-butyl.

29. The compound of any one of claims 1 to 28, wherein L^{1a} is a bond or -O-.

30. The compound of any one of claims 1 to 29, wherein L^{1a} is a bond.

31. The compound of any one of claims 1 to 30, wherein L^{1b} is optionally substituted C_1-C_4 alkylene.

32. The compound of claim 31, wherein L^{1b} is C_1-C_4 alkylene substituted with oxo or C_3-C_6 cycloalkyl.

33. The compound of claim 32, wherein L^{1b} is C_1-C_4 alkylene substituted with oxo or cyclopropyl.

34. The compound of any one of claims 1 to 33, wherein L^1 is $–(CH_2)_4–$, $–(CH_2)_3–$, $–(CH_2)_2–$, $–CH_2–$ –cyclopropyl-$(CH_2)_3–$, –cyclopropyl-$(CH_2)_2–$, $–O(CH_2)_3–$, $–O(CH_2)_2–$, or $–O(CH_2)–$.

35. The compound of any one of claims 1 to 34, wherein R^1 is a bond, -O-, $-NR^{1a}-$, $-NR^{1a}$-C_1-C_6alkylene-, $-NR^{1a}$-CO-, -CO-$NR^{1a}-$, $-NR^{1a}$-SO_2-, or -SO_2-NR^{1a}.

36. The compound of claim 35, wherein R^1 is $-NR^{1a}-$.

37. The compound of claim 35, wherein R^1 is a bond.

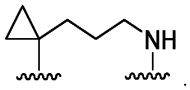
38. The compound of any one of claims 1 to 36, wherein R^{1a} is hydrogen, -C(=O)H, C_1-C_3 alkyl, C_1-C_3 alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl.

39. The compound of claim 38, wherein R^{1a} is hydrogen.

40. The compound of claim 38, wherein R^{1a} is -CH_2-cyclopropyl.

41. The compound of claim 38, wherein R^{1a} is -SO_2-CH_3.

42. The compound of any one of claims 1 to 35, wherein L^1-R^1 is:



43. The compound of any one of claims 1 to 35, wherein L^1-R^1 is $–(CH_2)_4NH–$, –cyclopropyl-$(CH_2)_3NH–$, $–(CH_2)_3NH–$, $–(CH_2)_3NCH_3–$, $–(CH_2)_3N$-(CH_2-cyclopropyl)–, $–(CH_2)_2NH–$, $–(CH_2)_3–$, $–(CH_2)_3–$, $–(CH_2)_2–$, $–CH_2–$, $–O(CH_2)_3–$, $–O(CH_2)_2–$, $–O(CH_2)_2O–$, $–O(CH_2)_2NH–$, $–(CH_2)_3NSO_2–$, $–(CH_2)_2N(SO_2Me)CH_2–$, $–(CH_2)_2N(Me)CH_2–$, $–(CH_2)_2N(CH_2$-cyclopropyl$)CH_2–$, $–(CH_2)_2NHCH_2–$, $–(CH_2)_2CONH–$, $–(CH_2)_2CONMe–$, $–(CH_2)_2CON(CH_2$-cyclopropyl$)–$, $–(CH_2)_2SO_2NH–$, $–(CH_2)_2NHCO–$, $–(CH_2)_2N(Me)CO–$, $–(CH_2)_2N(CH_2$-cyclopropyl$)CO–$, or $–(CH_2)_2NHSO_2–$.

44. The compound of claim 43, wherein L^1-R^1 is $–(CH_2)_4NH–$ or $–(CH_2)_3NH–$.

45. The compound of any one of claims 1 to 44, wherein each R^3 is independently -$N(R^{3a})_2$, -$N(SO_2R^{3b})R^{3a}$, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-OR^{3b}, -NH-$S(O)_2$-R^{3c}, or optionally substituted 5- to 8- membered heterocycle.

46. The compound of any one of claims 1 to 45, wherein each R^3 is independently -$NR^{3a}S(O)_2$-$(CH_2)_m$-OR^{3b} or -NR^{3a}-$S(O)_2$-$(CH_2)_m$-R^{3a}.

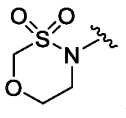
47. The compound of claim 45, wherein R^3 is optionally substituted 5- to 8- membered heterocycle, which is optionally substituted with one or more substituents selected from oxo, methyl, and methoxy.

48. The compound of claim 45 or 46, wherein each R^{3a} is independently hydrogen, methyl, or ethyl, wherein the ethyl is optionally substituted with one or more substituents selected from methyl and -OH.

49. The compound of any one of claims 45 or 46, wherein R^{3b} is hydrogen, methyl, ethyl, or propyl.

50. The compound of claim 45, wherein R^{3c} is oxetanyl.

51. The compound of claim 45, wherein m is 2.

52. The compound of claim 45, wherein each R^3 is independently $-NHSO_2(CH_2)_2OH$, $-NHSO_2C(CH_3)_2CH_2OH$, $-NHSO_2C(cyclopropyl)CH_2OH$, $-NHSO_2CH(CH_3)CH_2OH$, $-NMeSO_2(CH_2)_2OH$, $-NHSO_2CH_2CH_3$, $-NHSO_2CHCH_2$, $-NHSO_2$-oxetanyl, $-NMeSO_2CH_3$, $-N(SO_2Me)(CH_2)_2OH$, or  .

53. The compound of claim 52, wherein each R^3 is independently $-NHS(O)_2-(CH_2)_2-OH$.

54. The compound of any one of claims 1 to 53, wherein n is 2.

55. The compound of any one of claims 1 to 54, wherein two R^4 combine to form a C_3-C_8 cycloalkyl.

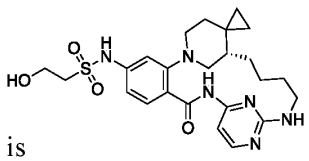
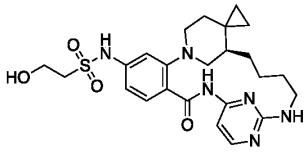
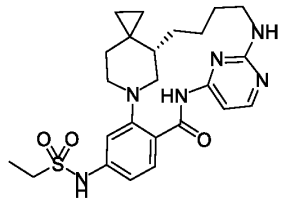
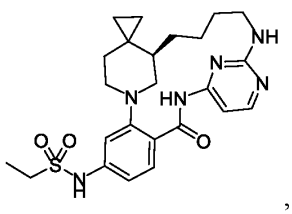
56. The compound of claim 55, wherein the two R^4 are attached to the same carbon atom.

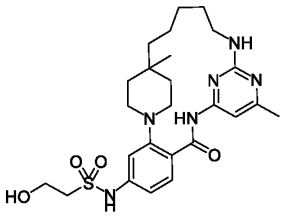
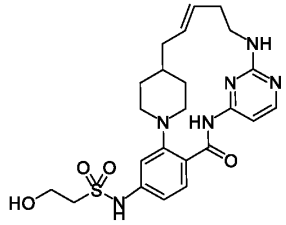
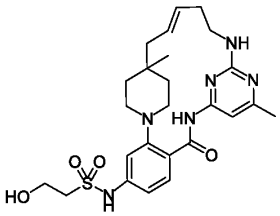
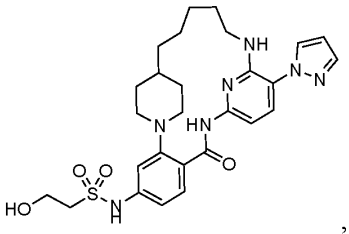
57. The compound of claim 54 or 55, wherein the two R^4 groups combine to form a cyclopropyl.

58. The compound of claim 54 or 55, wherein the two R^4 groups combine to form a cyclobutyl.

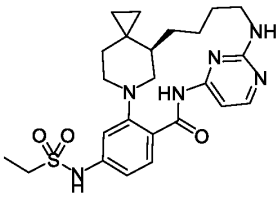
59. The compound of claim 54, wherein the two R^4 are attached to different carbon atoms.

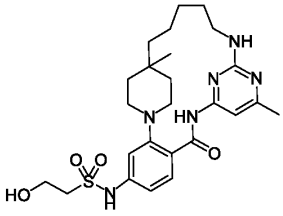
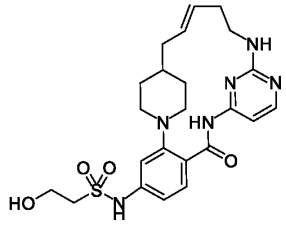
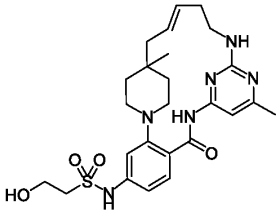
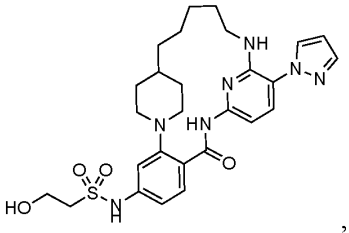
60. The compound of claim 59, wherein the two R^4 groups combine to form a (1R,5S)-8-azabicyclo[3.2.1]octane.

61. The compound of claim 1, wherein the compound is  ,  ,  ,  ,

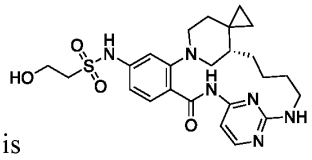





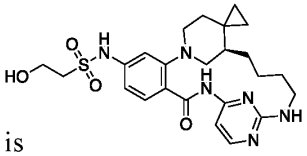
, or a pharmaceutically acceptable salt or solvate of any one thereof.

