Macrocyclic compounds as RAS inhibitors for the treatment of cancer

TECHNICAL FIELD

The present invention belongs to the field of medicine, and specifically, relates to macrocyclic compounds with stereoisomers, pharmaceutically acceptable salts, solvates, eutectic or deuterated compounds, and their used in the treatment of RAS protein-mediated related diseases

BACKGROUND

The RAS protein (including KRAS4A, KRAS4B, HRAS, and NRAS) is a small, membrane-bound guanine nucleotide-binding protein that acts as a molecular switch by cycling between an active GTP-bound state and an inactive GDP-bound state. When RAS binds to GEF family proteins such as SOS1, its conformation changes, reducing its affinity for GDP and causing its dissociation from GDP and binding to GTP in the high concentration in the environment, thus becoming active. In normal cells, activation of receptor tyrosine kinases such as epidermal growth factor receptor (EGFR) promotes the exchange of GDP and GTP in RAS, activating RAS, which plays a key role in regulating cell survival, proliferation, and differentiation through multiple cascading reactions, including the PI3K-AKT-mTOR, RAF-MEK-ERK, and RALGDS-RAL pathways. Mutations in RAS are often driving forces for carcinogenesis and tumor development, as they disrupt the guanine exchange cycle and lock RAS in the activated state, continuously activating downstream signaling pathways and leading to the development of tumors.

RAS mutations occur in approximately 19% of all cancers and play an important role in tumor occurrence and progression. Among them, KRAS is the most commonly mutated subtype, followed by NRAS and HRAS. KRAS mutations commonly occur in pancreatic ductal adenocarcinoma, lung adenocarcinoma, and colorectal adenocarcinoma, while NRAS mutations have a relatively higher frequency in hematologic malignancies such as chronic myeloid leukemia and acute myeloid leukemia, as well as in malignant melanoma, thyroid cancer, and laryngeal cancer. HRAS mutations are less common in human cancers, but have a relatively higher mutation rate in head and neck squamous cell carcinoma, bladder cancer, salivary gland carcinoma, and oral cancer.

In May 2021, the FDA approved AMG510 of Amgen, making it the first approved KRAS-targeted drug of the world for the treatment of patients with locally advanced or advanced non-small cell lung cancer harboring mutations in the KRAS G12C gene, this also marked a major breakthrough in the treatment of KRAS G12C mutations. In December 2022, MRTX849 of Mirati therapeutics was also successfully approved for marketing in United States, which was the second marketed oral inhibitor in the world that specifically optimizes the KRAS G12C mutant. The approval of these two drugs marked a successful breakthrough in KRAS, the most difficult druggable target in history, and has become a milestone achievement. However, in the current clinical research, mutations of various subtypes of RAS protein (KRAS, NRAS and HRAS) was reflected in pan-tumor species, and the treatment of a single mutation could not improve the objective remission rate of patients. At present, there are no highly effective inhibitors to meet various clinical needs, and the emergence of RAS molecular glue is expected to successfully solve this problem.

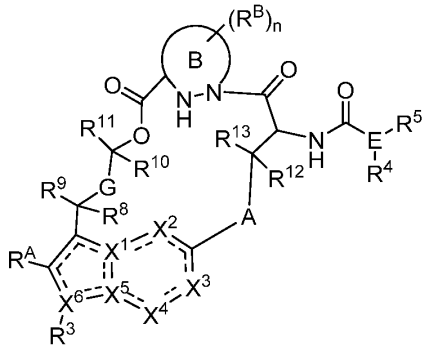
The RAS molecular glue can simultaneously bind to highly activated RAS (RAS-ON) proteins and a ubiquitously expressed protein in cells, forming a tricomplex to occupy binding sites for RAS interacting

proteins such as SOS1 and RAF1, keeping RAS protein in a locked state alone, unable to activate downstream signaling pathways, thereby blocking RAS signaling pathway transmission and inhibiting tumor growth. Therefore, there is an urgent clinical need to develop an inhibitor of RAS molecular glue type with good activity and high druggability.

SUMMARY OF THE INVENTION

Provided herein are Ras inhibitors as molecular glues. The approach described herein entails formation of a high affinity three-component complex between a synthetic ligand and two intracellular proteins which do not interact under normal physiological conditions: The target of interest (e.g. Ras), and a widely expressed cytosolic chaperone in cells (e.g. cyclophilin A). More specifically, in some embodiments, the Ras molecular glues described herein induce a new binding pocket in Ras by forming a three-component complex with high-affinity between the Ras protein and the cytosolic chaperone, cyclophilin A. Without being bound by theory, the inventors believe that one way the inhibitory effect on Ras is effected by compounds of the invention and the three-component complexes they form is by steric occlusion of the interaction site between Ras and downstream effector molecules, such as RAF and PI3K, which are required for propagating the oncogenic signal.

In the first aspect, the present invention provides a compound, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I);



(I)

wherein

n is 0, 1, 2, or 3;

A is optionally substituted 5 to 6-membered heterocycloalkylene, optionally substituted 5 to 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

B is selected from optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 3 to 6-membered heterocycloalkenylene, optionally substituted 4 to 11-membered bicyclic cycloalkylene, or optionally substituted 4 to 11-membered bicyclic heterocycloalkylene;

G is optionally substituted C_{1-6} alkylene;

R^8 and R^9 are each independently selected from hydrogen, deuterium, halogen, hydroxy, cyano, optionally substituted C_{1-3} alkyl, or R^8 and R^9 combine with the atoms to which they are attached to form an optionally substituted C_{3-6} cycloalkyl or a carbonyl;

R^{10} and R^{11} are each independently selected from hydrogen, deuterium, halogen, hydroxy, cyano, optionally substituted C_{1-3} alkyl, or R^{10} and R^{11} combine with the atoms to which they are attached to form an optionally substituted C_{3-6} cycloalkyl or a carbonyl;

R^{12} and R^{13} are each independently selected from hydrogen, deuterium, halogen, hydroxy, optionally substituted C_{1-3} alkyl, -O(C_{1-6} alkyl), -S(C_{1-6} alkyl) or -N(C_{1-6} alkyl)(C_{1-6} alkyl); furthermore, the C_{1-6} alkyl may be further optionally substituted;

R^A is optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl (or 4 to 7-membered heterocycloalkyl), optionally substituted 5 to 8-membered aryl, optionally substituted 5 to 8-membered heteroaryl, optionally substituted 8 to 10-membered fused bicyclic aryl or optionally substituted 8 to 10-membered fused bicyclic heteroaryl;

R^B is selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, optionally substituted C_{3-6} cycloalkyl, or optionally substituted C_{3-6} heterocycloalkyl (or 4 to 7- membered heterocycloalkyl); or provided that when n exceeds 1, any two of R^B combine with the atoms to which they are attached to form a 3 to 6-membered ring, wherein the ring can be optionally substituted with halogen, hydroxy, and C_{1-3} alkyl;

X^1 is N or C;

X^2 is N or -CR^a-;

X^3 is N or -CR^b-;

X^4 is N or -CR^c-;

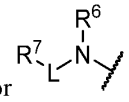
X^5 is N or C;

X^6 is S, O, N, or -CH-;

R^a, R^b, and R^c are each independently hydrogen, halogen, cyano, C_{1-3} alkyl, C_{1-3} alkoxyl, C_{1-3} haloalkyl, C_{1-3} haloalkoxyl, C_{3-6} cycloalkyl, or C_{3-6} heterocycloalkyl (or 4 to 7-membered heterocycloalkyl);

R^3 is absent, or selected from hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl, provided that when X^6 is O or S, R^3 is absent;

E is a bond, or selected from N, or -CR^d-, wherein R^d is selected from hydrogen, halogen, hydroxy, cyano, carboxyl, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkoxyl, C_{1-6} aminoalkyl, C_{1-6} hydroxyalkyl, or -NR^eR^f; wherein R^e and R^f are independently selected from hydrogen, or optionally substituted C_{1-6} alkyl;

R^4 is hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{3-10} cycloalkenyl, optionally substituted C_{3-10} heterocycloalkyl (or 4 to 12-membered heterocycloalkyl), optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or ;

R^5 is hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl, furthermore, the C_{1-6} alkyl or C_{3-6} cycloalkyl may be further optionally substituted;

or R^4 and R^5 combine with the atoms to which they are attached to form a ring, wherein the ring is selected from optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 4 to

11-membered bicyclic cycloalkyl, optionally substituted 4 to 11-membered bicyclic heterocycloalkyl;

wherein

L is absent, or selected from -CH_2-, -C(O)-, -CHR^g- or -$C(R^g)_2$-, wherein R^g is optionally substituted C_{1-6} alkyl;

R^6 is hydrogen, or optionally substituted C_{1-6} alkyl;

R^7 is optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{3-10} heterocycloalkyl (or 3 to 10-membered heterocycloalkyl), optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl;

or L, R^6 and R^7 combine with the atoms to which they are attached to form a ring, wherein the ring is selected from optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 4 to 11-membered bicyclic cycloalkyl, optionally substituted 4 to 11-membered bicyclic heterocycloalkyl.

In the second aspect, the present invention provides a pharmaceutical composition comprising the compound according to the first aspect the stereoisomer thereof, the pharmaceutically acceptable salt thereof, the metabolite thereof, the prodrug thereof, the solvate thereof or the solvate of the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In the third aspect, the present invention provides a use of the compound according to the first aspect the stereoisomer thereof, the pharmaceutically acceptable salt thereof, the metabolite thereof, the prodrug thereof, the solvate thereof or the solvate of the pharmaceutically acceptable salt thereof in the preparation of a medicament used for the treatment of cancer.

DESCRIPTION OF THE DRAWINGS

Fig.1 The reference compound and the representative Compound A significantly inhibited the interaction of RAF1 with active RAS^{Mutant} protein or RAS^{WT} protein.

Fig. 2 The reference compound and the representative Compound A significantly inhibited the cell viability of KRAS mutant cells.

Fig. 3 Tumor volume changes and tumor growth inhibition ratio (TGI) after administrating vehicle or test articles to female Balb/c nude mice bearing HPAC PDAC tumors. Data endpoints represent mean ± SEM. p.o.: oral administration; QD: once a day; mpk: mg/kg.

Fig. 4 Tumor volume changes and tumor growth inhibition ratio (TGI) after administrating vehicle or test articles to female Balb/c nude mice bearing PK59 PDAC tumors. Data endpoints represent mean ± SEM. p.o.: oral administration; QD: once a day; mpk: mg/kg.

Fig. 5 Tumor volume changes and tumor growth inhibition ratio (TGI) after administrating vehicle or test articles to male Balb/c nude mice bearing HPAC PDAC tumors. Data endpoints represent mean ± SEM. p.o.: oral administration; QD: once a day; mpk: mg/kg.

Fig. 6 Tumor volume changes and tumor growth inhibition ratio (TGI) after administrating vehicle or test articles to male Balb/c nude mice bearing LU99 NSCLC tumors. Data endpoints represent mean ± SEM. p.o.: oral administration; QD: once a day; mpk: mg/kg.

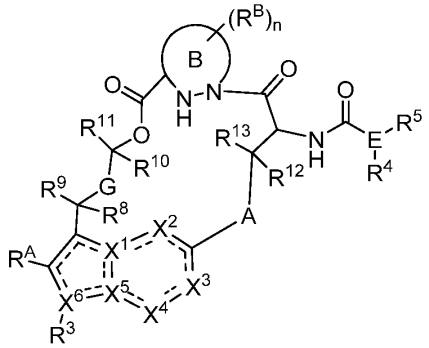
Fig. 7 and Fig. 8 Bioluminescence signal changes tumor growth inhibition ratio (TGI) after administrating vehicle or test articles to female BALB/c nude mice bearing NCI-H1373-luc intracranial tumors.

Data endpoints represent mean ± SEM.

EMBODIMENTS FOR CARRYING OUT THE INVENTION

After extensive and in-depth research, the inventors have unexpectedly developed a kind of novel compounds that can effectively inhibit the interaction of RAF1 with active RAS^{Mutant} protein or RAS^{WT} protein and proliferation of KRAS-related tumor cells. In addition, some compounds of the present invention also showed significantly improved activity than the positive control compounds (such as compound Ref. 1) in animal model studies, even though the compounds of the present invention showed similar activities to in the positive control compounds in vitro studies. The present invention is completed on this basis.

In one aspect, the present invention provides a compound of formula (I):

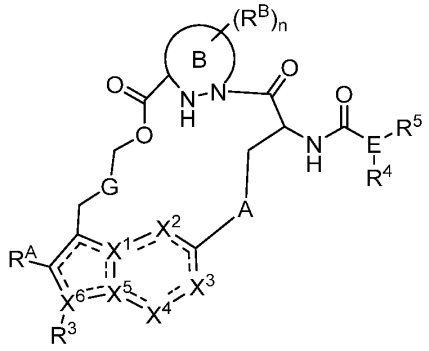


(I)

or a pharmaceutically acceptable salt thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt, wherein the variables are as described above.

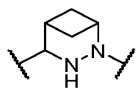
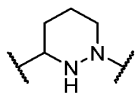
In some embodiments, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} is H。

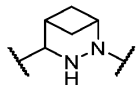
In some embodiments, the compound of formula (I) is a compound of formula (I-1)

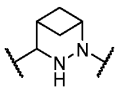
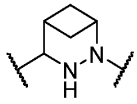
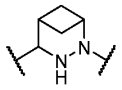


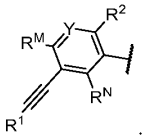
(I-1)

wherein X^1, X^2, X^3, X^4, X^5, X^6, A, B, E, G, R^A, R^B, R^3, R^4, R^5 and n are as defined in formula I.

In some embodiments, B is optionally substituted  or .

In some embodiments, B is optionally substituted .

In some embodiments,  or deuterated ; preferably, .

In some embodiments, R^A is . In some embodiments, R^1 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl, optionally substituted 5 to 8-membered aryl, optionally substituted 5 to 8-membered heteroaryl, optionally substituted 8 to 10-membered fused bicyclic aryl, optionally substituted 8 to 10-membered fused bicyclic heteroaryl, optionally substituted -C_{1-2} alkylene-C_{3-6} cycloalkyl, optionally substituted -C_{1-2} alkylene-C_{3-6} heterocycloalkyl, optionally substituted -C_{1-2} alkylene-5 to 8-membered aryl, optionally substituted -C_{1-2} alkylene-5 to 8-membered heteroaryl, optionally substituted -C_{1-2} alkylene-8 to 10-membered fused bicyclic aryl, and optionally substituted -C_{1-2} alkylene-8 to 10-membered fused bicyclic heteroaryl (preferably, R^1 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl, optionally substituted 5 to 8-membered aryl, optionally substituted 5 to 8-membered heteroaryl, optionally substituted 8 to 10-membered fused bicyclic aryl, and optionally substituted 8 to 10-membered fused bicyclic heteroaryl); furthermore, the C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, C_{1-6} hydroxyalkyl (preferably the C_{1-6} alkyl) may be further optionally substituted.

In some embodiments, R^1 is optionally substituted -C_{1-2} alkylene-C_{3-6} cycloalkyl, optionally substituted -C_{1-2} alkylene-C_{3-6} heterocycloalkyl, optionally substituted -C_{1-2} alkylene-5 to 8-membered aryl, optionally substituted -C_{1-2} alkylene-5 to 8-membered heteroaryl, optionally substituted -C_{1-2} alkylene-8 to 10-membered fused bicyclic aryl, and optionally substituted -C_{1-2} alkylene-8 to 10-membered fused bicyclic heteroaryl; preferably, is optionally substituted -C_{1-2} alkylene-C_{3-6} cycloalkyl, optionally substituted -C_{1-2} alkylene-C_{3-6} heterocycloalkyl; more preferably, optionally substituted -methylene-C_{3-6} heterocycloalkyl.

In some embodiments, "C_{3-6} heterocycloalkyl" is selected from heterocycloalkyl for $R^{1'}$ as defined in formula VI, VII or VIII.

In some embodiments, in R^1, when the C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, or C_{1-6} hydroxyalkyl (preferably, the C_{1-6} alkyl) is further substituted, the substituent is selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl, optionally substituted 5 to 8-membered aryl, optionally substituted 5 to 8-membered heteroaryl, optionally substituted 8 to 10-membered fused bicyclic aryl, optionally substituted 8 to 10-membered fused bicyclic heteroaryl; preferably, the substituent is selected from the group consisting of optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl, optionally substituted 5 to 8-membered aryl, optionally substituted 5 to 8-membered heteroaryl, optionally substituted 8 to 10-membered fused bicyclic aryl, optionally substituted 8 to 10-membered fused bicyclic heteroaryl; more preferably, the substituent is optionally sub-

stituted C_{3-6} heterocycloalkyl.

In some embodiments, in R^1, optionally substituted means unsubstituted or being substituted with one or more (e.g., 1, 2 or 3) substituents selected from the group consisting of deuterium, halogen, C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{1-6} deuteroalkyl, C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl, $-CONR^iR^{ii}$ (e.g., $-CON(C_{1-6}$ alkyl$)_2$), $-S(O)_2R^i$ (e.g., $-S(O)_2(C_{1-6}$ alkyl)), and $-S(O)(=N-R^i)R^{ii}$ (e.g., ).

In some embodiments, in R^1, optionally substituted means unsubstituted or being substituted with one or more (e.g., 1, 2 or 3) substituents selected from the group consisting of deuterium, halogen, C_{1-6} alkyl, C_{1-6} hydroxyalkyl, and C_{1-6} deuteroalkyl.

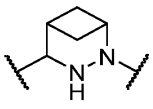
In some embodiments, R^1 is $-(CH_2)-R^{1'}$, and $R^{1'}$ is as defined in formula VI, VII, or VIII.

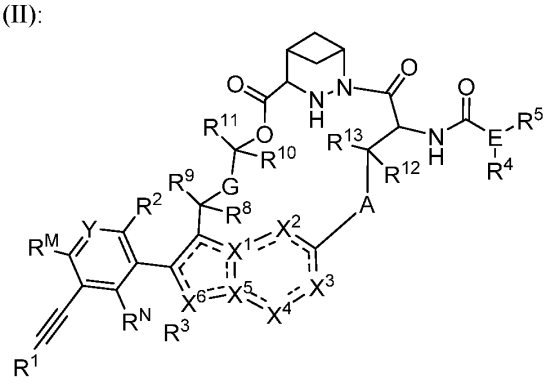
In some embodiments, R^M and R^N are each independently selected from hydrogen, halogen, hydroxy, cyano, carboxyl, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl; furthermore, the C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, C_{1-6} hydroxyalkyl may be further optionally substituted. In some embodiments, R^M and R^N are each independently selected from hydrogen, and C_{1-6} alkyl.

In some embodiments, Y is -CH- or N; preferably, Y is N.

In some embodiments, R^2 is optionally substituted C_{1-6} alkoxy, or optionally substituted C_{1-6} alkyl; preferably, R^2 is optionally substituted C_{1-6} alkyl.

In some embodiments, in R^2, optionally substituted means unsubstituted or being substituted with one or more (e.g., 1, 2 or 3) substituents selected from the group consisting of deuterium, C_{1-6} alkoxy, C_{1-6} deuteroalkoxy, and C_{1-6} haloalkoxy.

In some embodiments of the present disclosure, B is , R^A is optionally substituted phenyl or optionally substituted 6-membered heteroaryl; in some embodiments, the compound of formula (I) is a compound of formula (II):



(II)

or a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof,

wherein

A is optionally substituted 5 to 6-membered heterocycloalkylene, optionally substituted 5 to

6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

G is optionally substituted C_{1-6} alkylene;

Y is -CH- or N;

R^8 and R^9 are each independently selected from hydrogen, deuterium, halogen, hydroxy, cyano, optionally substituted C_{1-3} alkyl, or R^8 and R^9 combine with the atoms to which they are attached to form an optionally substituted C_{3-6} cycloalkyl or a carbonyl;

R^{10} and R^{11} are each independently selected from hydrogen, deuterium, halogen, hydroxy, cyano, optionally substituted C_{1-3} alkyl, or R^{10} and R^{11} combine with the atoms to which they are attached to form an optionally substituted C_{3-6} cycloalkyl or a carbonyl;

R^{12} and R^{13} are each independently selected from hydrogen, deuterium, halogen, hydroxy, optionally substituted C_{1-3} alkyl, -O(C_{1-6} alkyl), -S(C_{1-6} alkyl) or -N(C_{1-6} alkyl)(C_{1-6} alkyl); furthermore, the C_{1-6} alkyl may be further optionally substituted;Y is -CH- or N;

X^1 is N or C;

X^2 is N or -CR^a-;

X^3 is N or -CR^b-;

X^4 is N or -CR^c-;

X^5 is N or C;

X^6 is S, O, N, or -CH-;

R^a, R^b, and R^c are each independently hydrogen, halogen, cyano, C_{1-3} alkyl, C_{1-3} alkoxyl, C_{1-3} haloalkyl, C_{1-3} haloalkoxyl, C_{3-6} cycloalkyl, or C_{3-6} heterocycloalkyl (or 3 to 6-membered heterocycloalkyl);

R^1 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 5 to 8-membered aryl, optionally substituted 5 to 8-membered heteroaryl, optionally substituted 8 to 10-membered fused bicyclic aryl or optionally substituted 8 to 10-membered fused bicyclic heteroaryl; furthermore, the C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, and C_{1-6} hydroxyalkyl may be further optionally substituted;

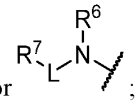
R^2 is optionally substituted C_{1-6} alkoxy, or optionally substituted C_{1-6} alkyl;

R^M and R^N are each independently selected from hydrogen, halogen, hydroxy, cyano, carboxyl, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl (or 4 to 7-membered heterocycloalkyl); furthermore, the C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, and C_{1-6} hydroxyalkyl may be further optionally substituted;

R^3 is absent, or selected from hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl, provided that when X^6 is O or S, R^3 is absent;

E is a bond, or selected from N, or -CR^d-, wherein R^d is selected from hydrogen, halogen, hydroxy, cyano, carboxyl, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkoxyl, C_{1-6} aminoalkyl, C_{1-6} hydroxyalkyl, or -NR^eR^f; wherein R^e and R^f are each independently selected from hydrogen, or optionally substituted C_{1-6} alkyl;

R^4 is hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally

substituted C_{3-10} cycloalkyl, optionally substituted C_{3-10} cycloalkenyl, optionally substituted C_{3-10} heterocycloalkyl (or 4 to 12-membered heterocycloalkyl), optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or ;

R^5 is hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl, furthermore, the C_{1-6} alkyl or C_{3-6} cycloalkyl may be further optionally substituted;

or R^4 and R^5 combine with the atoms to which they are attached to form a ring, wherein the ring is selected from optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 4 to 11-membered bicyclic cycloalkyl, optionally substituted 4 to 11-membered bicyclic heterocycloalkyl.

wherein

L is absent, or selected from $-CH_2-$, -C(O)-, $-CHR^g-$ or $-C(R^g)_2-$, wherein R^g is optionally substituted C_{1-6} alkyl;

R^6 is hydrogen, or optionally substituted C_{1-6} alkyl;

R^7 is optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{3-10} heterocycloalkyl (or 4 to 12-membered heterocycloalkyl), optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl;

or L, R^6 and R^7 combine with the atoms to which they are attached to form a ring, wherein the ring is selected from optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 4 to 11-membered bicyclic cycloalkyl, optionally substituted 4 to 11-membered bicyclic heterocycloalkyl.

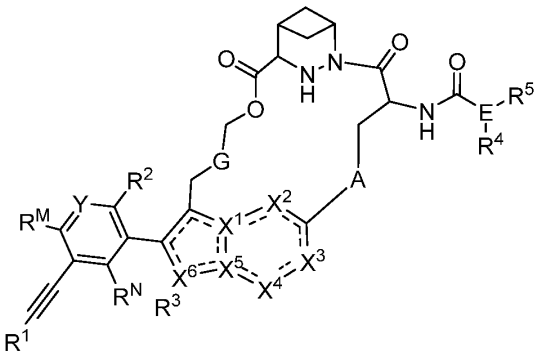
In some embodiments, X^1 is C, and/or X^2 is $-CR^a-$(preferably -CH-), and/or X^3 is $-CR^b-$(preferably –CH-), and/or X^4 is $–CR^c-$(preferably -CH-), and/or X^5 is -C-.

In some embodiments, R^a, R^b, and R^c are each independently selected from the group consisting of hydrogen, halogen, cyano, C_{1-3} alkyl, C_{1-3} alkoxyl, C_{1-3} haloalkyl, and C_{1-3} haloalkoxyl; preferably, R^a, R^b, and R^c are each independently hydrogen, or C_{1-3} alkyl.

In some embodiments of the present disclosure, X^1, X^2, X^3, X^4 and X^5 are -CH-, R^M and R^N are hydrogen.

In some embodiments of the present disclosure, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are each independently selected from hydrogen, deuterium, halogen, hydroxy, cyano, optionally substituted C_{1-3} alkyl; preferably, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are each independently hydrogen.

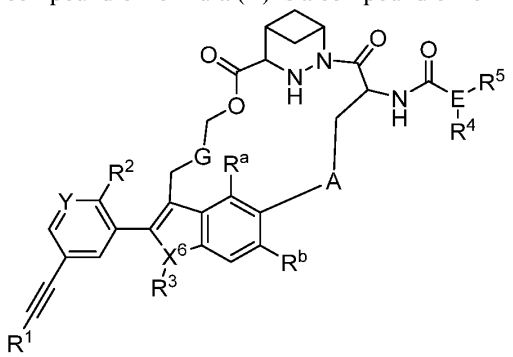
In some embodiments, the compound of formula (II) is a compound of formula (II-1)



(II-1)

wherein X^1, X^2, X^3, X^4, X^5, X^6, A, B, E, G, Y, R^M, R^N, R^1, R^3, R^4, R^5 and n are as defined in formula II.

In some embodiments, the compound of formula (II) is a compound of formula (III):



(III)

or a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof,

wherein

A is optionally substituted 5 to 6-membered heterocycloalkylene, optionally substituted 5 to 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

G is optionally substituted C_{1-6} alkylene;

Y is -CH- or N;

X^6 is S, O, N, or -CH-;

R^a and R^b are each independently hydrogen, halogen, cyano, C_{1-3} alkyl, C_{1-3} alkoxyl, C_{1-3} haloalkyl, C_{1-3} haloalkoxyl, C_{3-6} cycloalkyl, or C_{3-6} heterocycloalkyl (or 4 to 7-membered heterocycloalkyl);

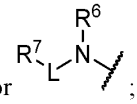
R^1 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl (or 4 to 7-membered heterocycloalkyl), optionally substituted 5 to 8-membered aryl, optionally substituted 5 to 8-membered heteroaryl, optionally substituted 8 to 10-membered fused bicyclic aryl or optionally substituted 8 to 10-membered fused bicyclic heteroaryl; furthermore, the C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, and C_{1-6} hydroxyalkyl may be further optionally substituted;

R^2 is optionally substituted C_{1-6} alkoxy, or optionally substituted C_{1-6} alkyl;

R^3 is absent, or selected from hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl, provided that when X^6 is O or S,

R^3 is absent;

E is a bond, or selected from N, or -CR^d-, wherein R^d is selected from hydrogen, halogen, hydroxy, cyano, carboxyl, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkoxyl, C_{1-6} aminoalkyl, C_{1-6} hydroxyalkyl, or -NR^eR^f; wherein R^e and R^f are independently selected from hydrogen, or optionally substituted C_{1-6} alkyl;

R^4 is hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{3-10} cycloalkenyl, optionally substituted C_{3-10} heterocycloalkyl (or 4 to 12-membered heterocycloalkyl), optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or ;

R^5 is hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl, furthermore, the C_{1-6} alkyl or C_{3-6} cycloalkyl may be further optionally substituted;

or R^4 and R^5 combine with the atoms to which they are attached to form a ring, wherein the ring is selected from optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 4 to 11-membered bicyclic cycloalkyl, optionally substituted 4 to 11-membered bicyclic heterocycloalkyl;

wherein

L is absent, or selected from -CH_2-, -C(O)-, -CHR^g- or -$C(R^g)_2$-, wherein R^g is optionally substituted C_{1-6} alkyl;

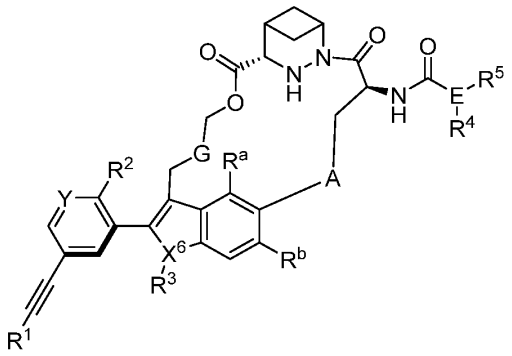
R^6 is hydrogen, or optionally substituted C_{1-6} alkyl;

R^7 is optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{3-10} heterocycloalkyl (or 3 to 10-membered heterocycloalkyl), optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl;

or L, R^6 and R^7 combine with the atoms to which they are attached to form a ring, wherein the ring is selected from optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 4 to 11-membered bicyclic cycloalkyl, optionally substituted 4 to 11-membered bicyclic heterocycloalkyl.

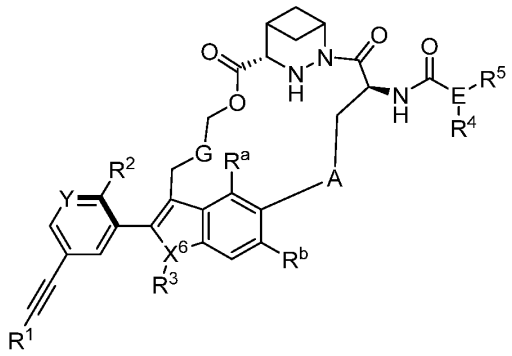
Furthermore, in the 5 to 6-membered heterocycloalkylene, 5 to 6-membered heteroarylene, C_{3-5} heterocycloalkyl (or 4 to 6-membered heterocycloalkyl), C_{3-6} heterocycloalkyl (or 4 to 7- membered heterocycloalkyl), 5 to 6-membered heteroaryl, 8 to 10-membered fused bicyclic heteroaryl, C_{1-6} heteroalkyl, C_{3-10} heterocycloalkyl, 5 to 10-membered heteroaryl, 3 to 10-membered heterocycloalkyl or 4 to 11-membered bicyclic heterocycloalkyl, the heteroatom is independently selected from one or more of N, O and S, and the number of the heteroatom is independently 1 to 4.

In some embodiments of the present disclosure, the compound of formula (III) is a compound of formula (IVa) or formula (IVb):



(IVa)

or



(IVb)

or a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof,

wherein

A is optionally substituted 5 to 6-membered heterocycloalkylene, optionally substituted 5 to 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

G is optionally substituted C_{1-6} alkylene;

Y is -CH- or N;

X^6 is S, O, N, or -CH-;

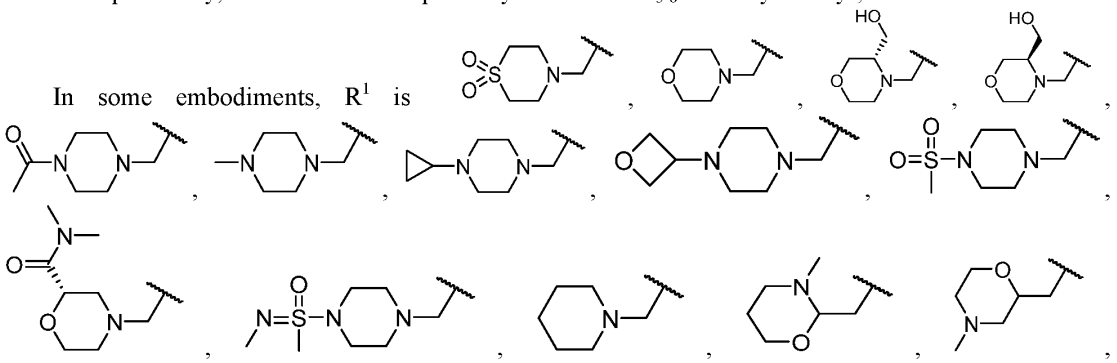
R^a and R^b are each independently hydrogen, halogen, cyano, C_{1-3} alkyl, C_{1-3} alkoxyl, C_{1-3} haloalkyl, C_{1-3} haloalkoxyl, C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl (or 4 to 7-membered heterocycloalkyl);

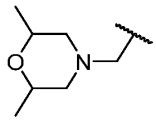
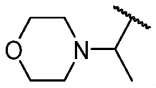
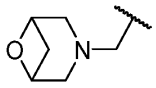
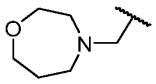
R^1 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl (or 4 to 7-membered heterocycloalkyl), optionally substituted 5 to 8-membered aryl, optionally substituted 5 to 8-membered heteroaryl, optionally substituted 8 to 10-membered fused bicyclic aryl or optionally substituted 8 to 10-membered fused bicyclic heteroaryl; furthermore, the C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, C_{1-6} hydroxyalkyl may be further optionally substituted;

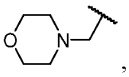
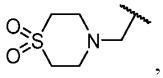
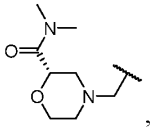
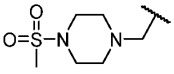
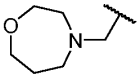
In some embodiments, R^1 is optionally substituted C_{1-6} alkyl;

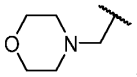
preferably, in R^1, the C_{1-6} alkyl is further substituted, the substituent is selected from optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl, optionally substituted 5 to 8-membered aryl, optionally substituted 5 to 8-membered heteroaryl, optionally substituted 8 to 10-membered fused bicyclic aryl, optionally substituted 8 to 10-membered fused bicyclic heteroaryl;

more preferably, the substituent is optionally substituted C_{3-6} heterocycloalkyl;

In some embodiments, R^1 is 

, ,  or ;

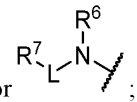
preferably, R^1 is , , ,  or ;

more preferably, R^1 is ;

R^2 is optionally substituted C_{1-6} alkoxy, or optionally substituted C_{1-6} alkyl;

R^3 is absent, or selected from hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl, provided that when X^6 is O or S, R^3 is absent;

E is a bond, or selected from N, or $-CR^d-$, wherein R^d is selected from hydrogen, halogen, hydroxy, cyano, carboxyl, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkoxyl, C_{1-6} aminoalkyl, C_{1-6} hydroxyalkyl, or $-NR^eR^f$; wherein R^e and R^f are independently selected from hydrogen, or optionally substituted C_{1-6} alkyl;

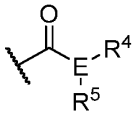
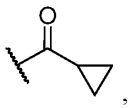
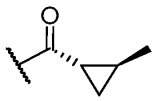
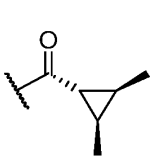
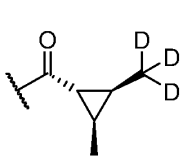
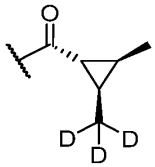
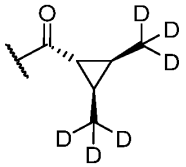
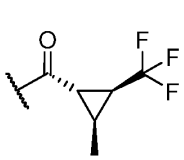
R^4 is hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{3-10} cycloalkenyl, optionally substituted C_{3-10} heterocycloalkyl (or 4 to 12-membered heterocycloalkyl), optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or ;

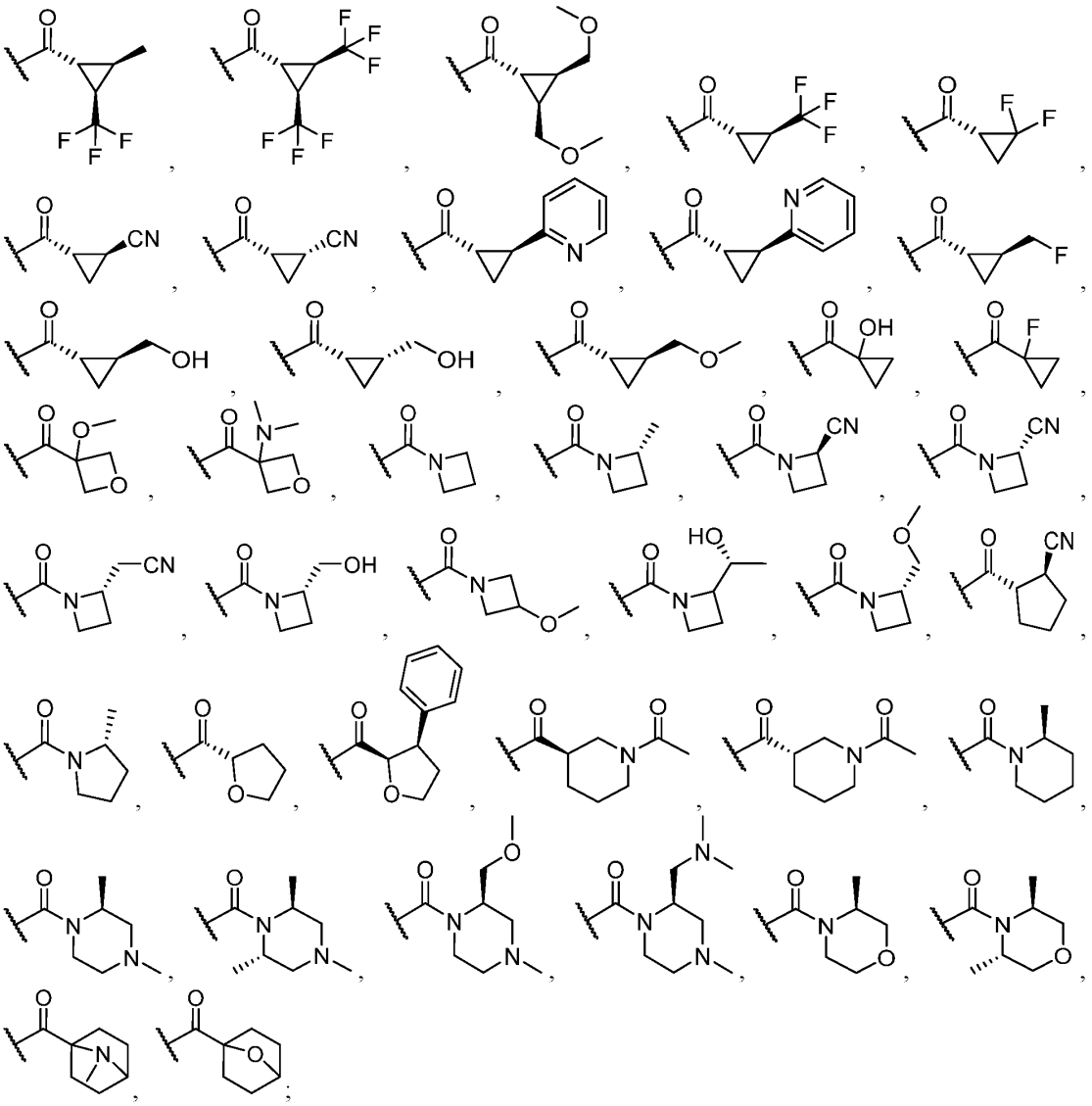
R^5 is hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl, furthermore, the C_{1-6} alkyl or C_{3-6} cycloalkyl may be further optionally substituted;