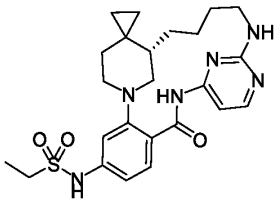
62. The compound of claim 1, wherein the compound is ,  ,

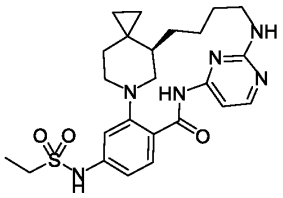





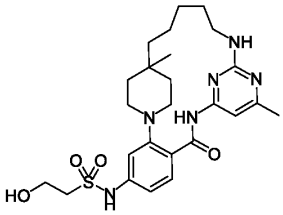
, or a pharmaceutically acceptable salt or solvate of any one thereof.

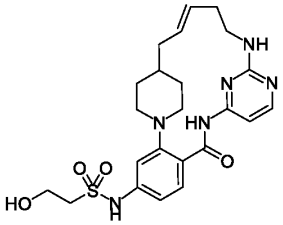
63. The compound of claim 1, wherein the compound is  or a pharmaceutically acceptable salt or solvate thereof.

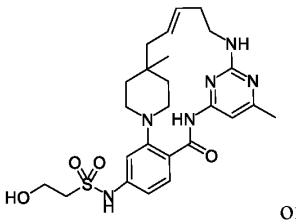
64. The compound of claim 1, wherein the compound is  or a pharmaceutically acceptable salt or solvate thereof.

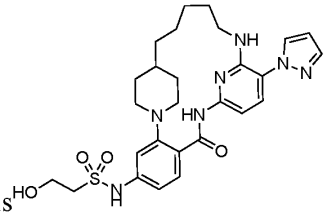
65. The compound of claim 1, wherein the compound is  or a pharmaceutically acceptable salt or solvate thereof.

66. The compound of claim 1, wherein the compound is  or a pharmaceutically acceptable salt or solvate thereof.

67. The compound of claim 1, wherein the compound is  or a pharmaceutically acceptable salt or solvate thereof.

68. The compound of claim 1, wherein the compound is  a pharmaceutically acceptable salt or solvate thereof.

69. The compound of claim 1, wherein the compound is  or a pharmaceutically acceptable salt or solvate thereof.

70. The compound of claim 1, wherein the compound is  or a pharmaceutically acceptable salt or solvate thereof.

71. A compound having the structure of a compound of Table 1 or a pharmaceutically acceptable salt thereof.

72. A pharmaceutical composition comprising a compound, or pharmaceutically acceptable salt or solvate thereof, as described in any one of claims 1 to 70 and a pharmaceutically acceptable excipient.

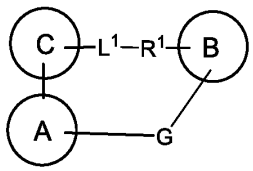
73. A method of treating cancer in a patient in need thereof, comprising administering to the patient a compound as described in any one of claims 1 to 70.

74. The method of claim 73 wherein the cancer is bladder cancer, endometrial cancer, lung squamous cell cancer, breast cancer, colon cancer, kidney cancer, liver cancer, lung cancer, small cell lung cancer, esophagus cancer, gall-bladder cancer, brain cancer, head and neck cancer, ovarian cancer, pancreas cancer, stomach cancer, cervix cancer, thyroid cancer, prostate cancer or skin cancer.

75. A method of inhibiting KIF18A comprising contacting the enzyme with a compound of any one of claims 1 to 70 or a composition of claim 71, or a pharmaceutically acceptable salt or solvate thereof.

76. A compound of any one of claims 1 to 70 or a composition of claim 71, or a pharmaceutically acceptable salt or solvate thereof, for use in a method of treating cancer.

77. An adduct comprising a KIF18A and a compound of Formula (B), wherein the structure of Formula (B) is:



(B)

wherein:

ring A is optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12-membered heteroaryl;

ring B is optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12-membered heteroaryl;

ring C is optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 5- to 12 membered heterocyclyl, optionally substituted C_6-C_{12} aryl or optionally substituted 5- to 12- membered heteroaryl;

G is -(C=O)-NH- or -NH-(C=O)-;

L^1 is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond, -O-, -NL^{1a1}-, -S-, or -SO_2-;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene;

R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-Q-, -NR^{1a}-CO-, -CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a};

R^{1a} is hydrogen, -C(=O)H, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl; and

Q is optionally substituted C_1-C_6alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene.

78. The adduct of claim 77, wherein ring A is optionally substituted C_6-C_{12} aryl.

79. The adduct of claim 78, wherein ring A is optionally substituted phenyl.

80. The adduct of any one of claims 77 to 79, wherein ring B is optionally substituted C_6 aryl or optionally substituted 5- to 6- membered heteroaryl.

81. The adduct of claim 80, wherein ring B is optionally substituted 6- membered heteroaryl.

82. The adduct of claim 80, wherein ring B is optionally substituted phenyl or optionally substituted pyridinyl.

83. The adduct of any one of claims 77 to 82, wherein ring C is optionally substituted C_3-C_{10} cycloalkyl or optionally substituted 5- to 12 membered heterocyclyl.

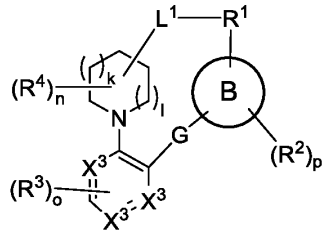
84. The adduct of claim 83, wherein ring C is optionally substituted 5- to 12- membered heterocyclyl.

85. The adduct of claim 84, wherein ring C is optionally substituted 5- to 8- membered heterocyclyl.

86. The adduct of claim 85, wherein ring C is optionally substituted 5- to 6- membered heterocyclyl.

87. The adduct of claim 86, wherein ring C is optionally substituted piperidinyl.

88. The adduct of claim 77, wherein the compound of Formula (B) has a structure of Formula (I-0):



(I-0)

wherein:

each X^3 is independently CH or N;

ring B is a 5- or 6- membered heteroaryl or phenyl;

L^1 is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond, -O-, -NL^{1a1}-, -S-, or -SO_2-;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene;

G is -(C=O)-NH- or -NH-(C=O)-;

R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-Q-, -NR^{1a}-CO-, -CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a};

R^{1a} is hydrogen, -C(=O)H, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

R^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

Q is optionally substituted C_1-C_6alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene;

each R^2 is independently halogen, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl, or two R^2 are taken together to form an oxo, an optionally substituted C_3-C_8 cycloalkyl, an optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl;

each R^{2a} is independently hydrogen or optionally substituted C_1-C_6 alkyl;

each R^3 is independently halogen, -CN, -$(CH_2)_m$-$N(R^{3a})_2$-, -OR^{3a}, -$N(R^{3a})_2$, -$N(SO_2R^{3b})R^{3a}$, -SR^{3a}, -SO_2R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-R^{3a}, -NH-S(O)(NH)-$(CH_2)_m$-R^{3a}, -NH-S(O)(NH)-R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-OR^{3b}, -NH-S(O)R^{3a}-$(CH_2)_m$-OR^{3b}, -NH-$S(O)_2$-R^{3c}, -$B(R^{3a})_3$, -$P(R^{3a})_3$, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl$_3$;

each R^{3a} is independently hydrogen, -C(O)OR^{3b}, optionally substituted C_1-C_6 alkyl, or -N(R^{3b})$_2$;

R^{3b} is hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_2-C_6 alkenyl;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, two or more R^4 combine to form a C_3-C_8 cycloalkyl, or two R^4 combine to form a C_1-C_3 alkylene bridge;

k is 0 to 2;

l is 0 to 2 ;

m is 1 to 6;

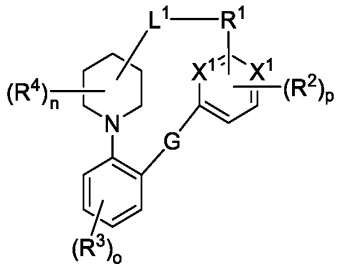
n is 0 to 9;

o is 1 to 4;

p is 0 to 4; and

wherein when any one of variable G, L^1, R^1, R^2, R^3, or R^4 are present, the bond to variable G, L^1, R^1, R^2, R^3 or R^4 replaces a hydrogen on a carbon or nitrogen atom.

89. The adduct of claim 88, wherein the compound of Formula (B) has the structure of Formula (I-0a):

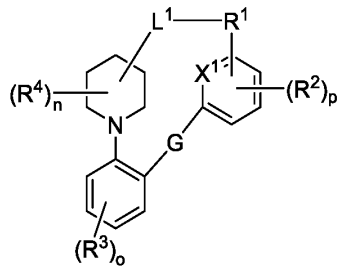


(I-0a)

wherein:

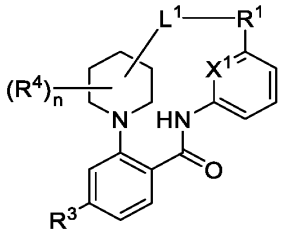
each X^1 is independently CH or N.

90. The adduct of any one of claims 77 to 89, wherein the compound of Formula (B) has a structure of Formula (I):



(I).