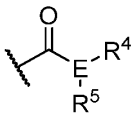
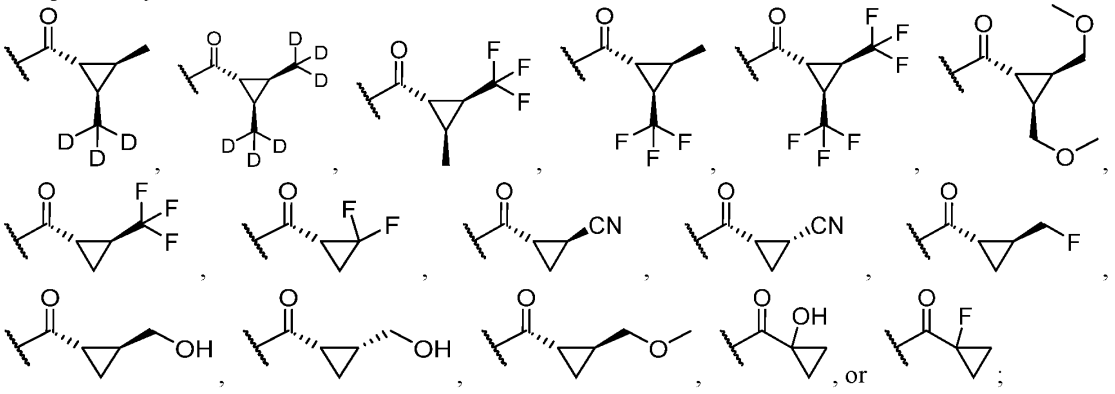
or R^4 and R^5 combine with the atoms to which they are attached to form a ring, wherein the ring is selected from optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 4 to 11-membered bicyclic cycloalkyl, optionally substituted 4 to 11-membered bicyclic heterocycloalkyl;

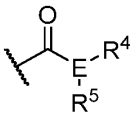
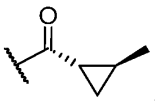
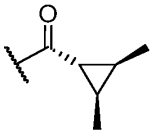
preferably, the ring is selected from optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 3 to 10-membered heterocycloalkyl;

more preferably, the ring is selected from optionally substituted 3 to 10-membered cycloalkyl;

In some embodiments of the present disclosure,  is , , , , , , ,



preferably,  is 

more preferably,  is , or ;

wherein

L is absent, or selected from -CH_2-, -C(O)-, -CHR^g- or -$C(R^g)_2$-, wherein R^g is optionally substituted C_{1-6} alkyl;

R^6 is hydrogen, or optionally substituted C_{1-6} alkyl;

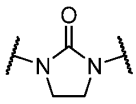
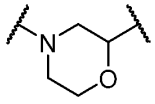
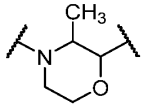
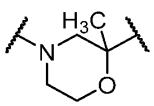
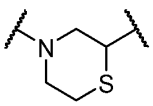
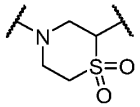
R^7 is optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{3-10} heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl;

or L, R^6 and R^7 combine with the atoms to which they are attached to form a ring, wherein the ring is selected from optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 4 to 11-membered bicyclic cycloalkyl, optionally substituted 4 to 11-membered bicyclic heterocycloalkyl.

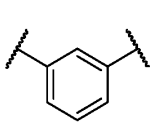
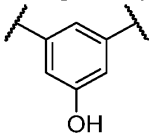
Furthermore, in the 5 to 6-membered heterocycloalkylene, 5 to 6-membered heteroarylene, C_{3-5} heterocycloalkyl, C_{3-6} heterocycloalkyl(or 3 to 6-membered heterocycloalkyl), 5 to 6-membered heteroaryl, 8 to 10-membered fused bicyclic heteroaryl, C_{1-6} heteroalkyl, C_{3-10} heterocycloalkyl (or 3 to 10-membered heterocycyoalkyl), 5 to 10-membered heteroaryl, 3 to 10-membered heterocycloalkyl or 4 to 11-membered bicyclic heteroalkyl, the heteroatom is independently selected from one or more of N, O and S, and the number of the heteroatom is independently 1 to 4.

In some embodiments, R^4 and R^5 combine with the atoms to which they are attached to form a ring, wherein the ring is optionally substituted 3 to 10-membered cycloalkyl; preferably, is optionally substituted 3 to 6-membered cycloalkyl such as optionally substituted cyclopropyl, optionally substituted cyclobutyl, optionally substituted cyclopentyl or optionally substituted cyclohexyl, more preferably, optionally substituted 3-membered cycloalkyl i.e., optionally substituted cyclopropyl.

In some embodiments of the present disclosure, the 5 to 6-membered heterocycloalkylene contains one or two heteroatoms; preferably the heteroatom is each independently selected from N, O and S.

In some embodiments of the present disclosure, A is optionally substituted 5 to 6-membered heterocycloalkylene, the heteroatom is independently selected from one or two of N, O and S, and the number of the heteroatom is independently 1 to 2.In some embodiments, A is , , , , , or .

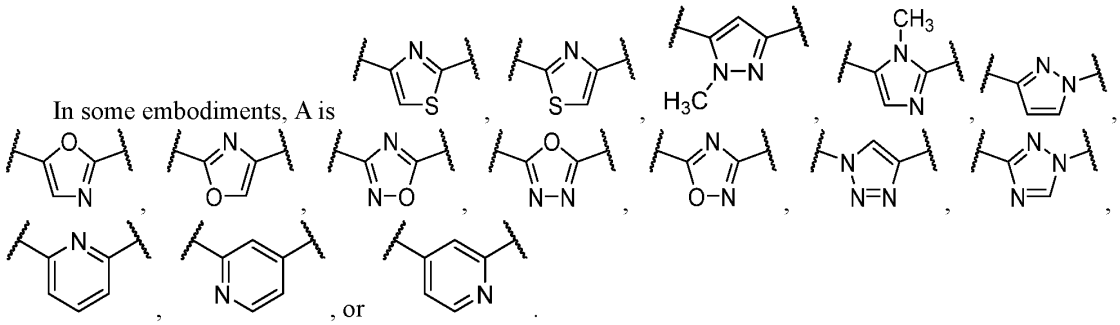
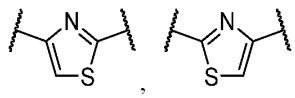
In some embodiments of the present disclosure, A is optionally substituted 5 to 6-membered arylene;

In some embodiments, A is , or .

In some embodiments of the present disclosure, the 5 to 6-membered heteroarylene contains one, two or three (preferably one or two) heteroatoms; preferably the heteroatom is each independently selected from N, O and S.

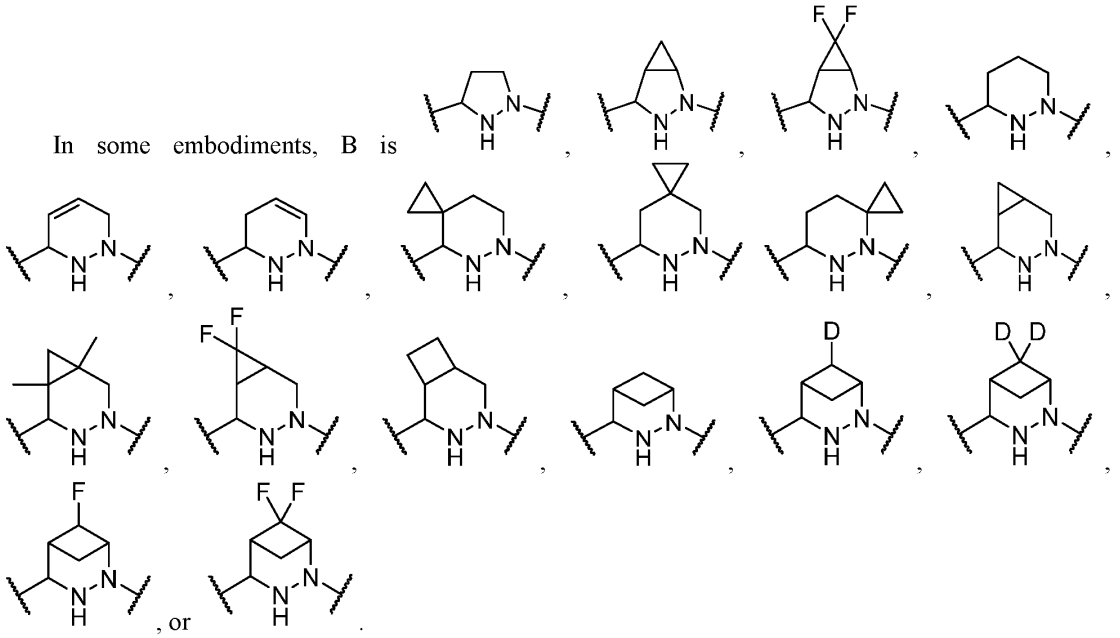
In some embodiments of the present disclosure, A is optionally substituted 5 to 6-membered heteroarylene, the heteroatom is independently selected from one or two of N, O and S, and the number of the heteroatom is independently 1 to 3.

In some embodiments of the present disclosure, A is optionally substituted 5-membered heteroarylene, the heteroatom is independently selected from N, O and S, and the number of the heteroatom is independently 1 to 2; preferably, one of the heteroatom is N, and the other, if present, is O or S.

In some embodiments, A is , or .

In some embodiments, A is .

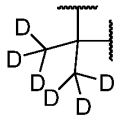
In some embodiments of the present disclosure, B is selected from the group consisting of optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 3 to 6-membered heterocycloalkenylene, optionally substituted 4 to 11-membered bicyclic alkylene, and optionally substituted 4 to 11-membered bicyclic heteroalkylene.

In some embodiments, B is , or .

In some embodiments of the present disclosure, G is optionally substituted C_{1-6} alkylene; preferabaly,

G is optionally substituted -C(C_{1-3}alkyl)$_2$-.

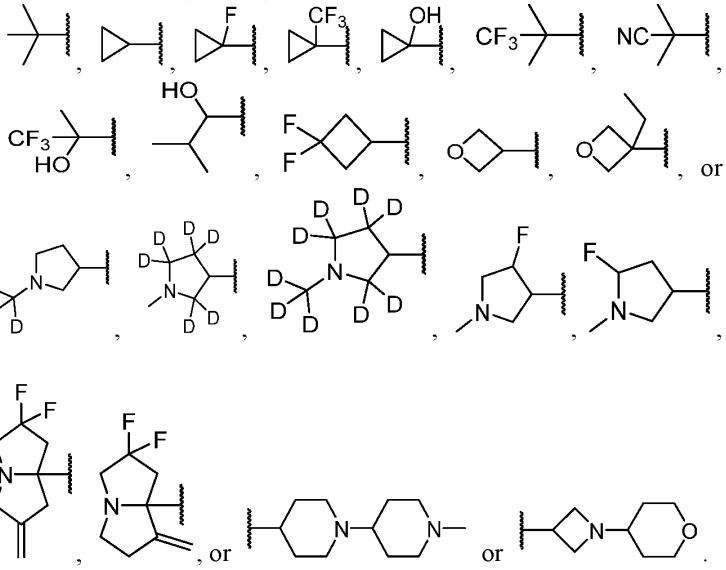
In some embodiments, in G, optionally substituted means unsubstitued or being substituted with one or more deuterium.

In some embodiments, G is  or .

In some embodiments of the present disclosure, Y is N.

In some embodiments of the present disclosure, X^6 is N.

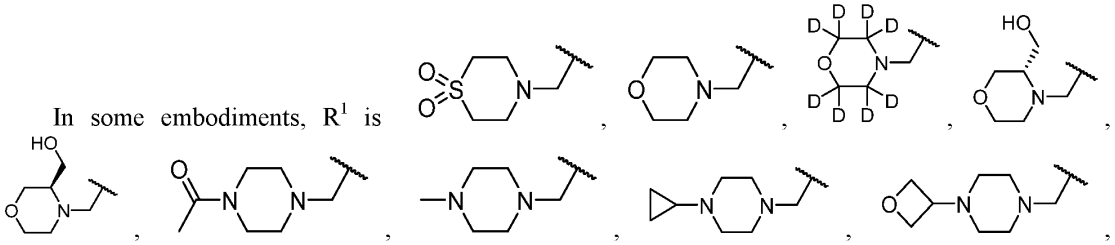
In some embodiments of the present disclosure, R^1 is C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, optionally substituted C_{3-6} cycloalkyl, or optionally substituted C_{3-6} heterocycloalkyl (or 3 to 6-membered heterocycloalkyl).

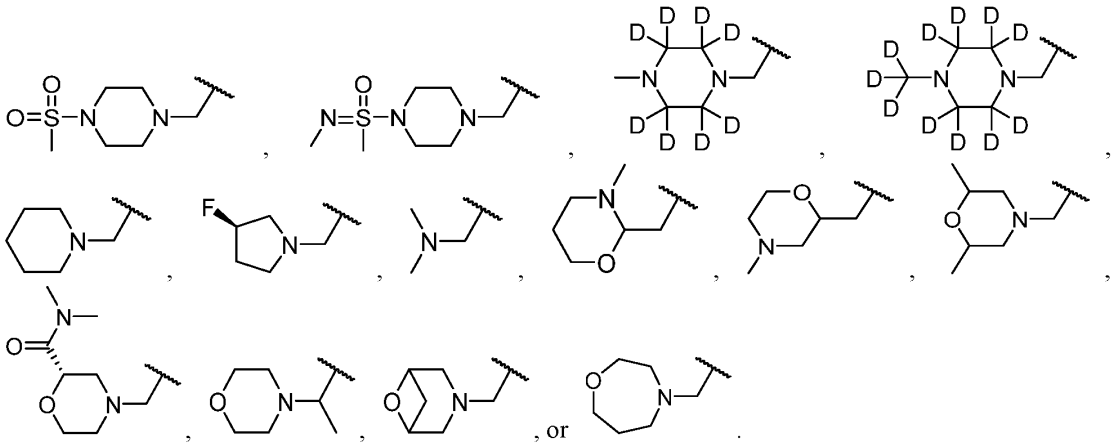
In some embodiments, R^1 is .

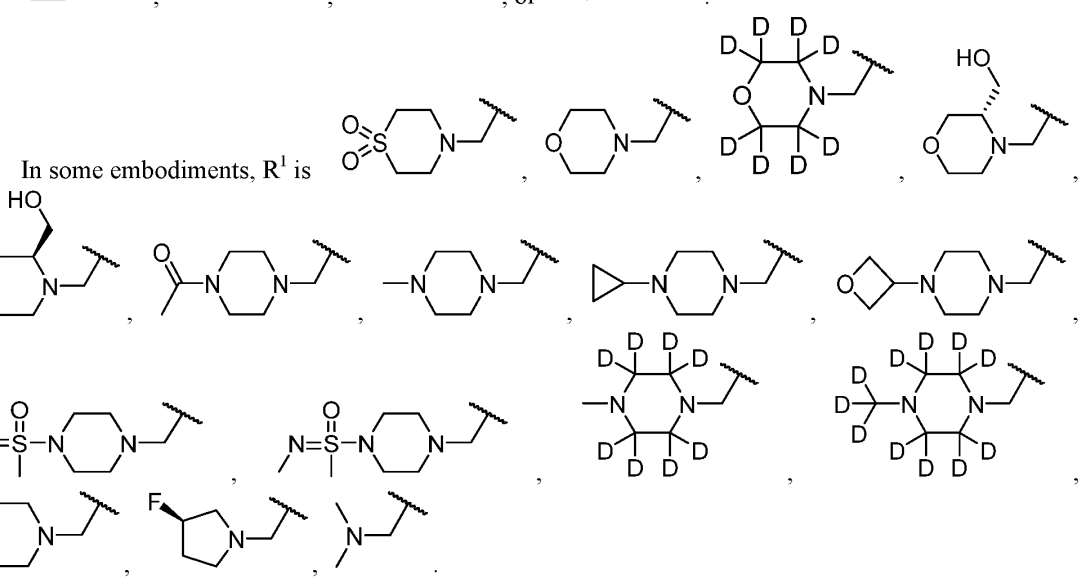
In some embodiments of the present disclosure, R^1 is C_{1-6} alkyl and the C_{1-6} alkyl is further substituted with optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl.

In some embodiments of the present disclosure, R^1 is C_1 alkyl; and the C_1 alkyl is further substituted with optionally substituted C_{3-6} heterocycloalkyl, wherein the heterocycloalkyl is saturated and the heterocycloalkyl is attached to the rest of the molecule via the N atom on the ring.

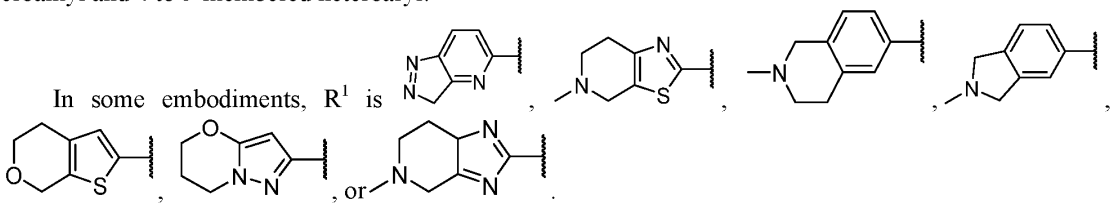
In some embodiments of the present disclosure, R^1 is C_1 alkyl; and the C_1 alkyl is further substituted with optionally substituted C_{3-6} heterocycloalkyl, wherein the heterocycloalkyl is saturated and the heterocycloalkyl is attached to the rest of the molecule via the N atom on the ring.and the C_{3-6} heterocycloalkyl is 5 to 7 menbered heterocycloalkyl and has l to 2 heteroatoms.

In some embodiments, R^1 is .

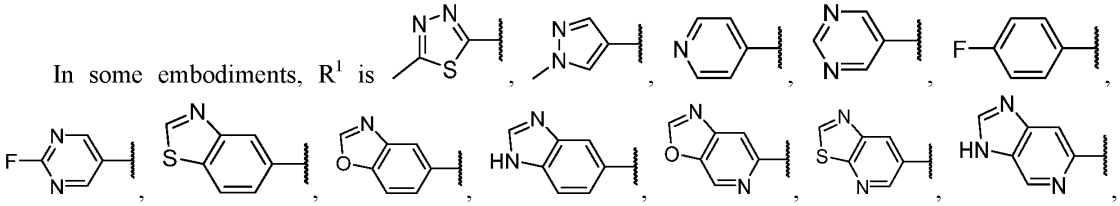


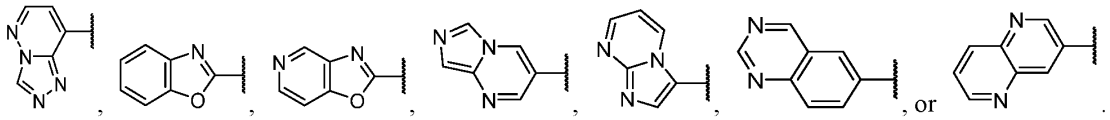
In some embodiments, R^1 is 

In some embodiments of the present disclosure, R^1 is optionally substituted 4 to 5-membered heteroalkyl and 4 to 5-membered heteroaryl.

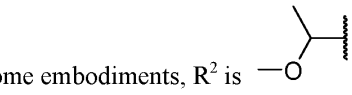
In some embodiments, R^1 is 

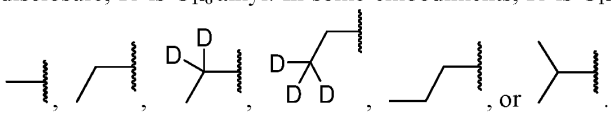
In some embodiments of the present disclosure, R^1 is optionally substituted 5 to 8-membered aryl, optionally substituted 5 to 8-membered heteroaryl, optionally substituted 8 to 10-membered fused bicyclic aryl or optionally substituted 8 to 10-membered fused bicyclic heteroaryl, the heteroatom is independently selected from one or two of N, O and S, and the number of the heteroatom is independently 1 to 4.

In some embodiments, R^1 is 

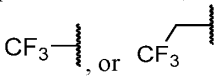


In some embodiments of the present disclosure, R^2 is optionally substituted C_{1-6} alkyl or optionally substituted C_{1-6} alkoxy.

In some embodiments, R^2 is , preferably, .

In some embodiments of the present disclosure, R^3 is C_{1-6} alkyl. In some embodiments, R^3 is C_{1-6} deuterated alkyl. In some embodiments, R^3 is .

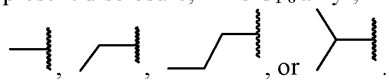
In some embodiments of the present disclosure, R^3 is C_{1-6} haloalky.

In some embodiments, R^3 is .

In some embodiments of the present disclosure, E is a bond, or selected from N, or $-CR^d-$, wherein R^d is selected from hydrogen, halogen, hydroxy, cyano, carboxyl, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkoxyl, C_{1-6} aminoalkyl, C_{1-6} hydroxyalkyl, or $-NR^eR^f$; wherein R^e and R^f are independently selected from hydrogen, or optionally substituted C_{1-6} alkyl; preferably, E is a bond, or selected from N, or $-CR^d-$, wherein R^d is selected from hydrogen, halogen, hydroxy or C_{1-6} alkyl.

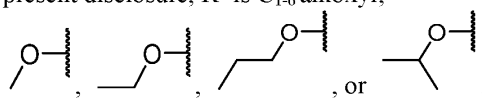
In some embodiments of the present disclosure, R^d is halogen; In some embodiments, R^d is -F, -Cl, -Br or -I; preferably, -F.

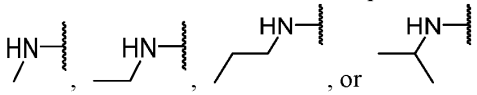
In some embodiments of the present disclosure, R^d is C_{1-6} alkyl;

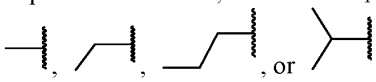
In some embodiments, R^d is .

In some embodiments of the present disclosure, R^d is C_{1-6} haloalkyl; In some embodiments, R^d is $-CF_3$.

In some embodiments of the present disclosure, R^d is C_{1-6} alkoxyl;

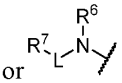
In some embodiments, R^d is .

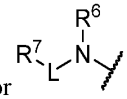
In some embodiments of the present disclosure, R^d is C_{1-6} aminoalkyl; In some embodiments, R^d is .

In some embodiments of the present disclosure, R^e or R^f is C_{1-6} alkyl; In some embodiments, R^e or R^f is independently selected from ; and preferably the other is hydrogen.

In some embodiments, L is selected from $-CH_2-$, -C(O)-, $-CHR^g-$ or $-C(R^g)_2-$, wherein R^g is optionally substituted C_{1-6} alkyl.

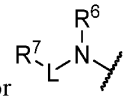
In some embodiments, R^4 is hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{3-10} heterocycloalkyl (or 4 to 12-membered heterocycloalkyl), optionally substituted 6 to 10-membered aryl, optionally substituted 5 to

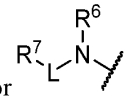
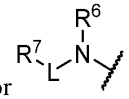
10-membered heteroaryl, or ;

preferably, R^4 is hydrogen, optionally substituted C_{1-6} alkyl, or .

In some embodiments, R^6 is hydrogen, or optionally substituted C_{1-6} alkyl; preferably, hydrogen, or C_{1-6} alkyl.

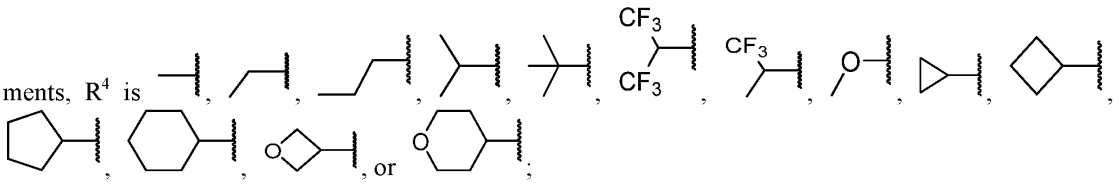
In some embodiments, R^7 is optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{3-10} heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl; preferably, R^7 is C_{1-6} alkyl, optionally substituted C_{3-10} cycloalkyl.

In some embodiments of the present disclosure, R^4 is hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{3-10} heterocycloalkyl (or 4 to 12-membered heterocycloalkyl), optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or ; wherein R^6 is hydrogen, or optionally substituted C_{1-6} alkyl; R^7 is optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{3-10} heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl.

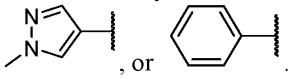
In some embodiments, in R^4, optionally substituted means unsubstituted or being substituted by one or more substituents selected from the group consisting of hydroxyl, cyano, halogen, and C_{1-6} alkyl. In some embodiments of the present disclosure, R^4 is hydrogen, C_{1-6} alkyl, 3 to 6-membered heterocycloalkyl, 3 to 6-membered cycloalkyl, 6 to 10-membered aryl, 5 to 10-membered heteroaryl, or , wherein R^6 is hydrogen, or C_{1-6} alkyl; R^7 is C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl; wherein the 3 to 10-membered heterocycloalkyl is optionally substituted by C_{1-6} alkyl, 6 to 10-membered aryl, -CO-O-C_{3-6} cycloalkyl or -CO-O-C_{1-6} alkyl; the 3 to 6-membered cycloalkyl is optionally substituted by hydroxyl, cyano, halogen, or C_{1-6} alkyl; in 3 to 10-membered heterocycloalkyl, the heteroatom is independently selected from one or more of N, O and S, and the number of the heteroatom is independently 1 to 3; more preferably, R^4 is hydrogen, C_{1-6} alkyl, or , wherein R^6 is hydrogen, or C_{1-6} alkyl; R^7 is C_{1-6} alkyl, 3 to 10-membered heterocycloalkyl.

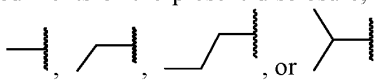
In some embodiments, in R^4, C_{3-10} heterocycloalkyl (or 4 to 12-membered heterocycloalkyl) contains 1 or 2 heteroatoms selected from the group consisting of N, O and S.

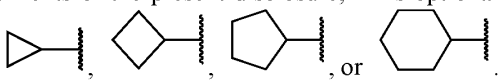
In some embodiments of the present disclosure, R^4 is optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{3-10} heterocycloalkyl, the heteroatom is N, O or S, and the number of the heteroatom is independently 1 to 2. In some embodi-

ments, R^4 is ;

In some embodiments of the present disclosure, R^4 is optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl.

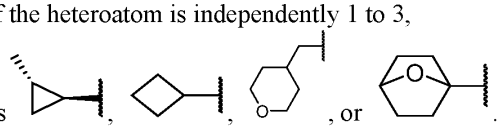
In some embodiments, R^4 is .

In some embodiments of the present disclosure, R^5 is optionally substituted C_{1-6} alkyl. In some embodiments, R^5 is .

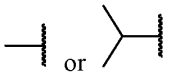
In some embodiments of the present disclosure, R^5 is optionally substituted C_{3-6} cycloalkyl. In some embodiments, R^5 is .

In some embodiments, in the ring formed by R^4, R^5 and the atoms to which they are attached, the heterocycloalkyl or the bicyclic heterocycloalkyl contains 1, 2 or 3 heteroatom selected from the group consisting of N, O and S.

In some embodiments of the present disclosure, R^4 and R^5 combine with the atoms to which they are attached to form a ring, wherein the ring is selected from optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 4 to 11-membered bicyclic cycloalkyl, optionally substituted 4 to 11-membered bicyclic heterocycloalkyl, the heteroatom is N, O or S, and the number of the heteroatom is independently 1 to 3,

preferably, the ring is .

In some embodiments, R^4 and R^5 combine with the atoms to which they are attached to form a ring, wherein the ring is optionally substituted 3 to 10-membered cycloalkyl; preferably, the ring is optionally substituted 3 to 4-membered cycloalkyl; more preferably, the ring is cy optionally substituted clopropyl; preferably, wherein optionally substituted means unsubstituted or being substituted with one or more substituents selected from the group consisting of C_{1-4} alkyl, C_{1-4} deuteroalkyl, cyano, C_{1-4} hydroxyalkyl, and C_{1-4} haloalkyl.

In some embodiments of the present disclosure, R^6 is optionally substituted C_{1-6} alkyl; In some embodiments, R^6 is .

In some embodiments, R^7 is optionally substituted C_{3-10} cycloalkyl, or optionally substituted C_{3-10} heterocycloalkyl.

In some embodiments, in R^7, substituents for C_{3-10} heterocycloalkyl are selected from the group consisting of halogen, C_{1-6} alkyl, 6 to 10-membered aryl, -CO-O-C_{3-6} cycloalkyl, -CO-O-C_{1-6} alkyl, -CO-C_{3-6} cycloalkyl, -CO-C_{1-6} alkyl, -CO-C_{1-6} alkenyl, and -CO-C_{1-6} alkynyl, and/or substituents for C_{3-10} cycloalkyl are selected from the group consisting of hydroxyl, cyano, halogen, or C_{1-6} alkyl.

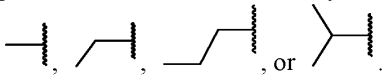
In some embodiments, in R^7, substituents for C_{3-10} heterocycloalkyl are selected from the group con-

sisting of C_{1-6} alkyl, 6 to 10-membered aryl, -CO-O-C_{3-6} cycloalkyl and -CO-O-C_{1-6} alkyl, and/or substituents for C_{3-10} cycloalkyl are selected from the group consisting of hydroxyl, cyano, halogen, or C_{1-6} alkyl.

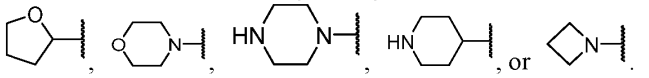
In some embodiments, in R^7, C_{3-10} heterocycloalkyl contains 1 to 3 heteroatoms selected from the group consisting of N, O and S.

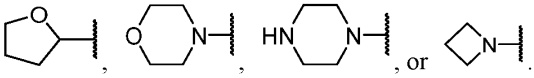
In some embodiments, R^7 is optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{3-10} heterocycloalkyl; preferably, the C_{3-10} heterocycloalkyl optionally substituted by C_{1-6} alkyl, C_{6-10} aryl , -CO-O-C_{3-6} cycloalkyl or -CO-O-C_{1-6} alkyl; the C_{3-10} cycloalkyl optionally substituted by hydroxyl, cyano, halogen, or C_{1-6} alkyl; in C_{3-10} heterocycloalkyl, the heteroatom is independently selected from one or more of N, O and S, and the number of the heteroatom is independently 1 to 3.

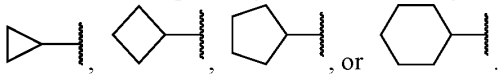
In some embodiments of the present disclosure, R^7 is C_{1-6} alkyl.

In some embodiments, R^7 is .

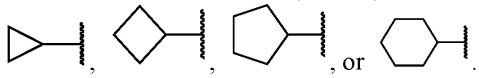
In some embodiments, R^7 is optionally substituted 3 to 6-membered heterocycloalkyl.

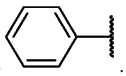
In some embodiments, in R^7, the 3 to 6-membered heterocycloalkyl contains 1 or 2 heteroatom selected from N, O or S; preferably, is .

In some embodiments of the present disclosure, R^7 is 3 to 6-membered heterocycloalkyl, preferably, the heteroatom is N, O or S, and the number of the heteroatom is independently 1 to 2. In some embodiments, R^7 is .

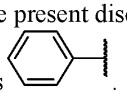
In some embodiments, R^7 is optionally substituted C_{3-6} cycloalkyl. In some embodiments, in R^7, the C_{3-6} cycloalkyl is .

In some embodiments of the present disclosure, R^7 is C_{3-6} cycloalkyl;

In some embodiments, R^7 is .

In some embodiments, R^7 is optionally substituted C_{6-10} aryl. In some embodiments, in R^7, the C_{6-10} aryl is .

In some embodiments of the present disclosure, R^7 is C_{6-10} aryl.

In some embodiments, R^7 is .

In some embodiments, R^7 is optionally substituted C_{1-6} alkyl or optionally substituted 3 to 6-membered heterocycloalkyl.

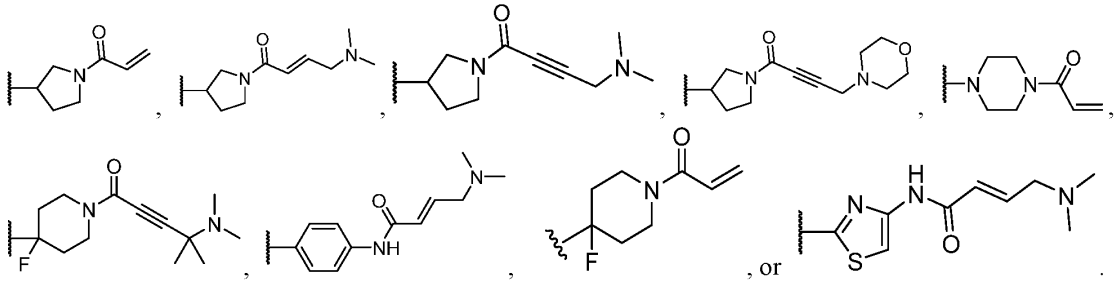
In some embodiments, in R^7, substituents for the 3 to 6-membered heterocycloalkyl is selected from -C(O)R^i or -NHC(O)R^i; wherein R^i is selected from the group consisting of C_{1-6} alkyl, -C_{2-6}alkenyl, C_{2-6} alkynyl; wherein the alkyl, alkenyl, or alkynyl is unsubtituted or one or more (such as 1, 2, 3 or 4) of H atom in the group being substituted with substituents selected from the group consisting of D, halogen, -CN, -OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} deuteroalkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, alkylamino.

In some embodiments, in R^7, substituents for the 3 to 6-membered heterocycloalkyl is selected from 6 to 10-membered aryl or -CO-O-C_{1-6} alkyl.

In some embodiments, in R^7, the 3- to 6-membered heterocycloalkyl contains 1 or 2 heteroatoms selected from N and O.

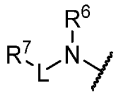
In some embodiments of the present disclosure, R^7 is C_{1-6} alkyl or 3 to 6-membered heterocycloalkyl; the 3 to 6-membered heterocycloalkyl optionally substituted by 6 to 10-membered aryl or -CO-O-C_{1-6} alkyl; in 3 to 6-membered heterocycloalkyl, the heteroatom is independently selected from one or two of N and O, and the number of the heteroatom is independently 1 to 2.

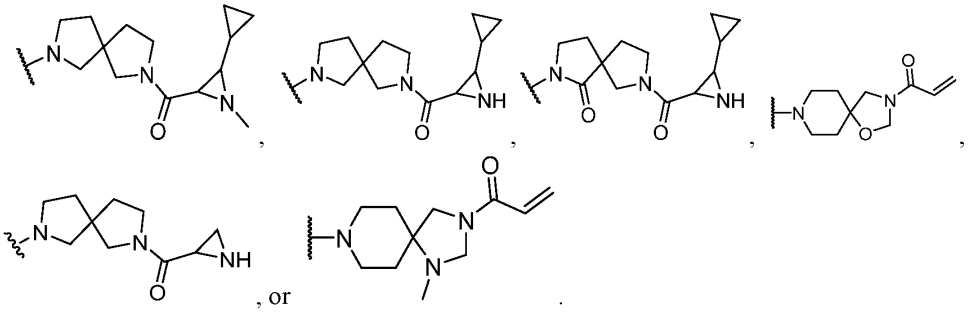
In some embodiments, R^7 is

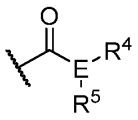
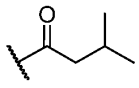
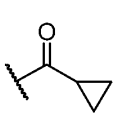


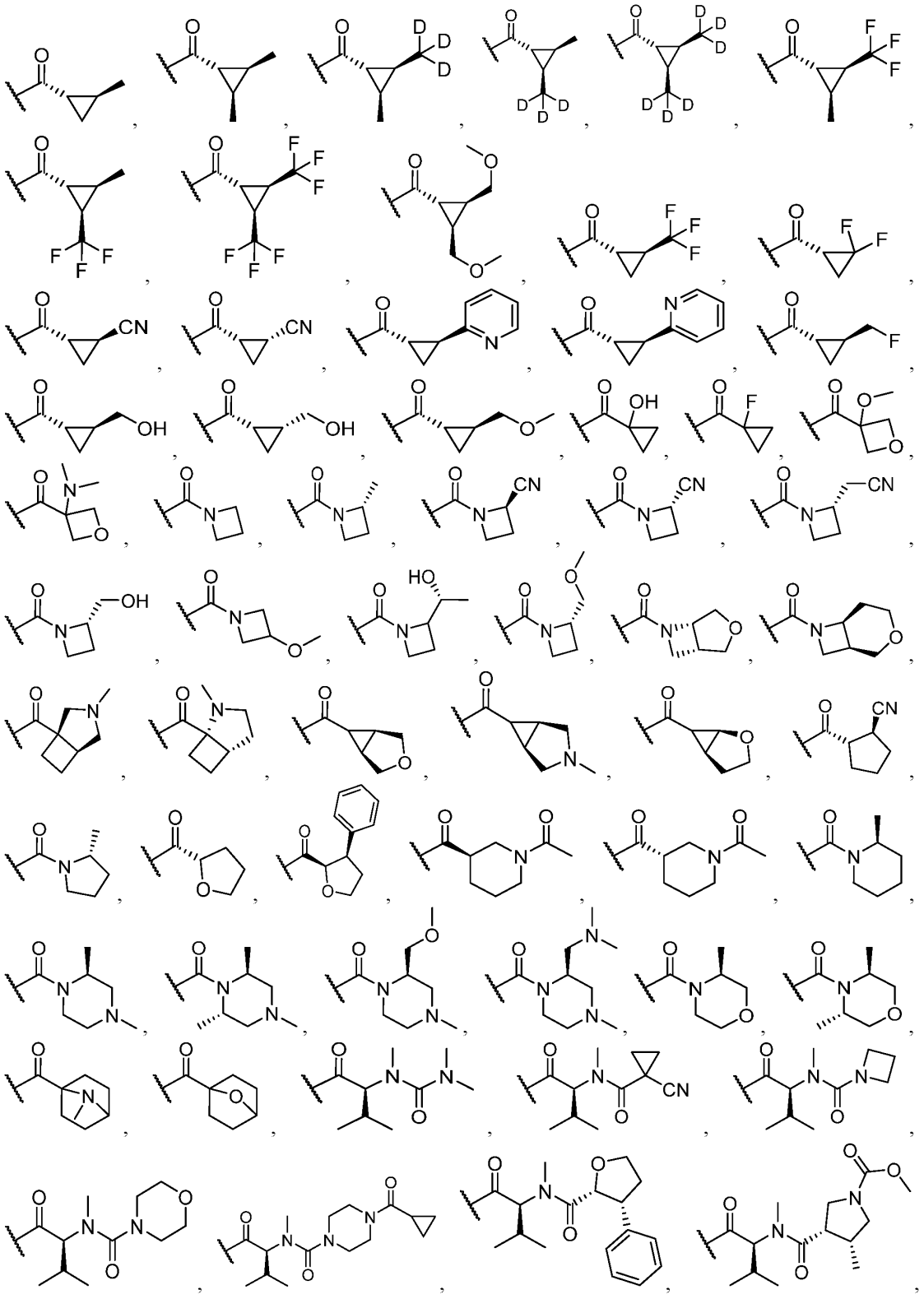
In some embodiments of the present disclosure, L, R^6 and R^7 combine with the atoms to which they are attached to form a ring, wherein the ring is selected from optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 4 to 11-membered bicyclic cycloalkyl, optionally substituted 4 to 11-membered bicyclic heterocycloalkyl.