91. The adduct of any one of claims 77 to 90, wherein the compound of Formula (B) has a structure of Formula (II):



(II)

wherein:

X^1 is CH or N;

$L^1$is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond, -O-, or -NL^{1a1}-;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

L^{1b} is optionally substituted C_1-C_8 alkylene;

R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-C_1-C_6alkylene-, -NR^{1a}-CO-,-CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a};

R^{1a} is hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

R^3 is halogen, -CN, -OR^{3a}, -$N(R^{3a})_2$, -SO_2R^{3a}, or -NH-$S(O)_2$-$(CH_2)_m$-OR^{3b},

each R^{3a} is independently hydrogen or C_1-C_6 alkyl;

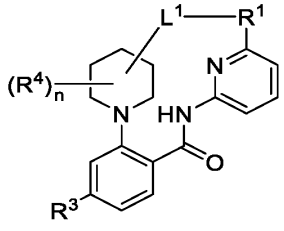
R^{3b} is hydrogen or C_1-C_6 alkyl;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, two or more R^4 combine to form a C_3-C_8 cycloalkyl, or two R^4 combine to form a C_1-C_3 alkylene bridge;

m is 1 to 3; and

n is 1 or 2.

92. The adduct of any one of claims 77 to 91, wherein the compound of Formula (B) has a structure of Formula (III-A):



(III-A)

wherein:

$L^1$is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond or -O-;

L^{1b} is optionally substituted C_1-C_8 alkylene;

R^1 is a bond, -O-, -NR^{1a}-, or -NR^{1a}-C_1-C_3 alkylene-;

R^{1a} is hydrogen, -C(=O)H, optionally substituted C_1-C_6 alkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl;

R^3 is halogen, -NH-$S(O)_2$-$(CH_2)_m$-R^{3a}, or -NH-$S(O)_2$-$(CH_2)_m$-OR^{3b},

R^{3a} is C_1-C_6 alkyl;

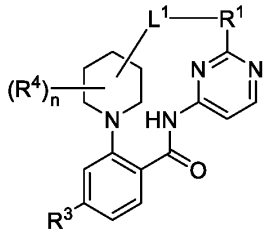
R^{3b} is hydrogen or C_1-C_6 alkyl;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, or two or more R^4 combine to form a C_3-C_8 cycloalkyl;

m is 1 to 3; and

n is 0 to 2.

93. The adduct of any one of claims 77 to 89, wherein the compound of Formula (B) has a structure of Formula (III-B):



(III-B)

wherein:

$L^1$is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond or -O-;

L^{1b} is optionally substituted C_1-C_8 alkylene;

R^1 is a bond, -O-, -NR^{1a}-, or -NR^{1a}-C_1-C_3 alkylene-

R^{1a} is hydrogen, -C(=O)H, optionally substituted C_1-C_6 alkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl;

R^3 is halogen, -NH-$S(O)_2$-$(CH_2)_m$-R^{3a}, or -NH-$S(O)_2$-$(CH_2)_m$-OR^{3b},

R^{3a} is C_1-C_6 alkyl;

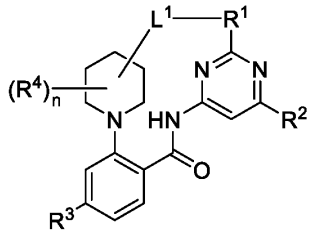
R^{3b} is hydrogen or C_1-C_6 alkyl;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, or two or more R^4 combine to form a C_3-C_8 cycloalkyl;

m is 1 to 3; and

n is 0 to 2.

94. The adduct of any one of claims 77 to 90, wherein the compound of Formula (B) has a structure of Formula (III-C):



(III-C)

wherein:

L^1 is a linker comprising the structure $-L^{1a}-L^{1b}-$;

L^{1a} is a bond, -O-, or $-NL^{1a1}-$;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or $-SO_2$-C_1-C_6 alkyl;

L^{1b} is optionally substituted C_1-C_8 alkylene;

R^1 is a bond, -O-, $-NR^{1a}-$, $-NR^{1a}$-C_1-C_6alkylene-, $-NR^{1a}$-CO-,-CO-$NR^{1a}-$, $-NR^{1a}$-SO_2-, -S-, $-SO_2-$, or $-SO_2$-NR^{1a};

R^{1a} is hydrogen, -C(=O)H, C_1-C_6 alkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl;

R^2 is halogen, $-OR^{2a}$, $-N(R^{2a})_2$, $-S(O)_2N(R^{2a})_2$, $-SO_2$-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_6 cycloalkyl;

each R^{2a} is independently hydrogen or C_1-C_6 alkyl;

R^3 is halogen, -CN, $-OR^{3a}$, $-N(R^{3a})_2$, $-SO_2R^{3a}$, or $-NH-S(O)_2-(CH_2)_m-OR^{3b}$,

R^{3a} is hydrogen or C_1-C_6 alkyl;

R^{3b} is hydrogen or C_1-C_6 alkyl;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, or two or more R^4 combine to form a C_3-C_8 cycloalkyl;

m is 1 to 3; and

n is 0, 1, or 2.

95. The adduct of any one of claims 77 to 94, wherein R^2 is halogen, $-OR^{2a}$, $-N(R^{2a})_2$, optionally substituted C_1-C_6 alkyl, or $-S(O)_2N(R^{2a})_2$.

96. The adduct of claim 95, wherein R^2 is C_1-C_6 alkyl.

97. The adduct of any one of claims 1 to 96, wherein R^2 is methyl.

98. The adduct of claim 95, wherein each R^{2a} is independently optionally substituted C_1-C_4 alkyl.

99. The adduct of claim 98, wherein each R^{2a} is independently methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, or tert-butyl.

100. The adduct of any one of claims 77 to 99, wherein L^{1a} is a bond or -O-.

101. The adduct of claim 100, wherein L^{1a} is a bond.

102. The adduct of any one of claims 77 to 101, wherein L^{1b} is optionally substituted C_1-C_4 alkylene.

103. The adduct of claim 102, wherein L^{1b} is C_1-C_4 alkylene substituted with oxo or C_3-C_6 cycloalkyl.

104. The adduct of claim 103, wherein L^{1b} is C_1-C_4 alkylene substituted with oxo or cyclopropyl.

105. The adduct of any one of claims 77 to 104, wherein L^1 is $–(CH_2)_4–$, $–(CH_2)_3–$, $–(CH_2)_2–$, $–CH_2–$ –cyclopropyl-$(CH_2)_3–$, –cyclopropyl-$(CH_2)_2–$, $–O(CH_2)_3–$, $–O(CH_2)_2–$, or $–O(CH_2)–$.

106. The adduct of any one of claims 77 to 105, wherein R^1 is a bond, -O-, $-NR^{1a}-$, $-NR^{1a}-C_1$-C_6alkylene-, $-NR^{1a}$-CO-, -CO-$NR^{1a}-$, $-NR^{1a}-SO_2-$, or $-SO_2-NR^{1a}$.

107. The adduct of claim 106, wherein R^1 is $-NR^{1a}-$.

108. The adduct of claim 107, wherein R^1 is a bond.

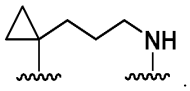
109. The adduct of any one of claims 77 to 107, wherein R^{1a} is hydrogen, C_1-C_3 alkyl, C_1-C_3 alkylene-C_3-C_6 cycloalkyl, or $-SO_2-C_1$-C_6 alkyl.

110. The adduct of claim 109, wherein R^{1a} is hydrogen.

111. The adduct of claim 109, wherein R^{1a} is $-CH_2$-cyclopropyl.

112. The adduct of claim 109, wherein R^{1a} is $-SO_2-CH_3$.

113. The adduct of any one of claims 77 to 106, wherein L^1-R^1 is:



.

114. The adduct of any one of claims 77 to 105, wherein L^1-R^1 is $–(CH_2)_4NH–$, –cyclopropyl-$(CH_2)_3NH–$, $–(CH_2)_3NH–$, $–(CH_2)_3NCH_3–$, $–(CH_2)_3N$-(CH_2-cyclopropyl)–, $–(CH_2)_2NH–$, $–(CH_2)_3–$, $–(CH_2)_3–$, $–(CH_2)_2–$, $–CH_2–$, $–O(CH_2)_3–$, $–O(CH_2)_2–$, $–O(CH_2)_2O–$, $–O(CH_2)_2NH–$, $–(CH_2)_3NSO_2–$, $–(CH_2)_2N(SO_2Me)CH_2–$, $–(CH_2)_2N(Me)CH_2–$, $–(CH_2)_2N(CH_2$-cyclopropyl$)CH_2–$, $–(CH_2)_2NHCH_2–$, $–(CH_2)_2CONH–$, $–(CH_2)_2CONMe–$, $–(CH_2)_2CON(CH_2$-cyclopropyl$)–$, $–(CH_2)_2SO_2NH–$, $–(CH_2)_2NHCO–$, $–(CH_2)_2N(Me)CO–$, $–(CH_2)_2N(CH_2$-cyclopropyl$)CO–$, or $–(CH_2)_2NHSO_2–$.

115. The adduct of claim 114, wherein L^1-R^1 is $–(CH_2)_4NH–$ or $–(CH_2)_3NH–$.

116. The adduct of any one of claims 77 to 115, wherein each R^3 is independently $-N(R^{3a})_2$, $-N(SO_2R^{3b})R^{3a}$, $-NR^{3a}-S(O)_2-(CH_2)_m-R^{3a}$, $-NR^{3a}-S(O)_2-(CH_2)_m-OR^{3b}$, $-NH-S(O)_2-R^{3c}$, or optionally substituted 5- to 8- membered heterocycle.