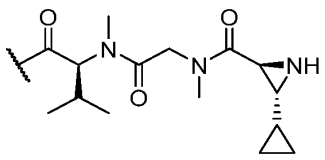
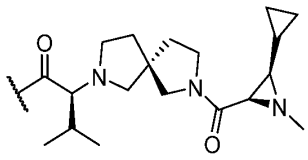
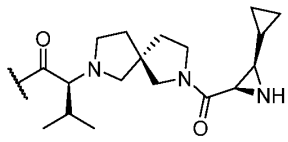
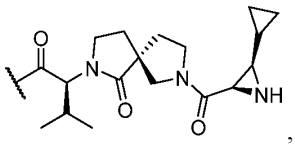
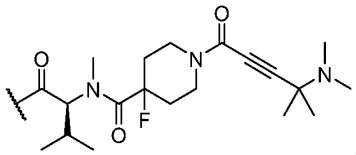
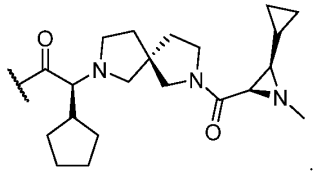
In some embodiments, substituents for the ring formed by L, R^6 and R^7 combined with the atoms to which they are attached is -C(O)R^i; wherein R^i is selected from the group consisting of C_{1-6} alkyl, -C_{2-6}alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, and 3 to 10-membered heterocycloalky; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, or heterocycloalky is unsubtituted or one or more (such as 1, 2, 3 or 4) of H atom in the group being substituted with substituents selected from the group consisting of D, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} deuteroalkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, alkylamino, and C_{3-6} cycloalkyl.

In some embodiments,  is



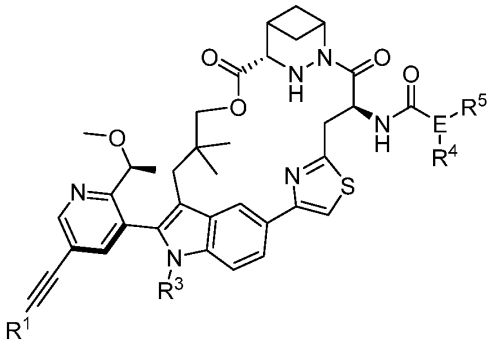
In some embodiments of the present disclosure,  is , ,




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or

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In some embodiments of the present disclosure, the "halogen" is F, Cl, Br or I; preferably, F.

In some embodiments of the present disclosure, the compound of formula (IVa) is a compound of formula (V):



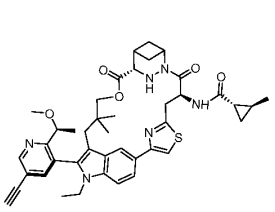
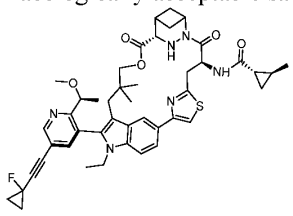
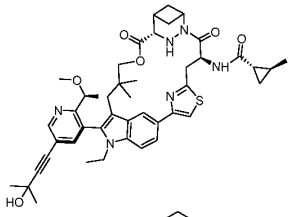
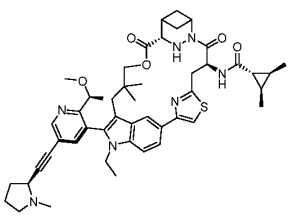
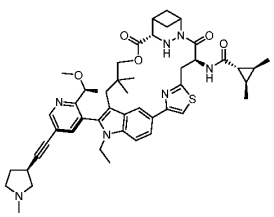
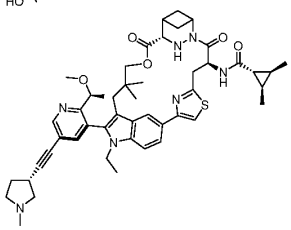
(V)

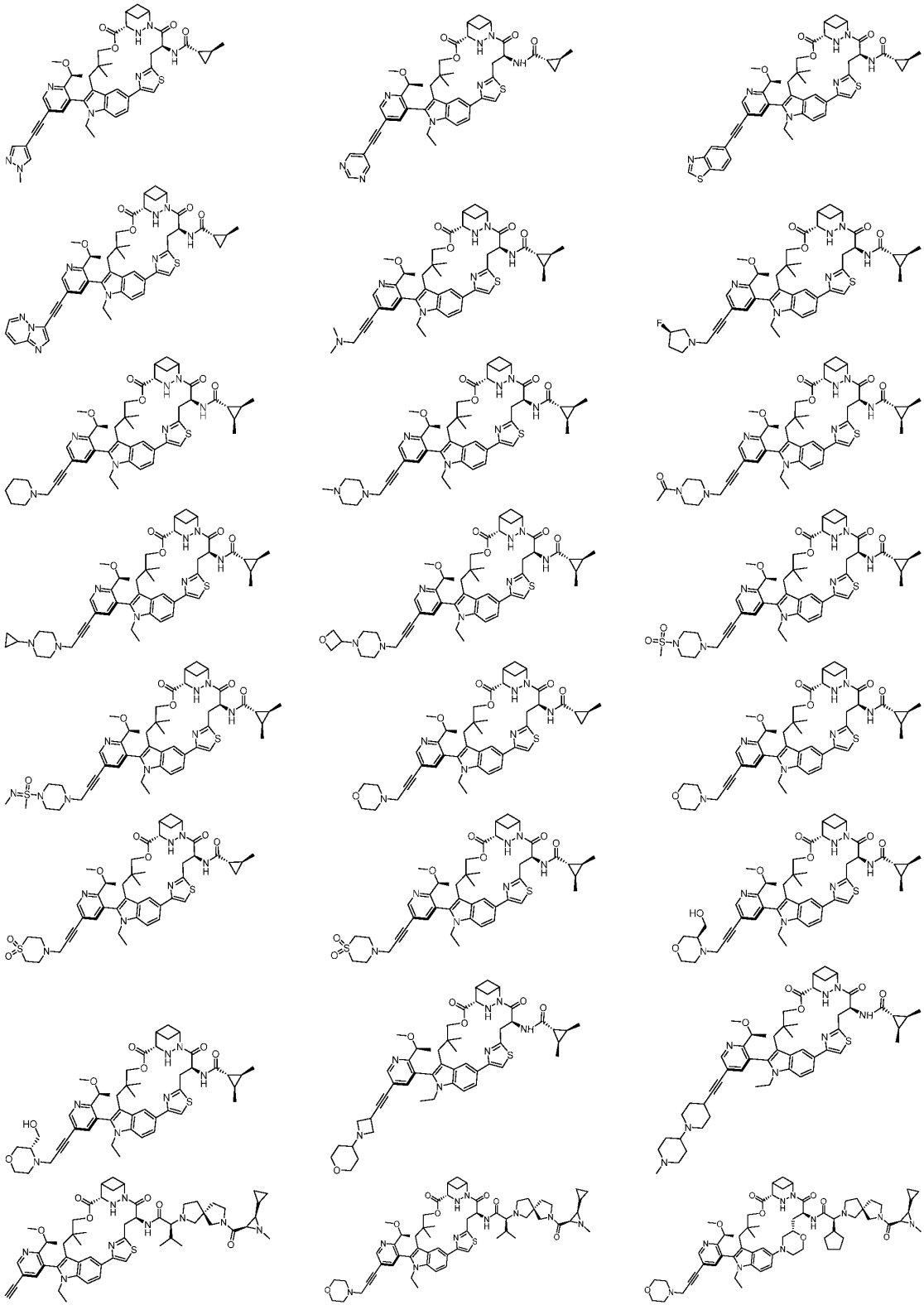
or a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein the variables are as described above.

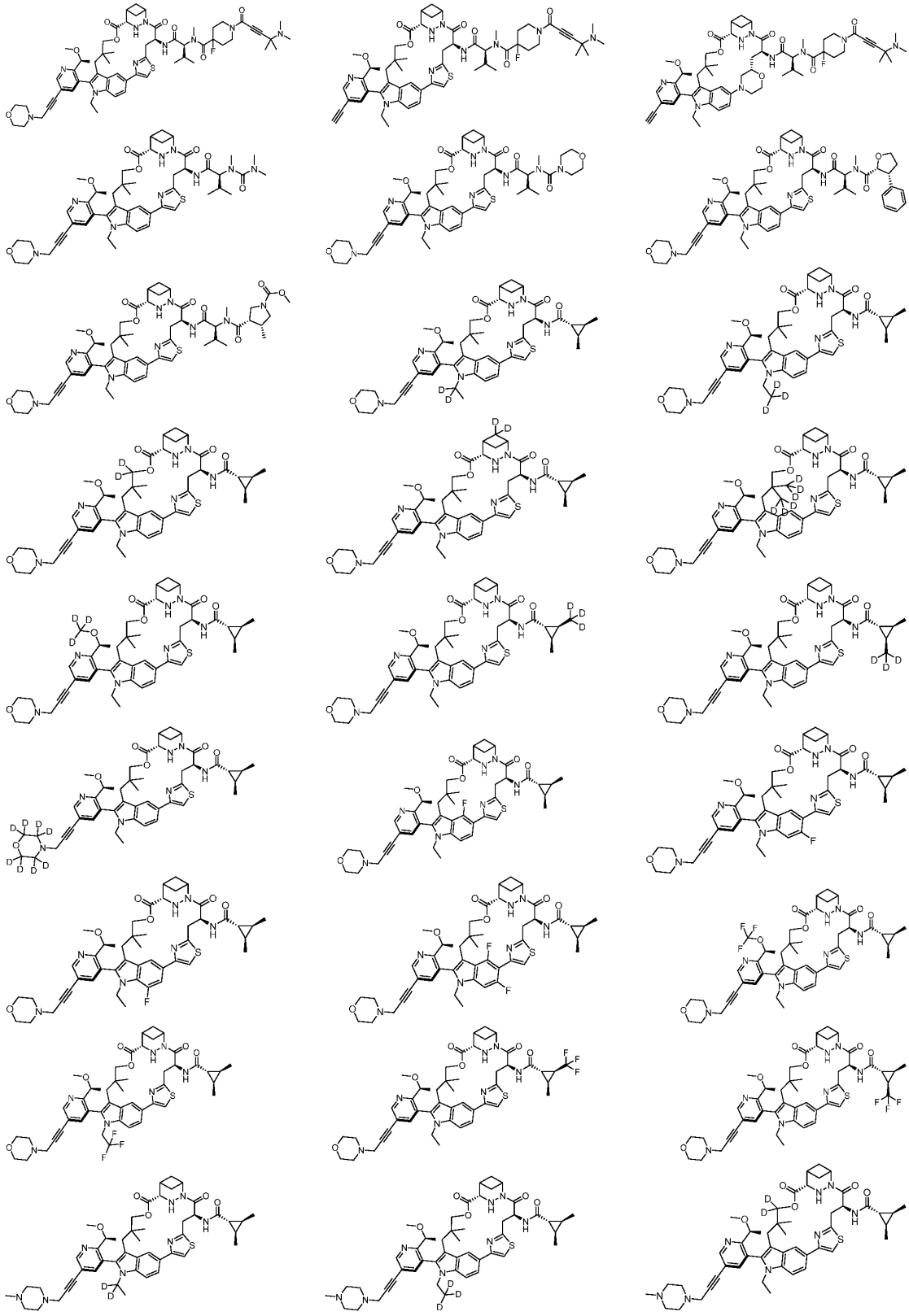
In some embodiments, X^1, X^2, X^3, X^4, X^5, X^6, A, B, E, G, L, Y, R^a, R^b, R^c, R^A, R^B, R^M, R^N, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and n are each independently corresponding groups in specific compound shown below or compounds of examples 1 to 30.

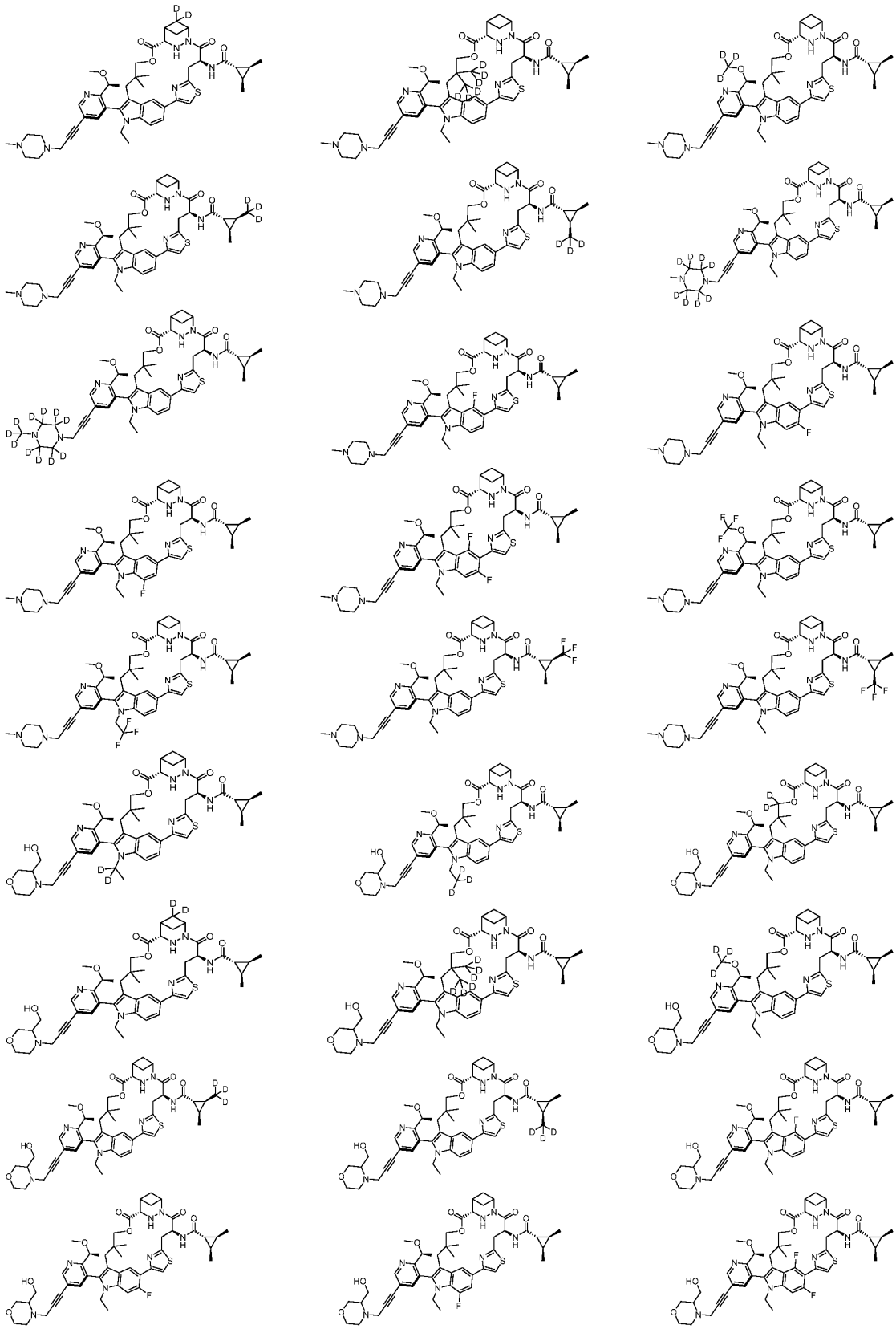
The present invention also has some schemes derived from any combination of the above-mentioned variables.

In another aspect, the present invention also provides, but is not limited to, the following compounds, and stereoisomers thereof or their pharmacologically acceptable salts:

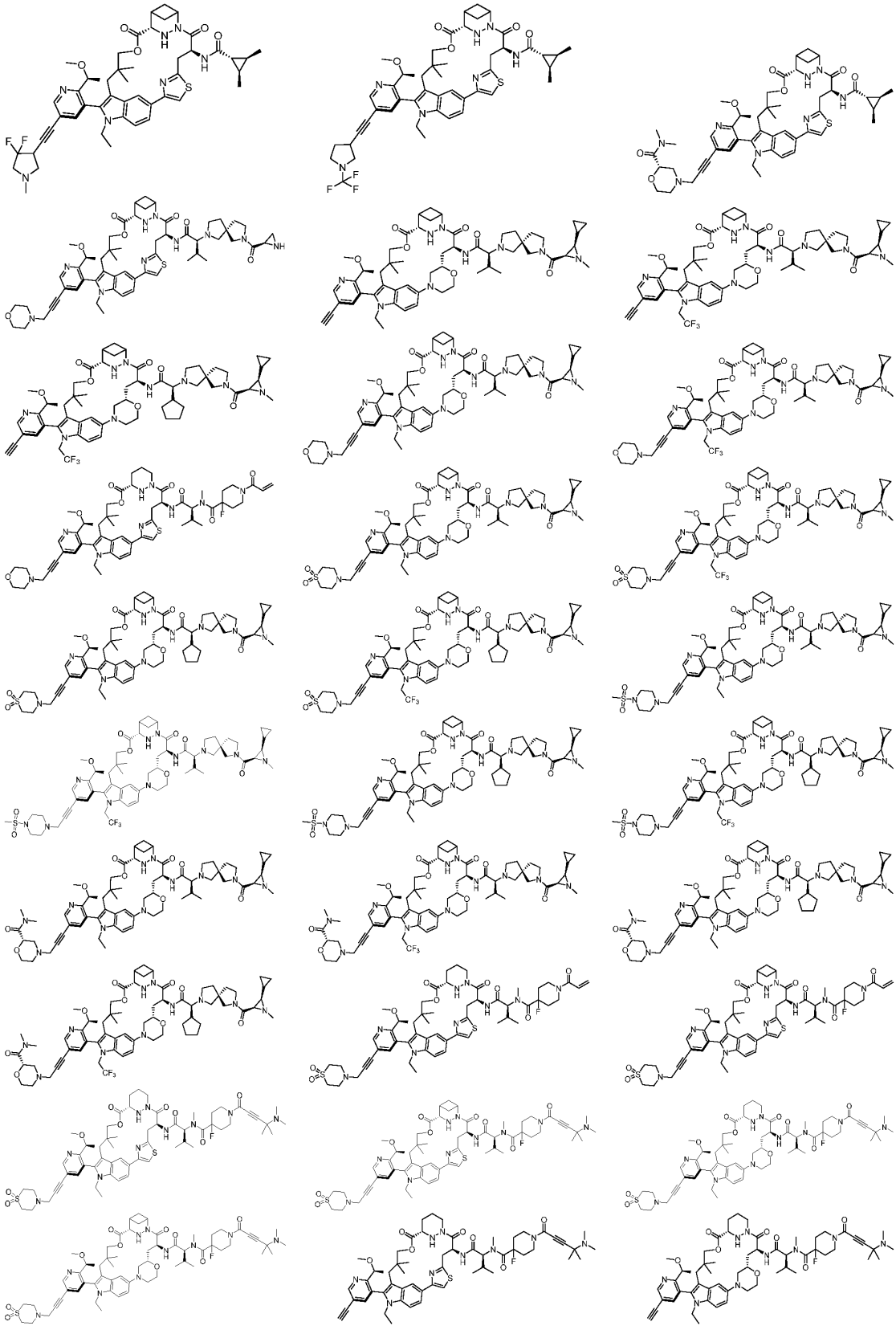







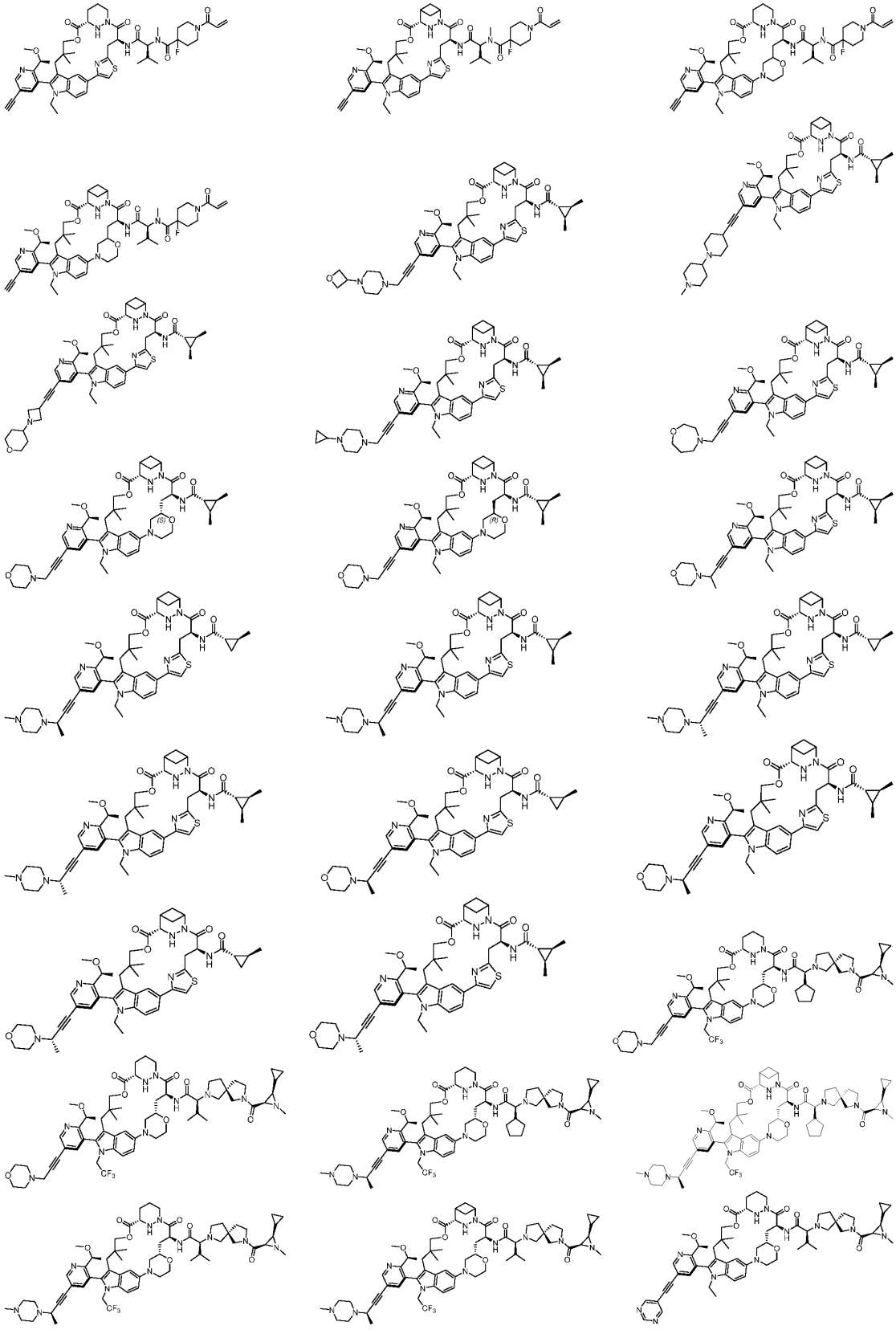




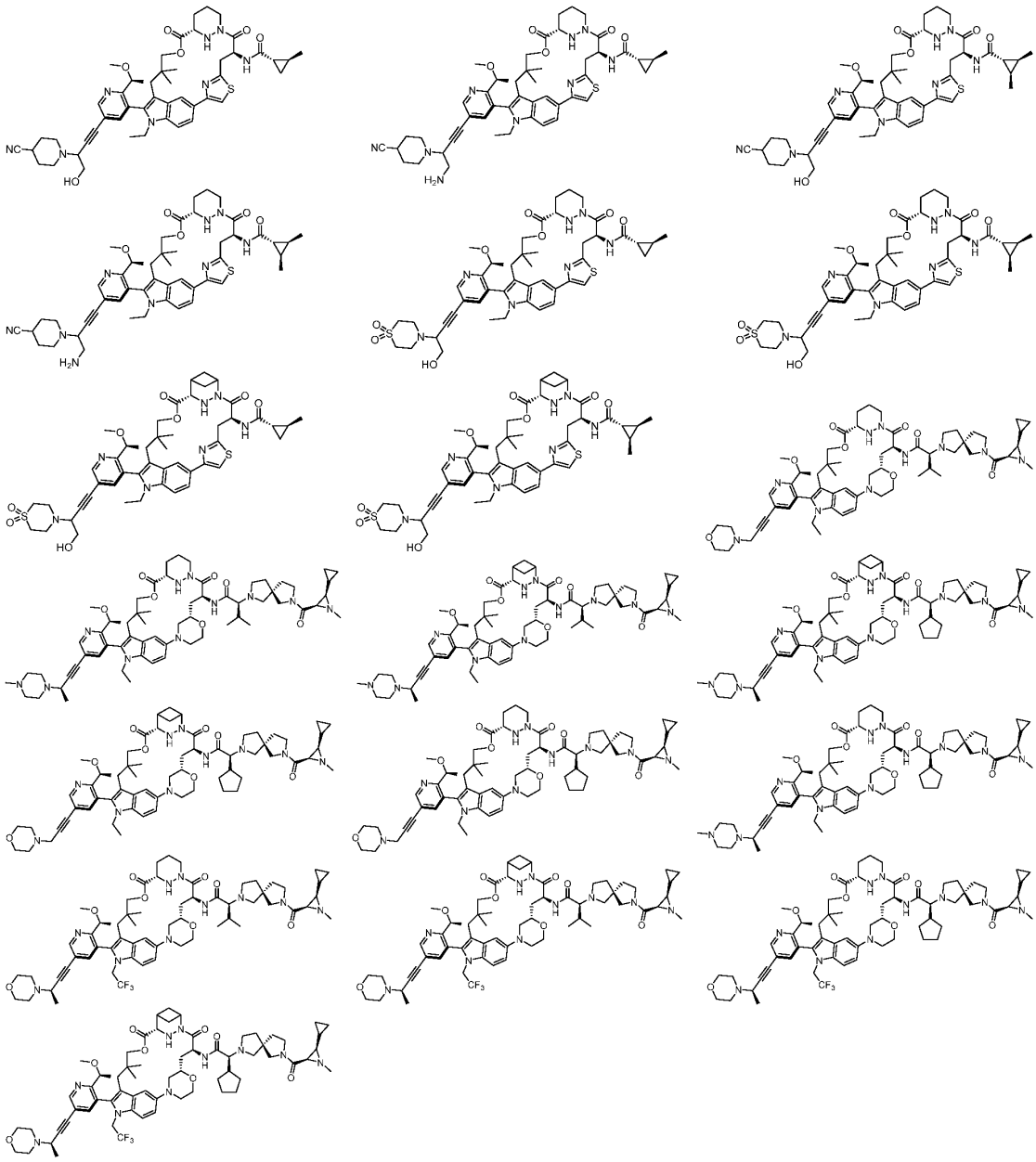








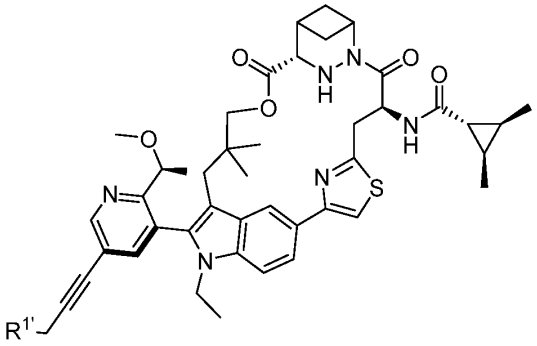




In some compounds of Formulas above, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present disclosure as described and claimed herein is meant to include all suitable isotopic variations of the compounds of Formulas above and embodiments thereof. For example, different isotopic forms of hydrogen (H) include protium (1H) and deuterium (2H, also denoted herein as D). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing in vivo half-life or reducing dosage requirements or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds can be prepared without undue experimentation by conventional techniques well known to

those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

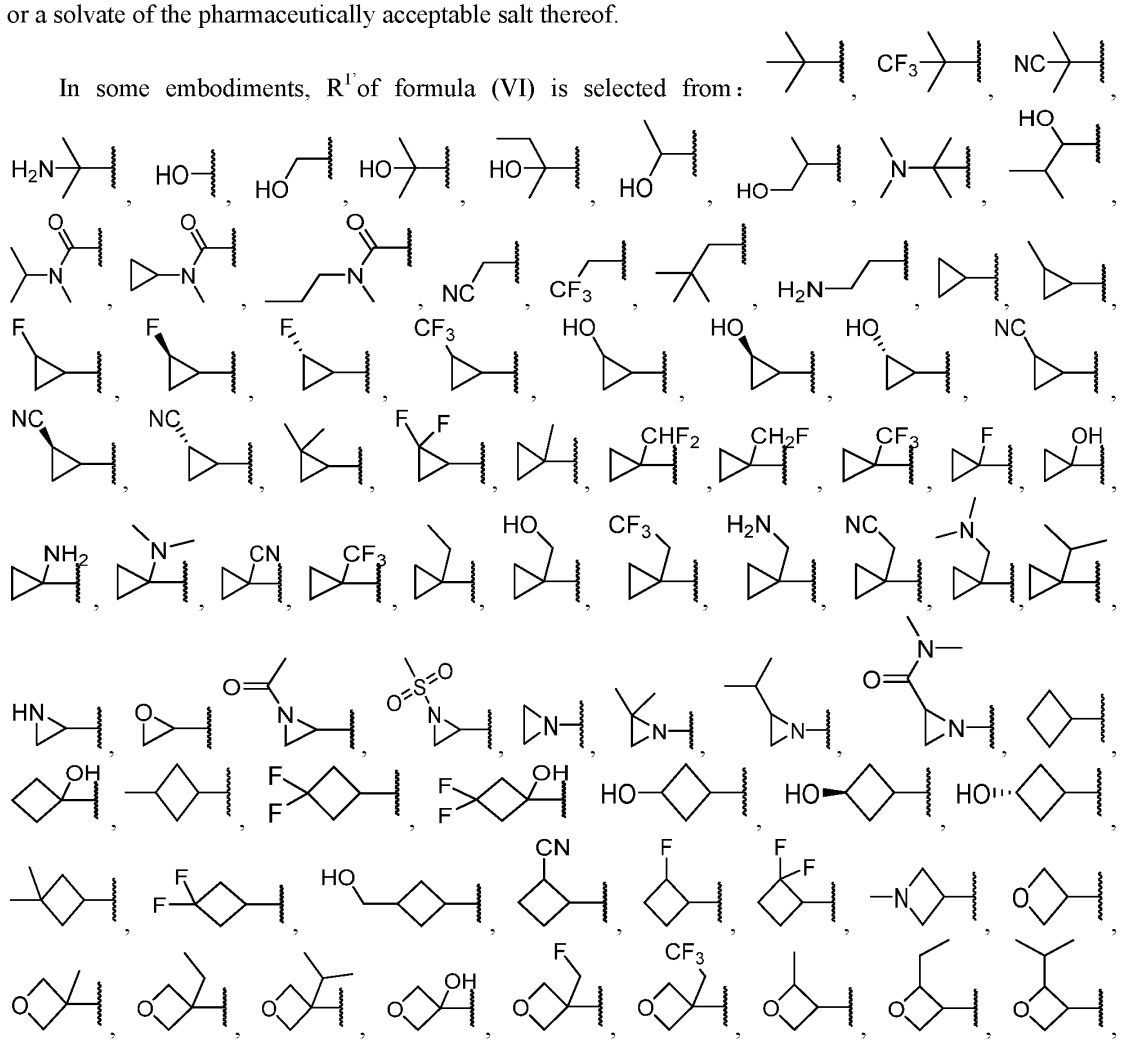
In some embodiments of the present disclosure, the compound of formula (V) is a compound of formula (VI):