117. The adduct of any one of claims 116, wherein each R^3 is independently $-NR^{3a}S(O)_2-(CH_2)_m-OR^{3b}$ or $-NR^{3a}-S(O)_2-(CH_2)_m-R^{3a}$.

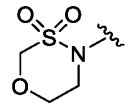
118. The adduct of claim 116, wherein R^3 is optionally substituted 5- to 8- membered heterocycle, which is optionally substituted with one or more substituents selected from oxo, methyl, and methoxy.

119. The adduct of claim 116 or 117, wherein each R^{3a} is independently hydrogen, methyl, or ethyl, wherein the ethyl is optionally substituted with one or more substituents selected from methyl and -OH.

120. The adduct of any one of claims 116 or 117, wherein R^{3b} is hydrogen, methyl, ethyl, or propyl.

121. The adduct of claim 115, wherein R^{3c} is oxetanyl.

122. The adduct of claim 116, wherein m is 2.

123. The adduct of claim 116, wherein each R^3 is independently $-NHSO_2(CH_2)_2OH$, $-NMeSO_2(CH_2)_2OH$, $-NHSO_2CH_2CH_3$, $-NHSO_2$-oxetanyl, $-NMeSO_2CH_3$, $-N(SO_2Me)(CH_2)_2OH$, or  .

124. The adduct of claim 123, wherein each R^3 is independently $-NHS(O)_2-(CH_2)_2-OH$.

125. The adduct of any one of claims 88 to 124, wherein n is 2.

126. The adduct of claim 125, wherein two R^4 combine to form a C_3-C_8 cycloalkyl.

127. The adduct of claim 126, wherein the two R^4 are attached to the same carbon atom.

128. The adduct of claim 127, wherein the two R^4 groups combine to form a cyclopropyl.

129. The adduct of claim 125, wherein the two R^4 are attached to different carbon atoms.

130. The adduct of claim 129, wherein two R^4 groups combine to form a (1R,5S)-8-azabicyclo[3.2.1]octane.

131. The adduct of any one of claims 77 to 130, wherein the compound of Formula (B) is a compound of Table 1 or a pharmaceutically acceptable salt thereof.

132. The adduct of any one of claims 77 to 131, wherein ring A is adjacent to the KIF18A between the KIF18 α4-helix and α6-helix.

133. The adduct of claim 132, wherein ring A is adjacent to the KIF18A between Leu285 residue and Tyr348 residue.

134. The adduct of any one of claims 77 to 133, wherein ring B is adjacent to a flat surface of the KIF18A α4-helix.

135. The adduct of claim 134, wherein ring B is adjacent to the KIF18A Gly289 residue or Asn293 residue.

136. The adduct of claim 135, wherein ring B interacts with the KIF18A Asn293 residue via a hydrogen bond.

137. The adduct of any one of claims 77 to 136, wherein ring C is adjacent to hydrophobic residues of the KIF18A.

138. The adduct of claim 137, wherein the hydrophobic residues of the KIF18A are in α4-helix or α6-helix, or a combination thereof.

139. The adduct of claim 138, wherein ring C is adjacent to the KIF18A Tyr112 residue, Leu284 residue, Leu288 residue, and Tyr348 residue.

140. The adduct of claim 137, wherein ring C is adjacent to the KIF18A Leu110 residue, Leu259 residue, Met328 residue, or a combination thereof.

141. The adduct of any one of claims 77 to 140, wherein L^1-R^1 is adjacent to the hydrophobic side chain of the KIF18A α6-helix and β-sheet.

142. The adduct of claim 141, wherein L^1-R^1 is adjacent to the Ala352 residue, Met328 residue, and Tyr112 residue of KIF18A.

143. The adduct of claim 141, wherein L^1-R^1 is adjacent to the hydrophobic side chain of the KIF18A β-sheet.

144. The adduct of claim 143, wherein the L^1-R^1 is adjacent to the KIF18A Leu110 residue, Leu259 residue, and Met328 residue.

145. The adduct of any one of claims 77 to 144, wherein R^1 interacts with the KIF18A α4-helix via a hydrogen bond.

146. The adduct of claim 145, wherein R^1 interacts with the KIF18A Asn293 residue via the hydrogen bond.

147. The adduct of any one of claims 88 to 145, wherein R^3 interacts with KIF18A via a hydrogen bond.

148. The adduct of claim 147, wherein R^3 interacts with the KIF18A Ser262 residue via a hydrogen bond.

149. A method of treating cancer in a patient in need thereof, comprising administering to the patient an adduct as described in any one of claims 77 to 148.

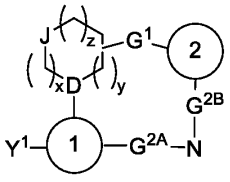
150. The method of claim 149 wherein the cancer is bladder cancer, endometrial cancer, lung squamous cell cancer, breast cancer, colon cancer, kidney cancer, liver cancer, lung cancer, small cell lung cancer, esophagus cancer, gall-bladder cancer, brain cancer, head and neck cancer, ovarian cancer, pancreas cancer, stomach cancer, cervix cancer, thyroid cancer, prostate cancer or skin cancer.

151. A method of inhibiting KIF18A, comprising forming an adduct as described in any one of claims 77 to 148, by contacting KIF18A with a compound of Formula (B).

152. A compound of any one of claims 77 to 148, or a pharmaceutically acceptable salt or solvate thereof, for use in a method of treating cancer.

153. A composition comprising a protein and a compound, wherein the protein is KIF18A, the compound is a compound of Formula (B), and the protein and the compound form the adduct of any one of claims 77 to 148.

154. A compound having the structure of Formula (IV-A), or a pharmaceutically acceptable salt or solvate, thereof:



(IV-A)

wherein:

Y^1 is an amide, sulfonamide, ether, cyclic amine, alkyl amine, aromatic heterocycle, or saturated heterocycle;

Ring 1 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl;

Ring 2 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl;

G^{2A} is a bond or -(C=O);

G^{2B} is a bond or -(C=O), wherein G^{2A} is not equal to G^{2B};

N is NH;

J is $CR^{J1}R^{J2}$, where R^{J1} and R^{J2} are independently selected from H, F, alkyl, or wherein R^{J1} and R^{J2} can be taken together to form a ring;

D is nitrogen or carbon;

x is 0, 1, or 2;

y is 0, 1, or 2;

z is 0 or 1; and

G^1 is a group configured to extend into a pocket of KIF18 located between an α6-helix and a β-sheet of KIF18a and to interact with at least one hydrophobic side chain of Ala352 in the α6-helix, Met328 in the β-sheet, and Tyr112 in the β-sheet.

155. The compound, or pharmaceutically acceptable salt or solvate thereof, of claim 154, wherein G^1 is further configured to hydrogen bond with Asn293 in an α4-helix of KIF18A.

156. The compound, or pharmaceutically acceptable salt or solvate thereof, of claim 154, wherein G^1 is further configured to interact with at least one hydrophobic side chain of Leu110, Leu259, and Met328 in the β-sheet of KIF18A.

157. The compound, or pharmaceutically acceptable salt or solvate thereof, of claim 154, wherein:

G^1 is -K-(r)-M-(p)-Q-;

K is -O- or $CR^{K1}R^{K2}$;

R^{K1} and R^{K2} are independently hydrogen, halogen (F), or C_1-C_6 alkyl; or R^{K1} and R^{K2} are combined to form a ring;

r is 0, 1, or 2;

M is $CR^{M3}R^{M4}$;

R^{M3} and R^{M4} are independently hydrogen or C_1-C_6 alkyl optionally substituted with halogen (fluorine);

p is 0, 1, or 2

Q is -O-, $-NR^5$-, $-SO_2$-, $-SO_2NR^5$- or $-NR^5SO_2$-;

R^5 is hydrogen or C_1-C_6 alkyl optionally substituted with halogen (fluorine); and

R^6 is hydrogen or optionally substituted alkyl.

158. The compound, or pharmaceutically acceptable salt or solvate thereof, of claim 155, wherein:

G^1 is represented by the formula -K-(r)-M-(p)-Q-;

K is O or $CR^{K1}R^{K2}$;

R^{K1} and R^{K2} are independently hydrogen, halogen (F), or C_1-C_6 alkyl; or R^{K1} and R^{K2} are combined to form a ring;

r is 0, 1, or 2;

M is $CR^{M3}R^{M4}$;

R^{M3} and R^{M4} are independently hydrogen or C_1-C_6 alkyl optionally substituted with halogen (fluorine);

p is 0, 1, or 2;

Q is -O-, $-NR^5$-, $-SO_2$-, $-SO_2NR^5$- or $-NR^5SO_2$-;

R^5 is hydrogen or C_1-C_6 alkyl optionally substituted with halogen (fluorine); and

R^6 is hydrogen.

159. The compound, or pharmaceutically acceptable salt or solvate thereof, of claim 156, wherein:

G^1 is -K-(r)-M-(p)-Q-;

K is $CR^{K1}R^{K2}$;

R^{K1} and R^{K2} are independently halogen (F), or C_1-C_6 alkyl; or R^{K1} and R^{K2} are combined to form a ring;

r is 0, 1, or 2;

M is $CR^{M3}R^{M4}$;

R^{M3} and R^{M4} are independently hydrogen or C_1-C_6 alkyl optionally substituted with halogen (fluorine);

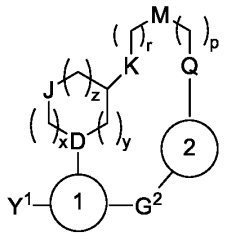
p is 0, 1, or 2;

Q is -O-, $-NR^5$-, $-SO_2$-, $-SO_2NR^5$- or $-NR^5SO_2$-;

R^5 is hydrogen or C_1-C_6 alkyl optionally substituted with halogen (fluorine); and

R^6 is hydrogen or optionally substituted alkyl.

160. A compound having the structure of Formula (IV-B), or a pharmaceutically acceptable salt or solvate thereof:



(IV-B)

wherein:

Y^1 is an amide, sulfonamide, ether, cyclic amine, alkyl amine, aromatic heterocycle, or saturated heterocycle;

Ring 1 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl;

Ring 2 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl;

D is nitrogen or carbon;

J is $CR^{J1}R^{J2}$, where R^{J1} and R^{J2} are independently selected from H, F, alkyl, or wherein R^{J1} and R^{J2} can be taken together to form a ring;

K is O or $CR^{K1}R^{K2}$;

R^{K1} and R^{K2} are independently hydrogen, halogen (F), or C_1-C_6 alkyl; or R^{K1} and R^{K2} are combined to form a ring;

x is 0, 1, or 2;

z is 0 or 1;

y is 0, 1, or 2;

M is $CR^{M3}R^{M4}$;

R^{M3} and R^{M4} are independently hydrogen or C_1-C_6 alkyl optionally substituted with halogen (fluorine);

Q is -O-, $-NR^5$-, or $-OR^6$-;

R^5 is hydrogen or C_1-C_6 alkyl optionally substituted with halogen (fluorine);

R^6 is hydrogen or optionally substituted alkyl;

r is 0, 1, or 2;

p is 0, 1, or 2; and

G^2 is a group configured to provide a linkage with Ar/HetAr ring 1 and Ar/hetAr ring 2.

161. The compound, or pharmaceutically acceptable salt or solvate thereof, of claim 160, wherein G^2 is further configured to provide a rigid and quasi-planar linkage with Ar/HetAr ring 1 and Ar/HetAr ring 2 to position the Ar/HetAr ring 1 and Ar/HetAr ring 2 in approximately a same plane and allow delocalization of electrons across the G^2, Ar/HetAr ring 1, and Ar/HetAr ring 2 in a conjugated system.

162. The compound, or pharmaceutically acceptable salt or solvate thereof, of claim 160, wherein G^2 is represented by the formula $-G^{2A}-N-G^{2B}-$;

N is NH or N is taken together with D to form a 5 or 6 membered ring;

G^{2A} and G^{2A} are independently a bond or -(C=X), provided that A and B are not both -(C=O).

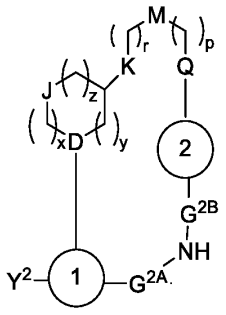
163. The compound, or pharmaceutically acceptable salt or solvate thereof, of claim 160, wherein G^2 is represented by the formula $-G^{2A}-N-G^{2B}-$

wherein N is NH; and

G^{2A} and G^{2B} are independently a bond or -(C=O), provided that A and B are not both -(C=O).

164. The compound, or pharmaceutically acceptable salt or solvate thereof, of claim 160, wherein N is taken together with D to form a 5 or 6 membered ring.

165. A compound having the structure of Formula (IV-C), or a pharmaceutically acceptable salt or solvate thereof:



(IV-C)

wherein:

Ring 1 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl;

Ring 2 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl;

D is nitrogen or carbon;

J is $CR^{J1}R^{J2}$, where R^{J1} and R^{J2} are independently selected from H, F, alkyl, or wherein R^{J1} and R^{J2} can be taken together to form a ring;

K is O or $CR^{K1}R^{K2}$;

R^{K1} and R^{K2} are independently hydrogen, halogen (F), or C_1-C_6 alkyl; or R^{K1} and R^{K2} are combined to form a ring;

x is 0, 1, or 2;

z is 0 or 1;

y is 0, 1, or 2;

M is $CR^{M3}R^{M4}$;

R^{M3} and R^{M4} are independently hydrogen or C_1-C_6 alkyl optionally substituted with halogen (fluorine);

Q is -O-, $-NR^5$-, $-SO_2$-, $-SO_2NR^5$- or $-NR^5SO_2$-;

R^5 is hydrogen or C_1-C_6 alkyl optionally substituted with halogen (fluorine);

R^6 is hydrogen or optionally substituted alkyl;

r is 0, 1, or 2;

p is 0, 1, or 2;

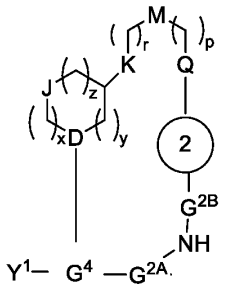
G^{2A} is a bond or -(C=O);

G^{2B} is a bond or -(C=O) , wherein G^{2A} is not equal to G^{2B}; and

Y^2 is a group configured to form one of more hydrogen bonds with one or more of: a backbone of KIF18A, a side chain of Ser262 of KIF18a, or a residue of α-tubulin.

166. The compound, or pharmaceutically acceptable salt or solvate thereof, of claim 165 wherein Y^2 is an amide, sulfonamide, ether, cyclic amine, alkyl amine, aromatic heterocycle, or saturated heterocycle.

167. A compound having the structure of Formula (IV-D), or a pharmaceutically acceptable salt or solvate thereof:



(IV-D)

wherein:

Y^1 is an amide, sulfonamide, ether, cyclic amine, alkyl amine, aromatic heterocycle, or saturated heterocycle;

Ring 2 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl;

D is nitrogen or carbon;

J is $CR^{J1}R^{J2}$, where R^{J1} and R^{J2} are independently selected from H, F, alkyl, or wherein R^{J1} and R^{J2} can be taken together to form a ring;

K is O or $CR^{K1}R^{K2}$;

R^{K1} and R^{K2} are independently hydrogen, halogen (F), or C_1-C_6 alkyl; or R^{K1} and R^{K2} are combined to form a ring;

x is 0, 1, or 2;

z is 0 or 1;

y is 0, 1, or 2;

M is $CR^{M3}R^{M4}$;

R^{M3} and R^{M4} are independently hydrogen or C_1-C_6 alkyl optionally substituted with halogen (fluorine);

Q is -O-, $-NR^5$-, $-SO_2$-, $-SO_2NR^5$- or $-NR^5SO_2$-;

R^5 is hydrogen or C_1-C_6 alkyl optionally substituted with halogen (fluorine);

R^6 is hydrogen or optionally substituted alkyl;

r is 0, 1, or 2;

p is 0, 1, or 2;

G^{2A} is a bond or -(C=O);

G^{2B} is a bond or -(C=O), wherein G^{2A} is not equal to G^{2B}; and

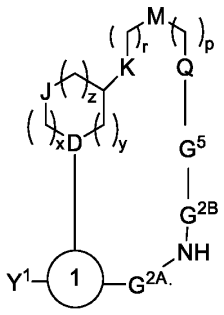
G^4 is a group configured to extend between side chains of Leu285 of a KIF18A α4-helix and Tyr348 of a KIF18A α6-helix.

168. The compound, or pharmaceutically acceptable salt or solvate thereof, of claim 167, wherein G^4 is further configured to hydrogen bond with KIF18A or to engage in water-mediated interactions with KIF18A or α-tubulin.

169. The compound, or pharmaceutically acceptable salt or solvate thereof, of claim 167, wherein G^4 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl and forms a cyclic conjugated π system.

170. The compound, or pharmaceutically acceptable salt or solvate thereof, of claim 168, wherein G^4 is an optionally substituted 5 to 12 membered heteroaryl and forms a cyclic conjugated π system.

171. A compound having the structure of Formula (IV-E), or a pharmaceutically acceptable salt or solvate thereof:



(IV-E)

wherein:

Y^1 is an amide, sulfonamide, ether, cyclic amine, alkyl amine, aromatic heterocycle, or saturated heterocycle;

Ring 1 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl;

D is nitrogen or carbon;

J is $CR^{J1}R^{J2}$, where R^{J1} and R^{J2} are independently selected from H, F, alkyl, or wherein R^{J1} and R^{J2} can be taken together to form a ring;

K is O or $CR^{K1}R^{K2}$;

R^{K1} and R^{K2} are independently hydrogen, halogen (F), or C_1-C_6 alkyl; or R^{K1} and R^{K2} are combined to form a ring;

x is 0, 1, or 2;

z is 0 or 1;

y is 0, 1, or 2;

M is $CR^{m3}R^{m4}$;

R^{M3} and R^{M4} are independently hydrogen or C_1-C_6 alkyl optionally substituted with halogen (fluorine);

Q is -O-, $-NR^5$-, $-SO_2$-, $-SO_2NR^5$- or $-NR^5SO_2$-;

R^5 is hydrogen or C_1-C_6 alkyl optionally substituted with halogen (fluorine);

R^6 is hydrogen or optionally substituted alkyl;

r is 0, 1, or 2;

p is 0, 1, or 2;

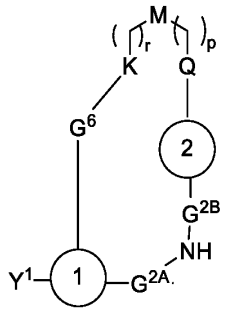
G^{2A} is a bond or -(C=O);

G^{2B} is a bond or -(C=O), wherein G^{2A} is not equal to G^{2B}; and

G^5 is a group configured to pack against a flat surface on a KIF18A α4-helix formed by Gly289 and to interact with a side chain of Asn293 in an KIF18A α4-helix, and optionally, to hydrogen bond with the side chain of Asn293.

172. The compound, or pharmaceutically acceptable salt or solvate thereof, of claim 171, wherein G^5 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl.

173. A compound having the structure of Formula (IV-F), or a pharmaceutically acceptable salt or solvate thereof:



(IV-F)

wherein:

Y^1 is an amide, sulfonamide, ether, cyclic amine, alkyl amine, aromatic heterocycle, or saturated heterocycle;

Ring 1 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl;

Ring 2 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl;

M is $CR^{M3}R^{M4}$;

R^3 and R^4 are independently hydrogen or C_1-C_6 alkyl optionally substituted with halogen (fluorine);

Q is -O-, -NR^5-, -SO_2-, -SO_2NR^5- or -NR^5SO_2-;

R^5 is hydrogen or C_1-C_6 alkyl optionally substituted with halogen (fluorine);

R^6 is hydrogen or optionally substituted alkyl;

r is 0, 1, or 2;

p is 0, 1, or 2;

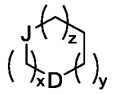
G^{2A} is a bond or -(C=O);

G^{2B} is a bond or -(C=O), wherein G^{2A} is not equal to G^{2B}; and

G^6 is a group configured to interact with hydrophobic side chains of Tyr112, Leu285, and Leu 288 in a KIF18A α4-helix and a hydrophobic side chain of Tyr348 in a KIF18a α6-helix.

174. The compound, or pharmaceutically acceptable salt or solvate thereof, of claim 173, wherein G^6 is further configured to interact with hydrophobic side chains of Leu110, Leu259, and Met328 in a KIF18A β-sheet.

175. The compound, or pharmaceutically acceptable salt or solvate thereof, of claim 174, wherein G^6 is represented by the formula:



wherein

D is nitrogen or carbon;

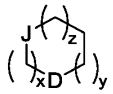
J is $CR^{J1}R^{J2}$, where R^{J1} and R^{J2} are independently selected from H, F, alkyl, or wherein R^{J1} and R^{J2} can be taken together to form a ring;

x is 0, 1, or 2;

z is 0 or 1; and

y is 0, 1, or 2.

176. The compound, or pharmaceutically acceptable salt or solvate thereof, of claim 175, wherein G^6 is represented by the formula:



wherein

D is nitrogen or carbon;

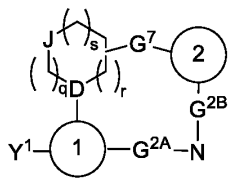
J is $CR^{J1}R^{J2}$, where R^{J1} and R^{J2} are independently selected from F or alkyl.

x is 0, 1, or 2;

z is 0 or 1; and

y is 0, 1, or 2.

177. A compound having the structure of Formula (IV-G) or a pharmaceutically acceptable salt or solvate, thereof:



(IV-G),

wherein

Y^1 is an amide, sulfonamide, ether, cyclic amine, alkyl amine, aromatic heterocycle, or saturated heterocycle;

Ring 1 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl;

Ring 2 is an optionally substituted C_6-C_{12} aryl or optionally substituted 5 to 12 membered heteroaryl;

G^{2A} is a bond or -(C=O);

G^{2B} is a bond or -(C=O), wherein G^{2A} is not equal to G^{2B};

N is NH;

J is $CR^{J1}R^{J2}$, where R^{J1} and R^{J2} are independently selected from H, F, alkyl, or wherein R^{J1} and R^{J2} can be taken together to form a ring;

D is nitrogen or carbon;

x is 0, 1, or 2;

y is 0, 1, or 2;

z is 0 or 1; and

G^7 represents a means, between ring 2 and ring 3, for extending into a pocket between an α6-helix and β-sheet of KIF18a and interacting with at least one hydrophobic side chain of Ala352 in the α6-helix, Met328 in the β-sheet, and Tyr112 in the β-sheet.

178. The compound, or pharmaceutically acceptable salt or solvate thereof, of claim 177, wherein

the means is a group having the formula -K-(r)-M-(p)-Q-;

K is O or $CR^{K1}R^{K2}$;

R^{K1} and R^{K2} are independently hydrogen, halogen (F), or C_1-C_6 alkyl; or R^{K1} and R^{K2} are combined to form a ring;

r is 0, 1, or 2;

M is $CR^{M3}R^{M4}$;

R^{M3} and R^{M4} are independently hydrogen or C_1-C_6 alkyl optionally substituted with halogen (fluorine);

p is 0, 1, or 2;

Q is -O-, $-NR^5$-, $-SO_2$-, $-SO_2NR^5$- or $-NR^5SO_2$-;

R^5 is hydrogen or C_1-C_6 alkyl optionally substituted with halogen (fluorine); and

R^6 is hydrogen or optionally substituted alkyl.

179. The compound, or pharmaceutically acceptable salt or solvate thereof, of claim 177, wherein

Q is -O-, or -NH2-;

R^5 is hydrogen; and

R^6 is hydrogen.

180. The compound, or pharmaceutically acceptable salt or solvate thereof, of claim 177, wherein

K is $CR^{K1}R^{K2}$; and

R^{K1} and R^{K2} are independently halogen (F), or C_1-C_6 alkyl; or R^{K1} and R^{K2} are combined to form a ring.

181. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein:

each X^3 is CH;

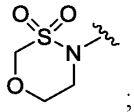
ring B is triazine, pyridine, pyrimidine, pyridazine, pyrazinone, pyrazine, or imidazopyrizine;

L^{1a} is a bond or -O-;

G is -(C=O)-NH-;

R^1 is $-NR^{1a}$-;

R^{1a} is hydrogen;

each R^3 is independently $-NHSO_2(CH_2)_2OH$, $-NHSO_2C(CH_3)_2CH_2OH$, $-NHSO_2C(cyclopropyl)CH_2OH$, $-NHSO_2CH(CH_3)CH_2OH$, $-NMeSO_2(CH_2)_2OH$, $-NHSO_2CH_2CH_3$, $-NHSO_2CHCH_2$, $-NHSO_2$-oxetanyl, $-NMeSO_2CH_3$, $-N(SO_2Me)(CH_2)_2OH$, or  ;

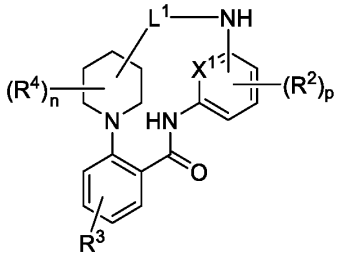
k is 0 or 1;

l is 0 or 1;

o is 1; and

p is 0 or 1.

182. The compound of claim 181, wherein the compound has the structure of Formula (I-a):



(I-a),

or a pharmaceutical salt or solvate thereof, wherein:

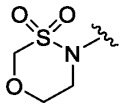
X^1 is CH or N;

L^1 is a linker comprising the structure $-L^{1a}$-L^{1b}-;

L^{1a} is a bond or -O-;

L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene;

each R^2 is independently halogen, $-OR^{2a}$, $-N(R^{2a})_2$, $-S(O)_2N(R^{2a})_2$, $-SO_2$-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl, or two R^2 are taken together to form an oxo, an optionally substituted C_3-C_8 cycloalkyl, an optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl; each R^{2a} is independently hydrogen or optionally substituted C_1-C_6 alkyl;

each R^3 is independently $-NHSO_2(CH_2)_2OH$, $-NHSO_2C(CH_3)_2CH_2OH$, $-NHSO_2C(cyclopropyl)CH_2OH$, $-NHSO_2CH(CH_3)CH_2OH$, $-NMeSO_2(CH_2)_2OH$, $-NHSO_2CH_2CH_3$, $-NHSO_2CHCH_2$, $-NHSO_2$-oxetanyl, $-NMeSO_2CH_3$, $-N(SO_2Me)(CH_2)_2OH$, or  ;

each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, two or more R^4 combine to form a C_3-C_8 cycloalkyl, or two R^4 combine to form a C_1-C_3 alkylene bridge;

k is 0 or 1;

l is 0 or 1;

n is 0 to 9;

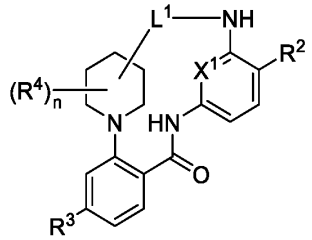
o is 1;

p is 0 or 1; and

wherein when any one of variable G, L^1, R^1, R^2, R^3, or R^4 are present, the bond to variable G, L^1, R^1, R^2, R^3 or R^4 replaces a hydrogen on a carbon or nitrogen atom.

183. The compound of claim 181 or claim 182, or a pharmaceutical salt or solvate thereof, wherein p is 1.

184. The compound of any one of claims 181 to 183, wherein the compound has the structure of Formula (II-a):



(II-a),

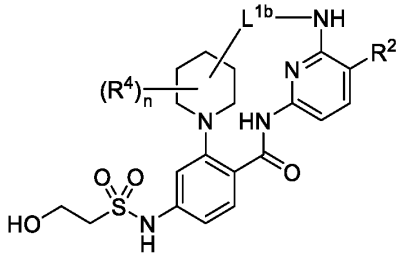
or a pharmaceutical salt or solvate thereof, wherein:

X^1 is CH or N.

185. The compound of any one of claims 181 to 184, or a pharmaceutical salt or solvate thereof, wherein L^{1a} is a bond.

186. The compound of any one of claims 181 to 185, or a pharmaceutical salt or solvate thereof, wherein R^3 is $-NHS(O)_2-(CH_2)_2-OH$.

187. The compound of any one of claims 181 to 186, wherein the compound has the structure of Formula (V), or a pharmaceutical salt or solvate thereof:



(V).

188. The compound of any one of claims 181 to 187, or a pharmaceutical salt or solvate thereof, wherein R^2 is a 5- to 8- membered heteroaryl.

189. The compound of any one of claims 181 to 188, or a pharmaceutical salt or solvate thereof, wherein R^2 is a furanyl, furanonyl, isothiazolyl, imidazolyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl.

190. The compound of any one of claims 181 to 189, or a pharmaceutical salt or solvate thereof, wherein R^2 is a pyrazolyl.

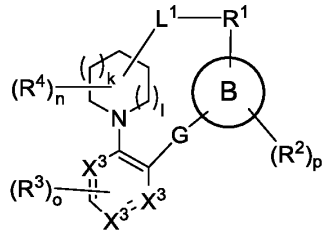
191. The compound of any one of claims 181 to 190, or a pharmaceutical salt or solvate thereof, wherein L^{1b} is optionally substituted C_1-C_6 alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene.

192. The compound of any one of claim 191, or a pharmaceutical salt or solvate thereof, wherein L^{1b} is optionally substituted C_2-C_6 alkenylene.

193. The compound of any one of claims 181 to 190, or a pharmaceutical salt or solvate thereof, wherein each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, or optionally substituted C_1-C_6 alkoxy.

194. The compound of any one of claims 181 to 190, or a pharmaceutical salt or solvate thereof, wherein n is 0.

195. A compound having the structure of Formula (I-1), or a pharmaceutically acceptable salt or solvate thereof:



(I-1)

wherein:

each X^3 is independently CH or N;

ring B is a 5- or 6- membered heteroaryl or phenyl;

L^1 is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond, -O-, -NL^{1a1}-, -S-, or -SO_2-;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene;

G is -(C=O)-NH- or -NH-(C=O)-;

R^1 is a bond, -O-, -NR^{1a}-, -NR^{1a}-Q-, -NR^{1a}-CO-, -CO-NR^{1a}-, -NR^{1a}-SO_2-, -S-, -SO_2-, or -SO_2-NR^{1a};

R^{1a} is hydrogen, -C(=O)R^{1a1}, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

R^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

Q is optionally substituted C_1-C_6alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene;

each R^2 is independently halogen, -CN, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl, or two R^2 are taken together to form an oxo, an optionally substituted C_3-C_8 cycloalkyl, an optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl;

each R^{2a} is independently hydrogen or optionally substituted C_1-C_6 alkyl;

each R^3 is independently halogen, -CN, -$(CH_2)_m$-$N(R^{3a})_2$-, -OR^{3a}, -$N(R^{3a})_2$, -$N(SO_2R^{3b})R^{3a}$, -SR^{3a}, -SO_2R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-R^{3a}, -NH-S(O)(NH)-R^{3a}, -NH-S(O)(NH)-$(CH_2)_m$-R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-OR^{3b}, -NH-S(O)R^{3a}-$(CH_2)_m$-OR^{3b}, -NH-$S(O)_2$-R^{3c}, -$B(R^{3a})_3$, -$P(R^{3a})_3$, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl;

each R^{3a} is independently hydrogen, -C(O)OR^{3b}, optionally substituted C_1-C_6 alkyl, or -N(R^{3b})$_2$;

R^{3b} is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, or optionally substituted C_3-C_6 cycloalkyl;

R^{3c} is C_3-C_8 cycloalkyl or 3- to 8- membered heterocycle;

each R^4 is independently halogen, -CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, two or more R^4 combine to form a C_3-C_8 cycloalkyl, or two R^4 combine to form a C_1-C_3 alkylene bridge;

k is 0 to 2;

l is 0 to 2 ;

m is 1 to 6;

n is 0 to 9;

o is 0 to 4;

p is 0 to 4; and

wherein when any one of variable G, L^1, R^1, R^2, R^3, or R^4 are present, the bond to variable G, L^1, R^1, R^2, R^3 or R^4 replaces a hydrogen on a carbon or nitrogen atom.

196. The compound of claim 195, or a pharmaceutical salt or solvate thereof, wherein ring B is phenyl or a 6-membered heteroaryl.

197. The compound of claim 195 or 196, or a pharmaceutical salt or solvate thereof, wherein ring B is a 6-membered heteroaryl.

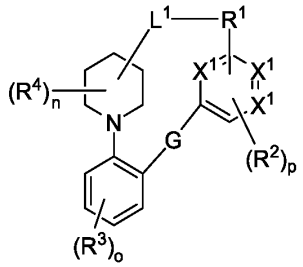
198. The compound of any one of claims 195 to 197, or a pharmaceutical salt or solvate thereof, wherein ring B is triazine, pyridine, pyrimidine, pyridazine, pyrazinone, pyrazine, or imidazopyrizine.

199. The compound of any one of claims 195 to 198, or a pharmaceutical salt or solvate thereof, wherein k is 0 or 1.

200. The compound of any one of claims 195 to 199, or a pharmaceutical salt or solvate thereof, wherein l is 0 or 1.

201. The compound of any one of claims 195 to 200, or a pharmaceutical salt or solvate thereof, wherein each X^3 is CH.

202. The compound of claim 195, having the structure of Formula (I-1a):



(I-1a)

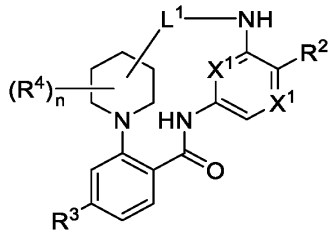
or a pharmaceutical salt or solvate thereof, wherein:

each X^1 is independently CH or N.

203. The compound of any one of claims 195 to 202, or a pharmaceutical salt or solvate thereof, wherein o is 1; and p is 0 to 1.

204. The compound of any one of claims 195 to 203, or a pharmaceutical salt or solvate thereof, wherein G is -(C=O)-NH-.

205. The compound of claim 195, wherein the compound has the structure of Formula (II-1):



(II-1)

or a pharmaceutical salt or solvate thereof, wherein:

each X^1 is independently CH or N;

L^1 is a linker comprising the structure $-L^{1a}-L^{1b}-$;

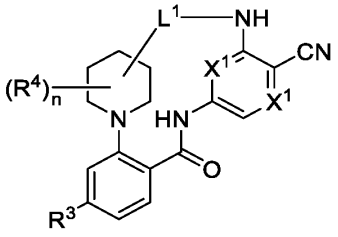
L^{1a} is a bond or -O-;

L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene; and

n is 1 or 2.

206. The compound of any one of claims 195 to 205, or a pharmaceutical salt or solvate thereof, wherein R^2 is halogen, -CN, $-OR^{2a}$, $-N(R^{2a})_2$, optionally substituted C_1-C_6 alkyl, or $-S(O)_2N(R^{2a})_2$.

207. The compound of claim 195, wherein the compound has the structure of Formula (III-1):



(III-1)

or a pharmaceutical salt or solvate thereof, wherein:

each X^1 is independently CH or N;

$L^1$is a linker comprising the structure -L^{1a}-L^{1b}-;

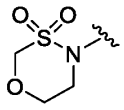
L^{1a} is a bond or -O-;

L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene; and

n is 1 or 2.

208. The compound of any one of claims 195 to 207, or a pharmaceutical salt or solvate thereof, wherein R^3 is -$N(R^{3a})_2$, -$N(SO_2R^{3b})R^{3a}$, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-OR^{3b}, -NH-$S(O)_2$-R^{3c}, or optionally substituted 5- to 8- membered heterocycle; each R^{3a} is independently hydrogen, methyl, or ethyl, wherein the ethyl is optionally substituted with one or more substituents selected from methyl and -OH; and R^{3b} is hydrogen, methyl, ethyl, or propyl.

209. The compound of any one of claims 195 to 208, or a pharmaceutical salt or solvate thereof, wherein R^3 is independently -$NHSO_2(CH_2)_2OH$, -$NMeSO_2(CH_2)_2OH$, -$NHSO_2CH_2CH_3$, -$NHSO_2$-oxetanyl, -$NMeSO_2CH_3$, -$N(SO_2Me)(CH_2)_2OH$, or



.

210. The compound of claim 195, or a pharmaceutical salt or solvate thereof, wherein each R^4 is independently halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 aminoalkyl, optionally substituted C_1-C_6 alkoxy, two or more R^4 combine to form a C_3-C_8 cycloalkyl, or two R^4 combine to form a C_1-C_3 alkylene bridge.

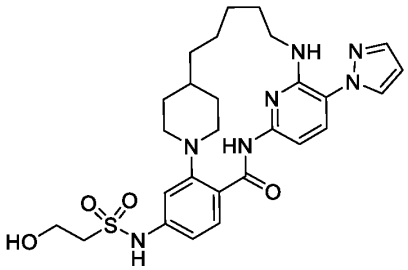
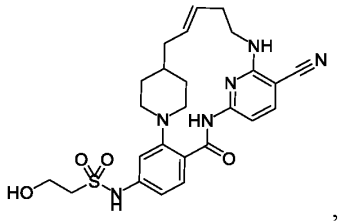
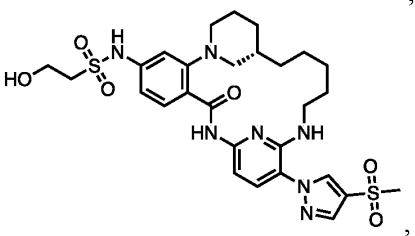
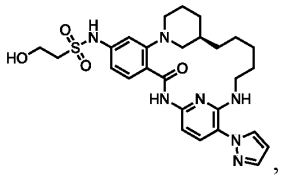
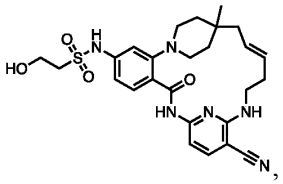
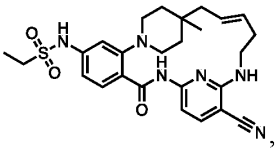
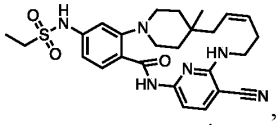
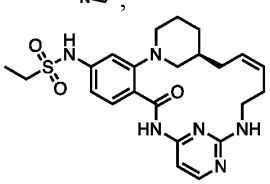
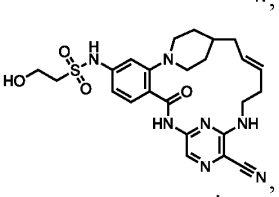
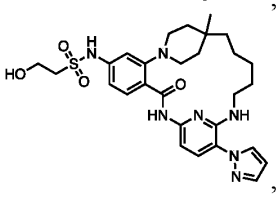
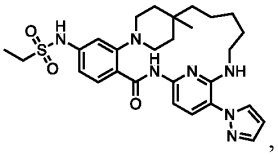
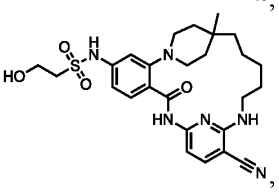
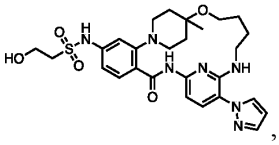
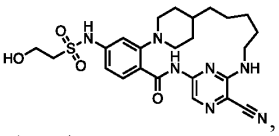
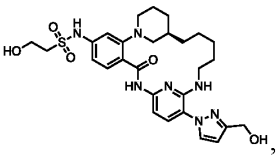
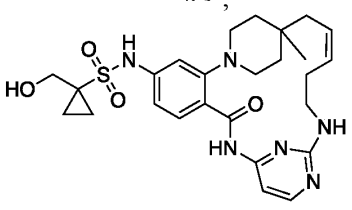
211. The compound of claim 195, or a pharmaceutical salt or solvate thereof, wherein R^{3b} is hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_2-C_6 alkenyl.

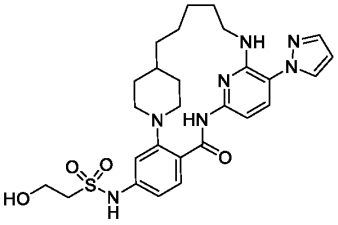
212. The compound of claim 195, or a pharmaceutical salt or solvate thereof, wherein each R^2 is independently halogen, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8-

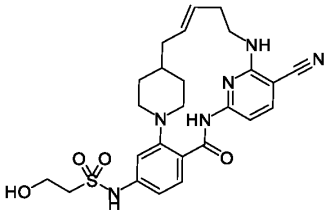
membered heteroaryl, or two R^2 are taken together to form an oxo, an optionally substituted C_3-C_8 cycloalkyl, an optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl.

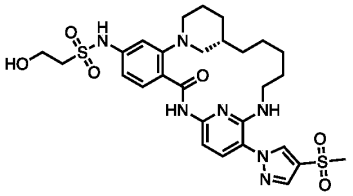
213. The compound of claim 195, wherein the compound is a compound of Formula (I-0), as described in claim 1, or a pharmaceutical salt or solvate thereof.

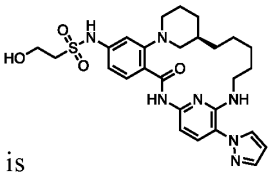
214. A compound selected from:

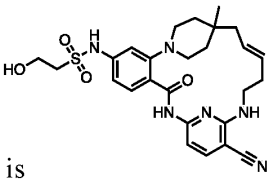

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, or a pharmaceutically acceptable salt or solvate thereof.

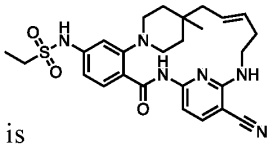
215. The compound of claim 214, wherein the compound is  or a pharmaceutically acceptable salt or solvate thereof.

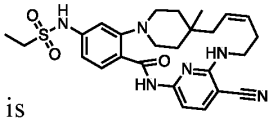
216. The compound of claim 214, wherein the compound is  or a pharmaceutically acceptable salt or solvate thereof.

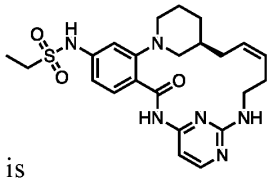
217. The compound of claim 214, wherein the compound is  or a pharmaceutically acceptable salt or solvate thereof.

218. The compound of claim 214, wherein the compound is  or a pharmaceutically acceptable salt or solvate thereof.

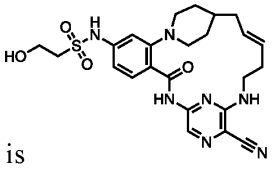
219. The compound of claim 214, wherein the compound is  or a pharmaceutically acceptable salt or solvate thereof.

220. The compound of claim 214, wherein the compound is  or a pharmaceutically acceptable salt or solvate thereof.

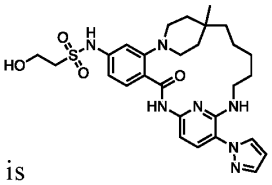
221. The compound of claim 214, wherein the compound is  or a pharmaceutically acceptable salt or solvate thereof.



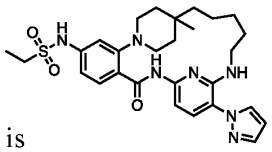
222. The compound of claim 214, wherein the compound is or a pharmaceutically acceptable salt or solvate thereof.



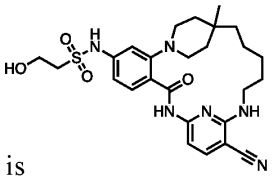
223. The compound of claim 214, wherein the compound is or a pharmaceutically acceptable salt or solvate thereof.



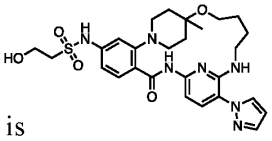
224. The compound of claim 214, wherein the compound is or a pharmaceutically acceptable salt or solvate thereof.



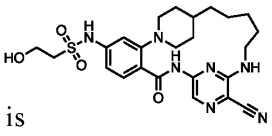
225. The compound of claim 214, wherein the compound is or a pharmaceutically acceptable salt or solvate thereof.



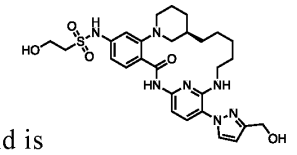
226. The compound of claim 214, wherein the compound is or a pharmaceutically acceptable salt or solvate thereof.

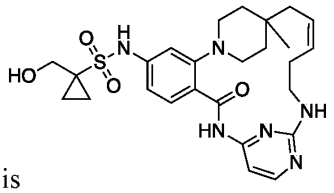


227. The compound of claim 214, wherein the compound is or a pharmaceutically acceptable salt or solvate thereof.



228. The compound of claim 214, wherein the compound is or a pharmaceutically acceptable salt or solvate thereof.

229. The compound of claim 214, wherein the compound is  or a pharmaceutically acceptable salt or solvate thereof.

230. The compound of claim 214, wherein the compound is  or a pharmaceutically acceptable salt or solvate thereof.

231. A pharmaceutical composition comprising a compound, or pharmaceutically acceptable salt or solvate thereof, as described in any one of claims 195 to 230, and a pharmaceutically acceptable excipient.

232. A method of treating cancer in a patient in need thereof, comprising administering to the patient a compound as described in any one of claims 195 to 230.

233. The method of claim 232 wherein the cancer is bladder cancer, endometrial cancer, lung squamous cell cancer, breast cancer, colon cancer, kidney cancer, liver cancer, lung cancer, small cell lung cancer, esophagus cancer, gall-bladder cancer, brain cancer, head and neck cancer, ovarian cancer, pancreas cancer, stomach cancer, cervix cancer, thyroid cancer, prostate cancer or skin cancer.

234. A method of inhibiting KIF18A comprising contacting the enzyme with a compound of any one of claims 195 to 230 or a composition of claim 231, or a pharmaceutically acceptable salt or solvate thereof.

235. A compound of any one of claims 195 to 230 or a composition of claim 231, or a pharmaceutically acceptable salt or solvate thereof, for use in a method of treating cancer.