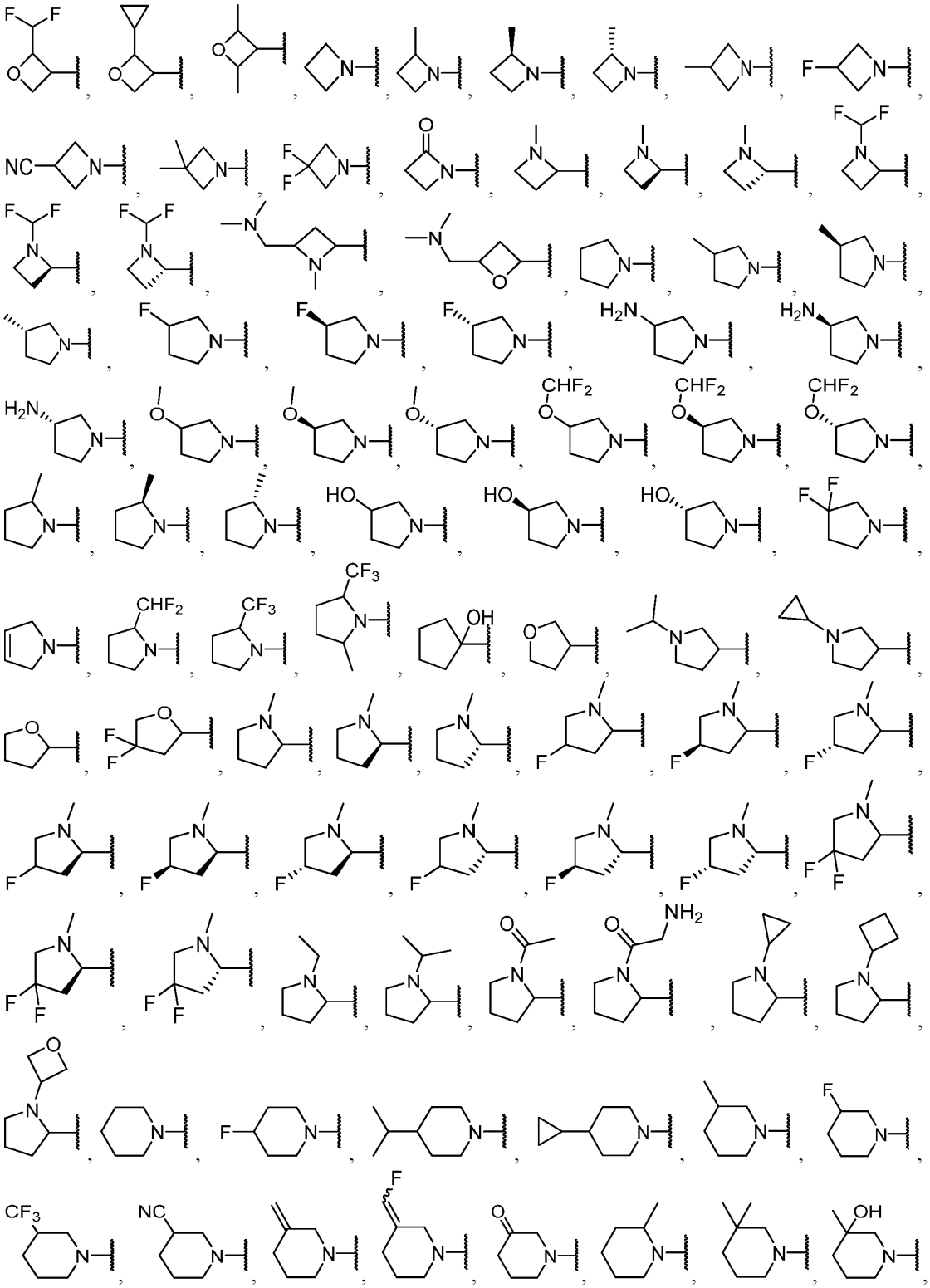


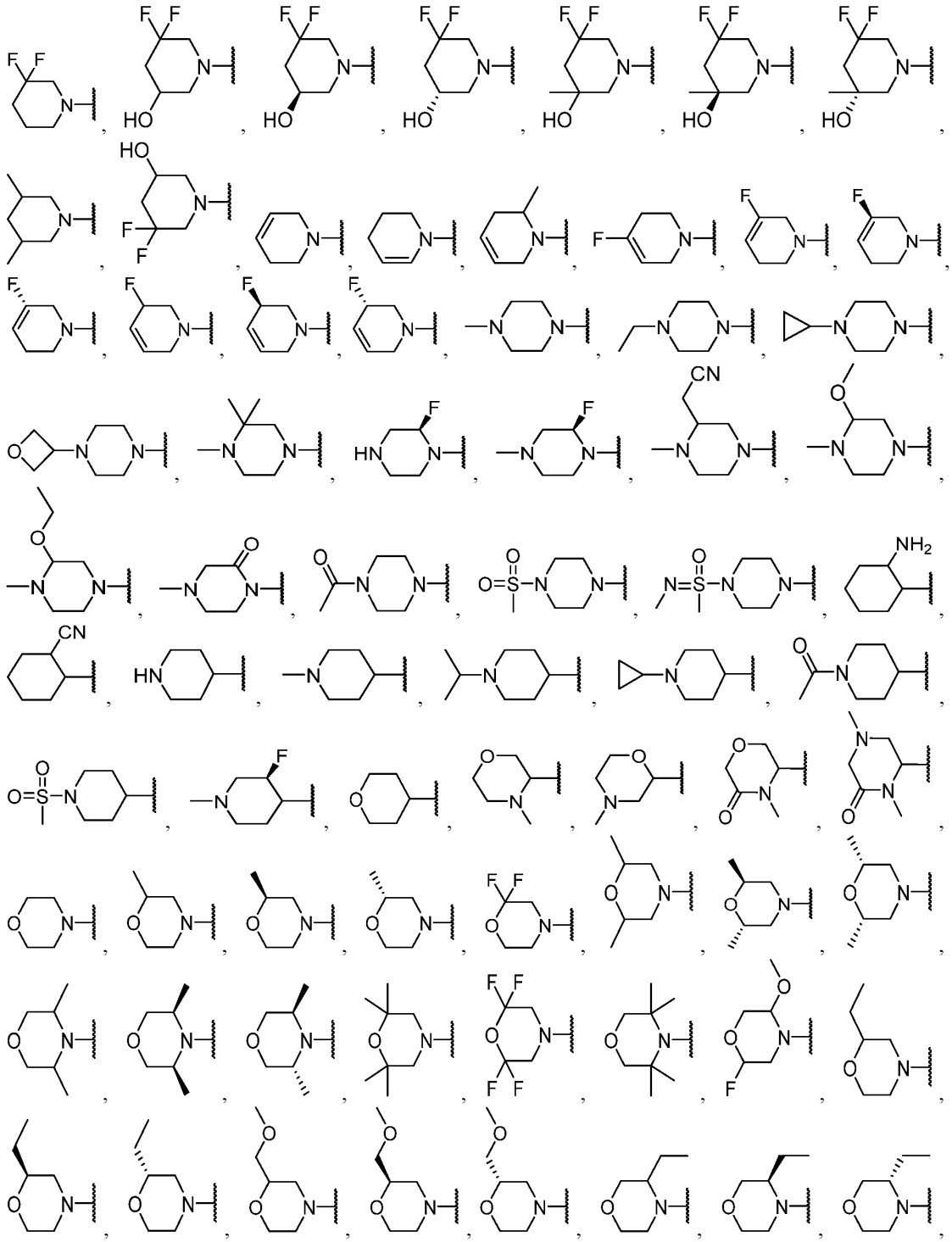
(VI)

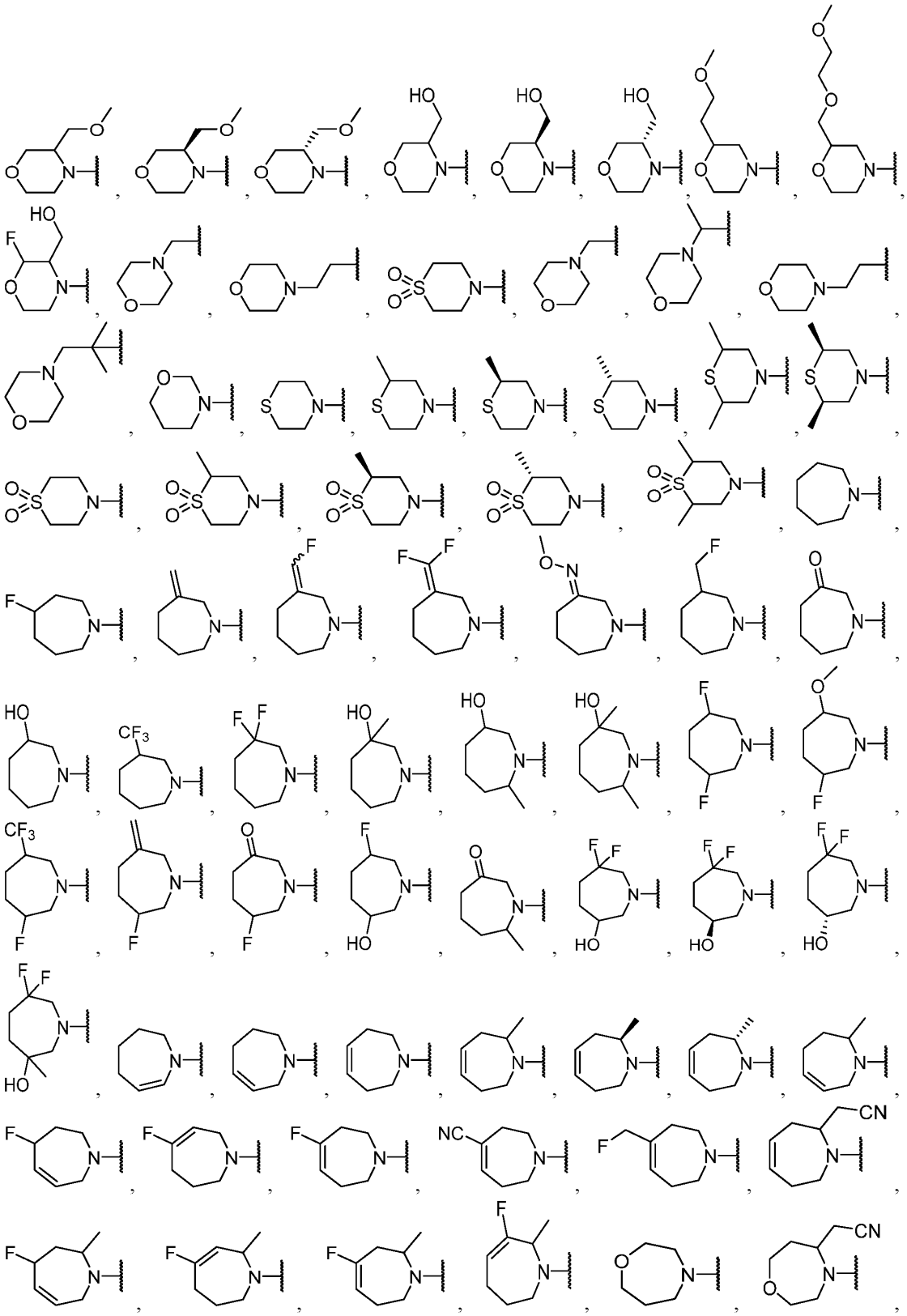
or a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof.

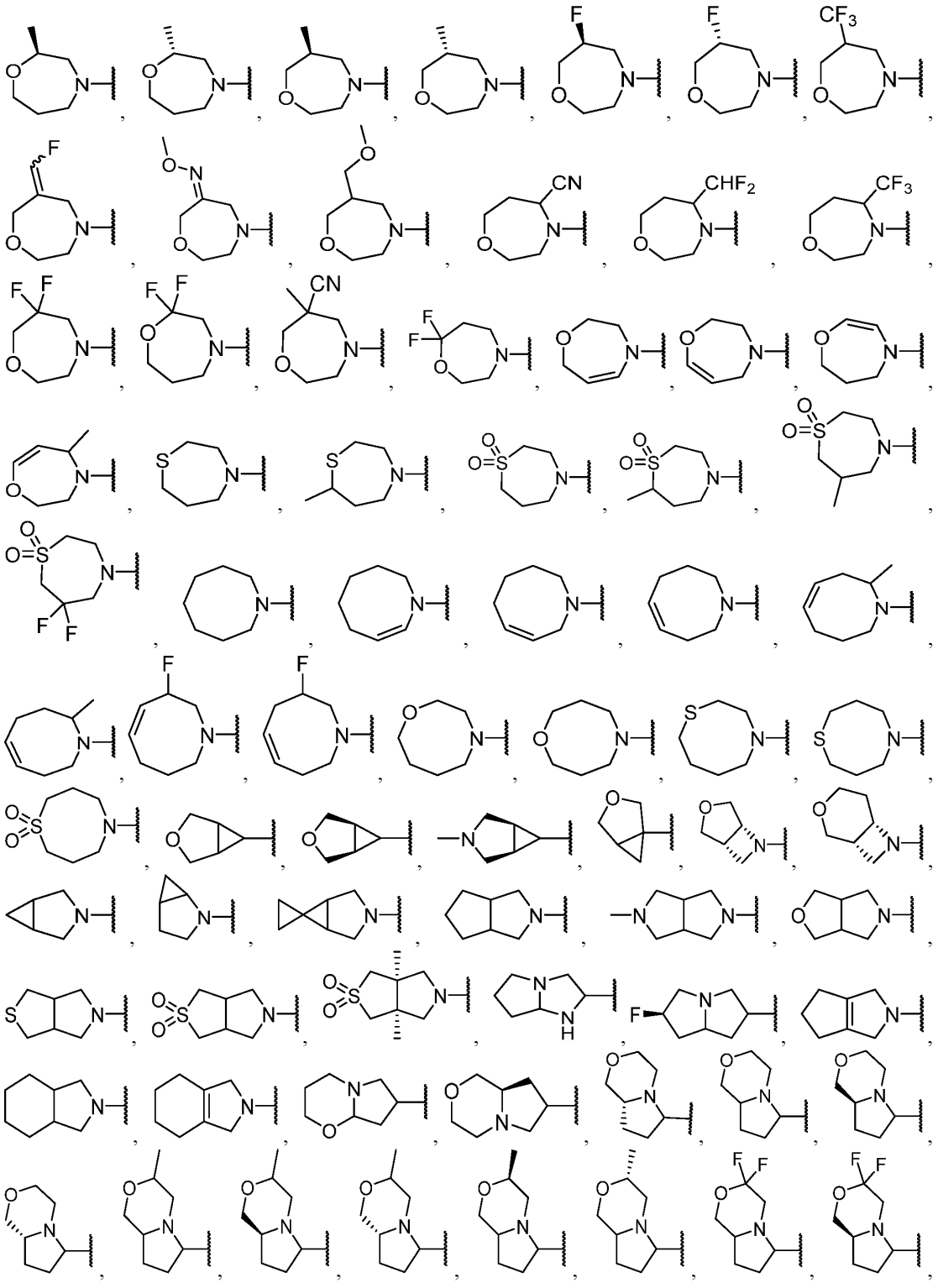
In some embodiments, $R^{1'}$ of formula (VI) is selected from:

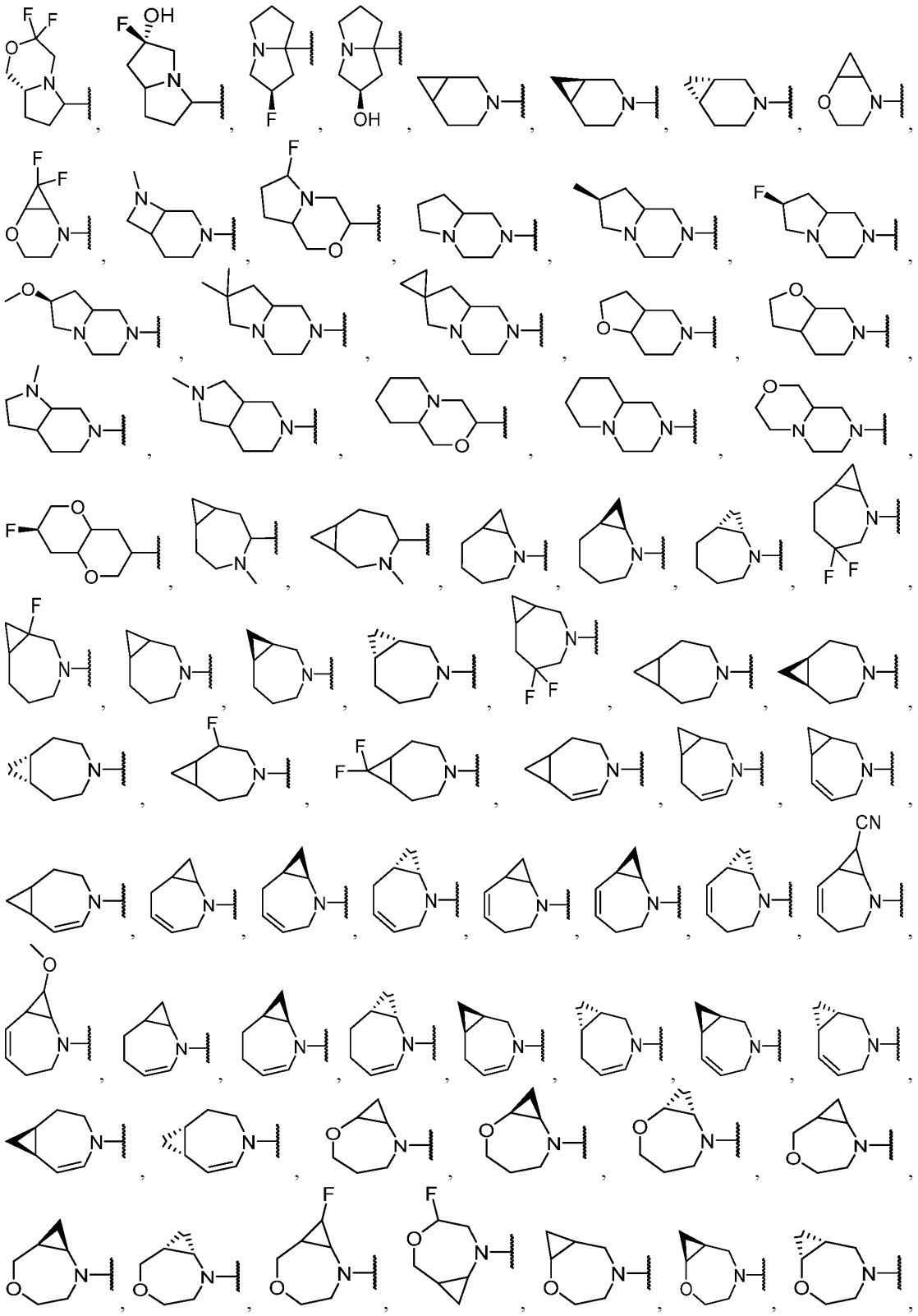


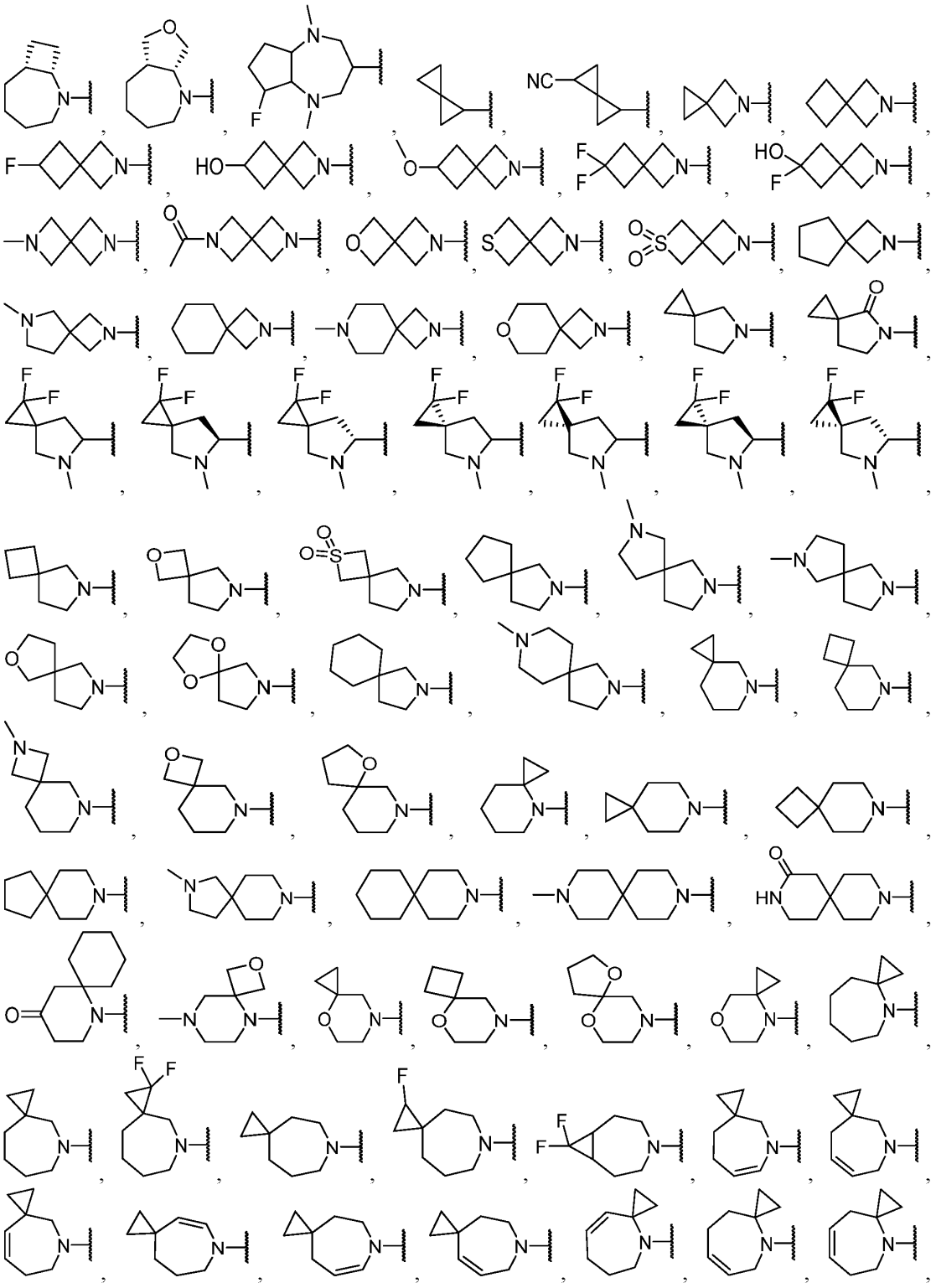


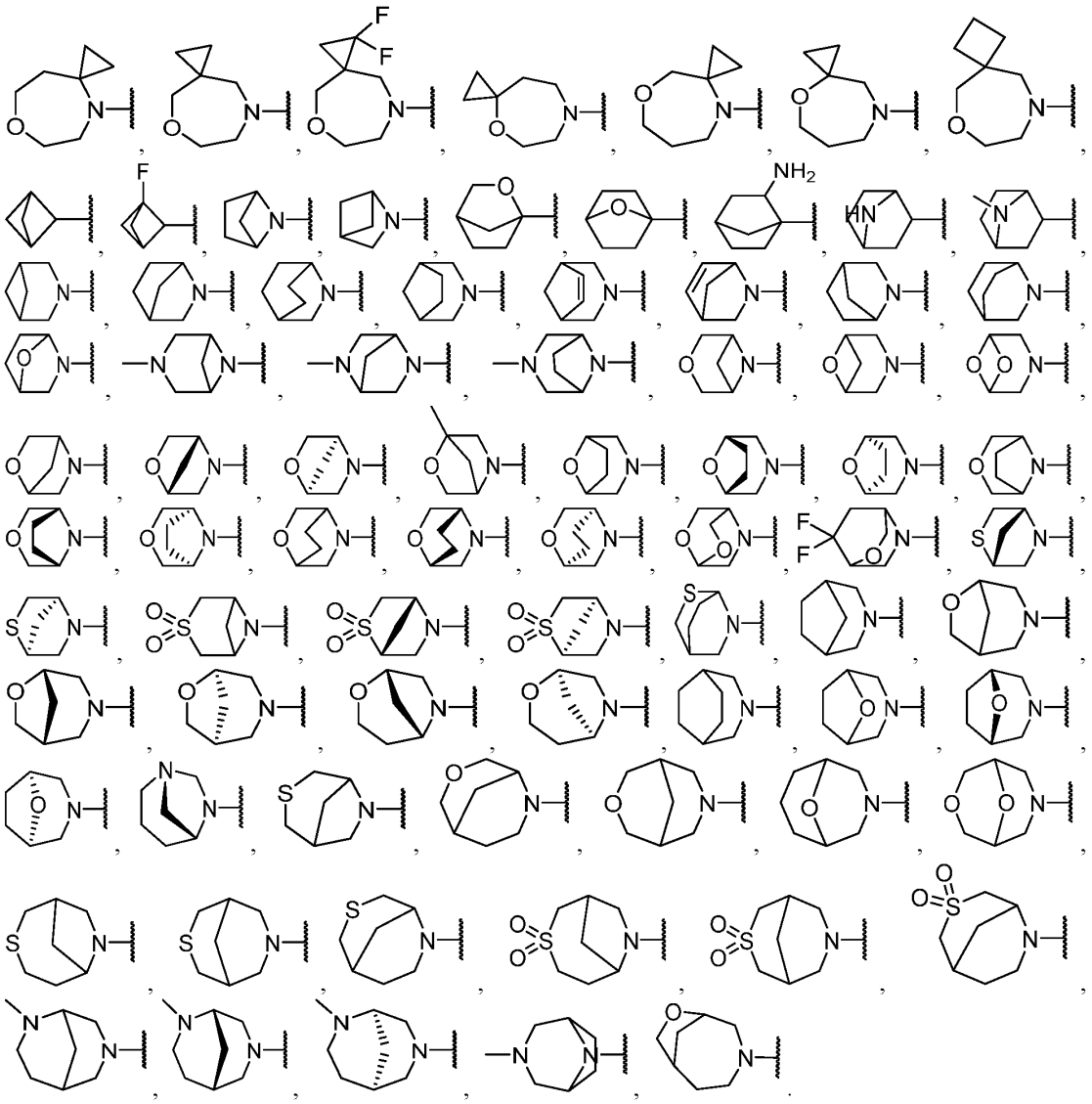




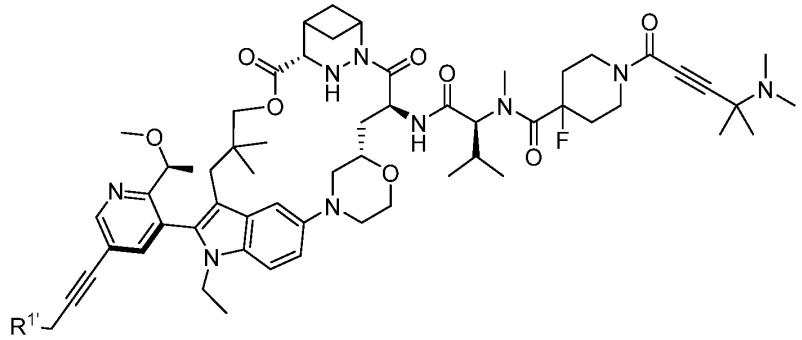




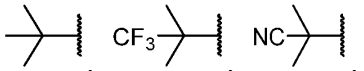


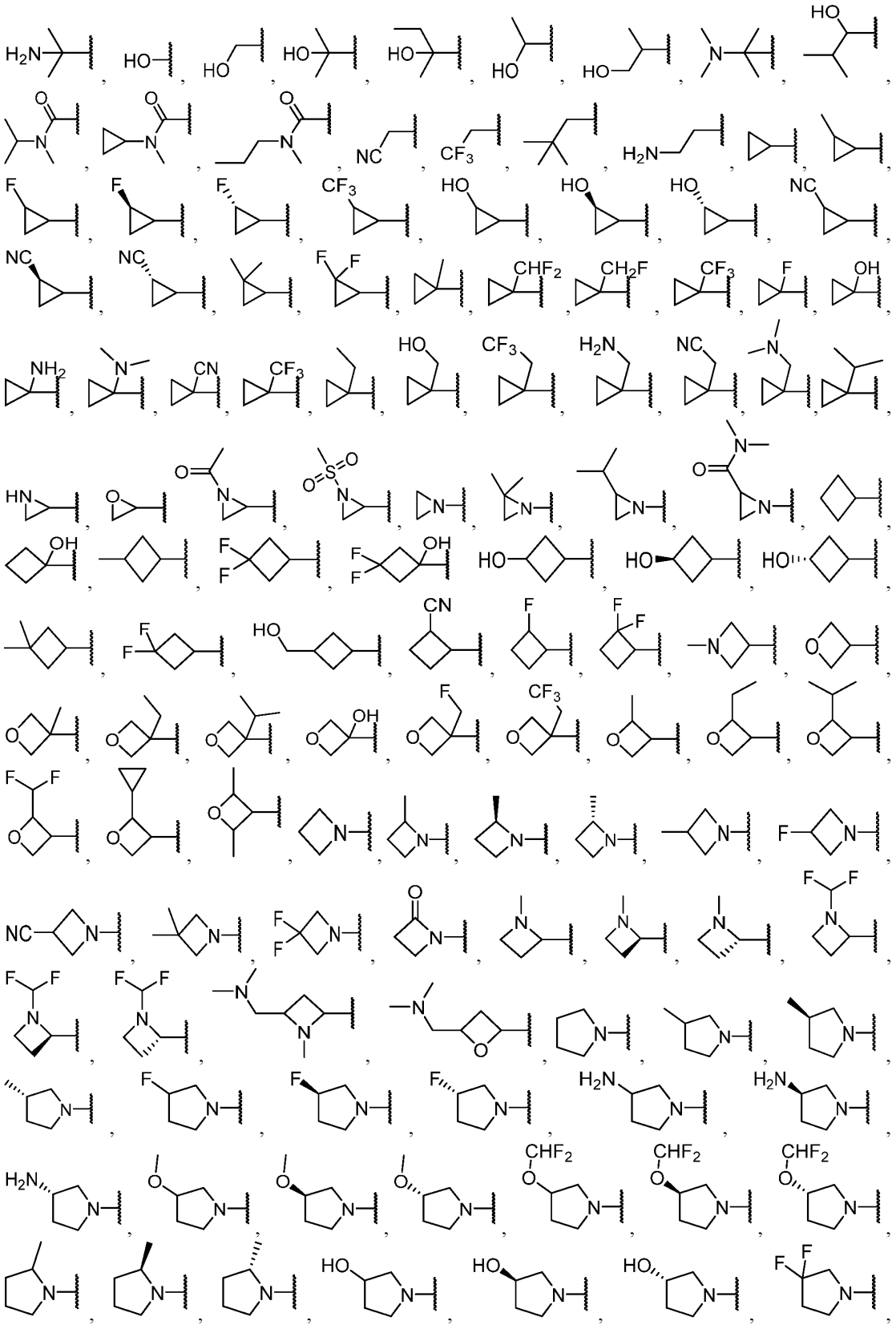


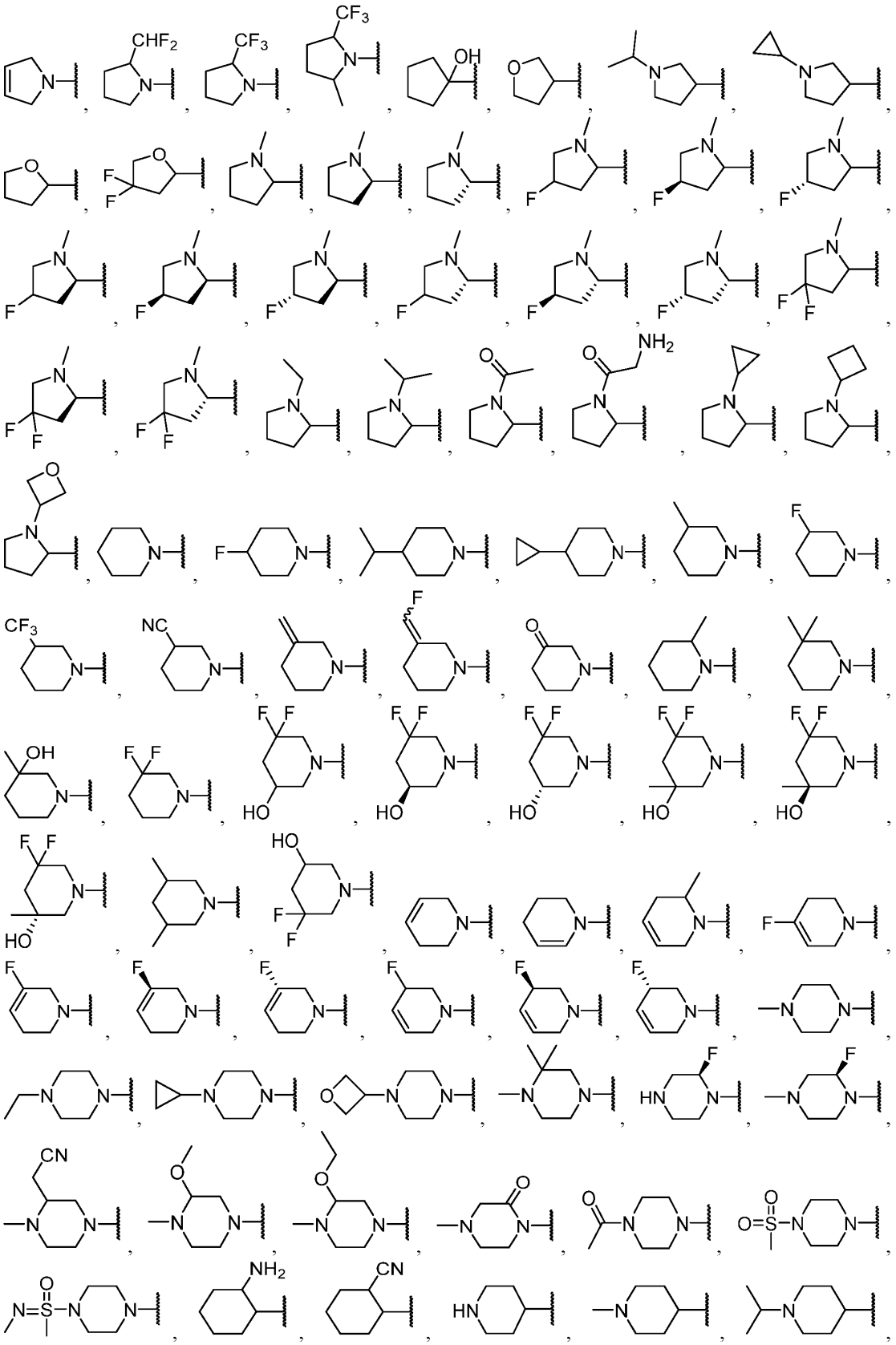
In some embodiments of the present disclosure, the compound of formula (IVa) is a compound of formula (VII):

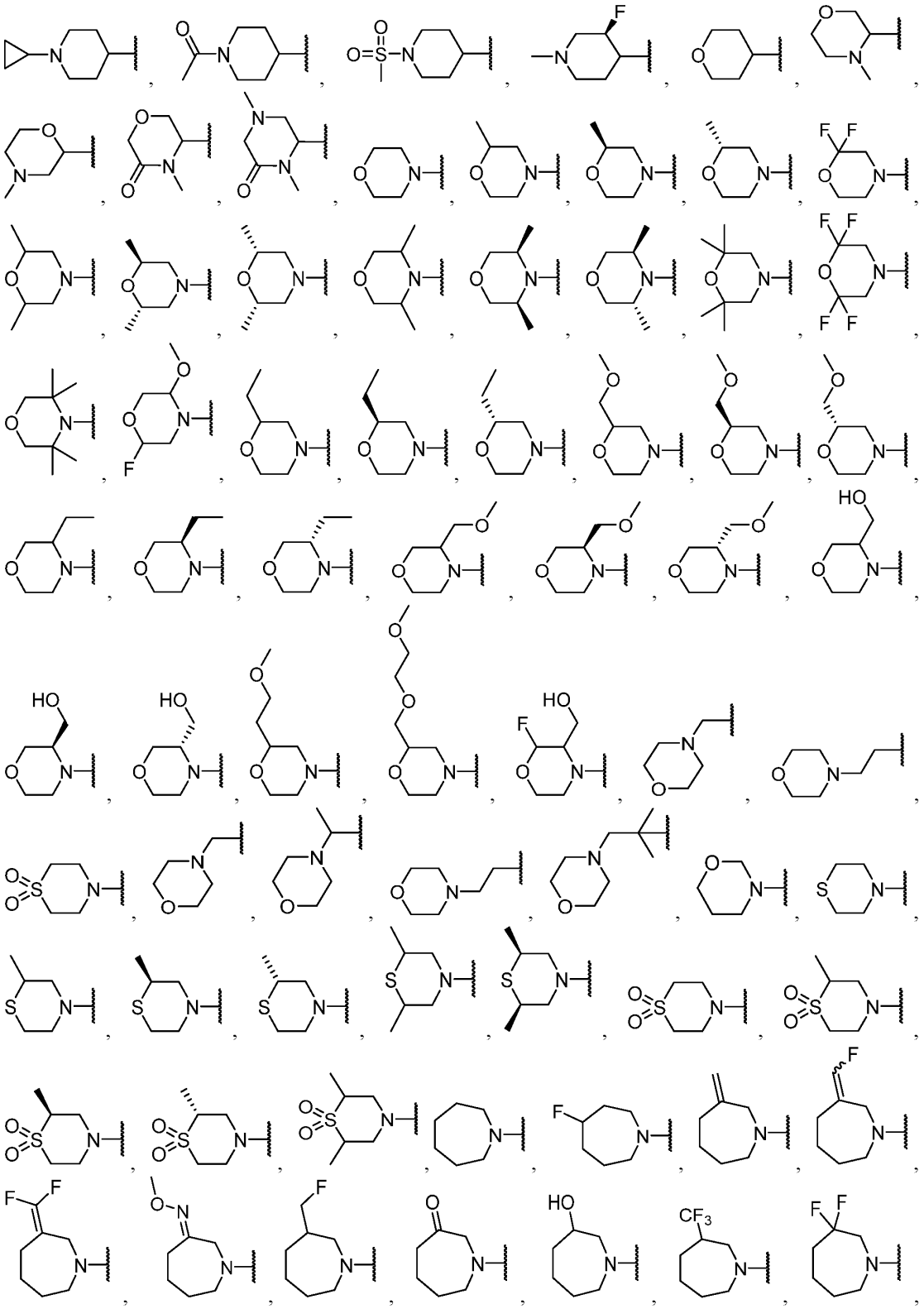


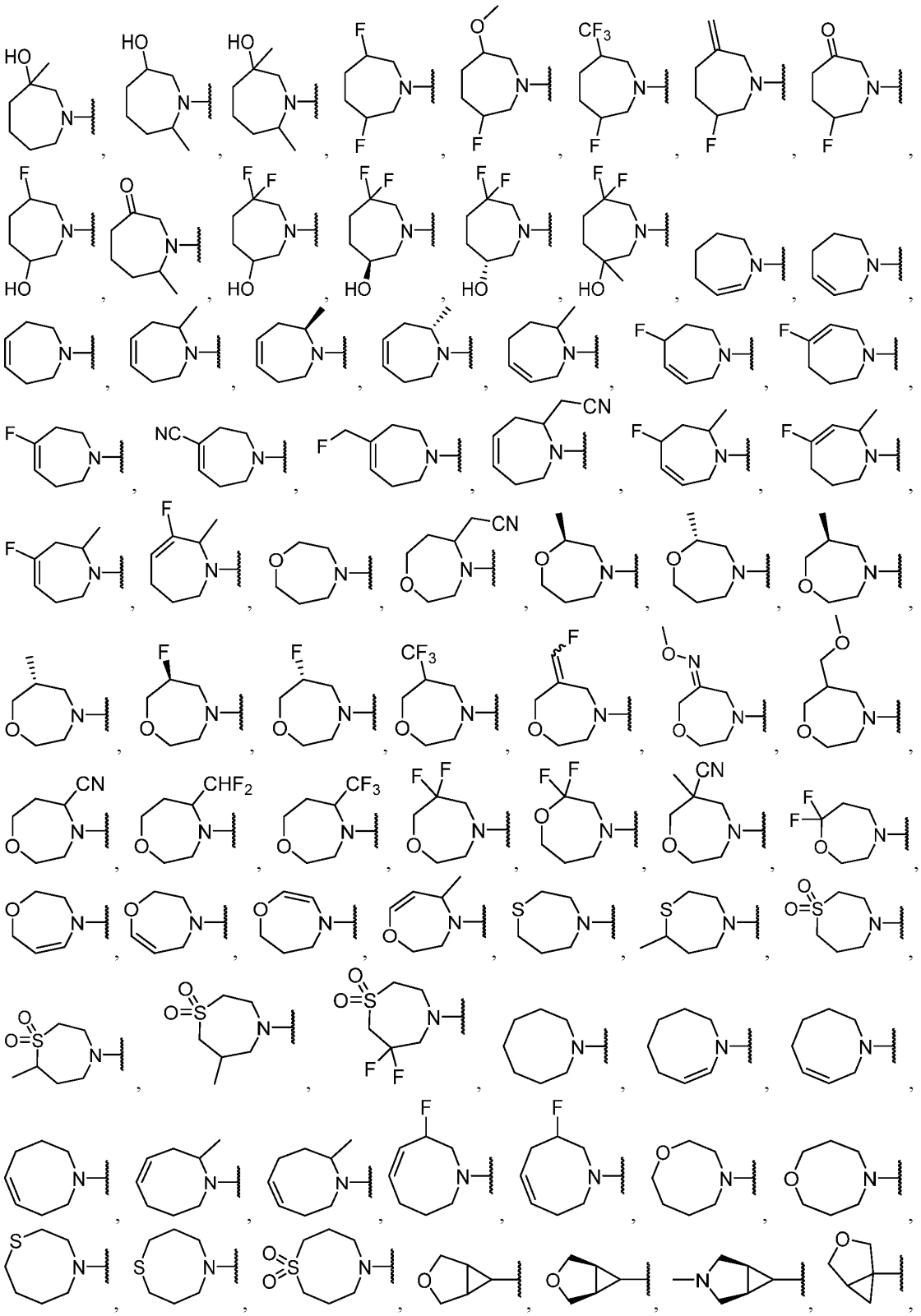
(VII)

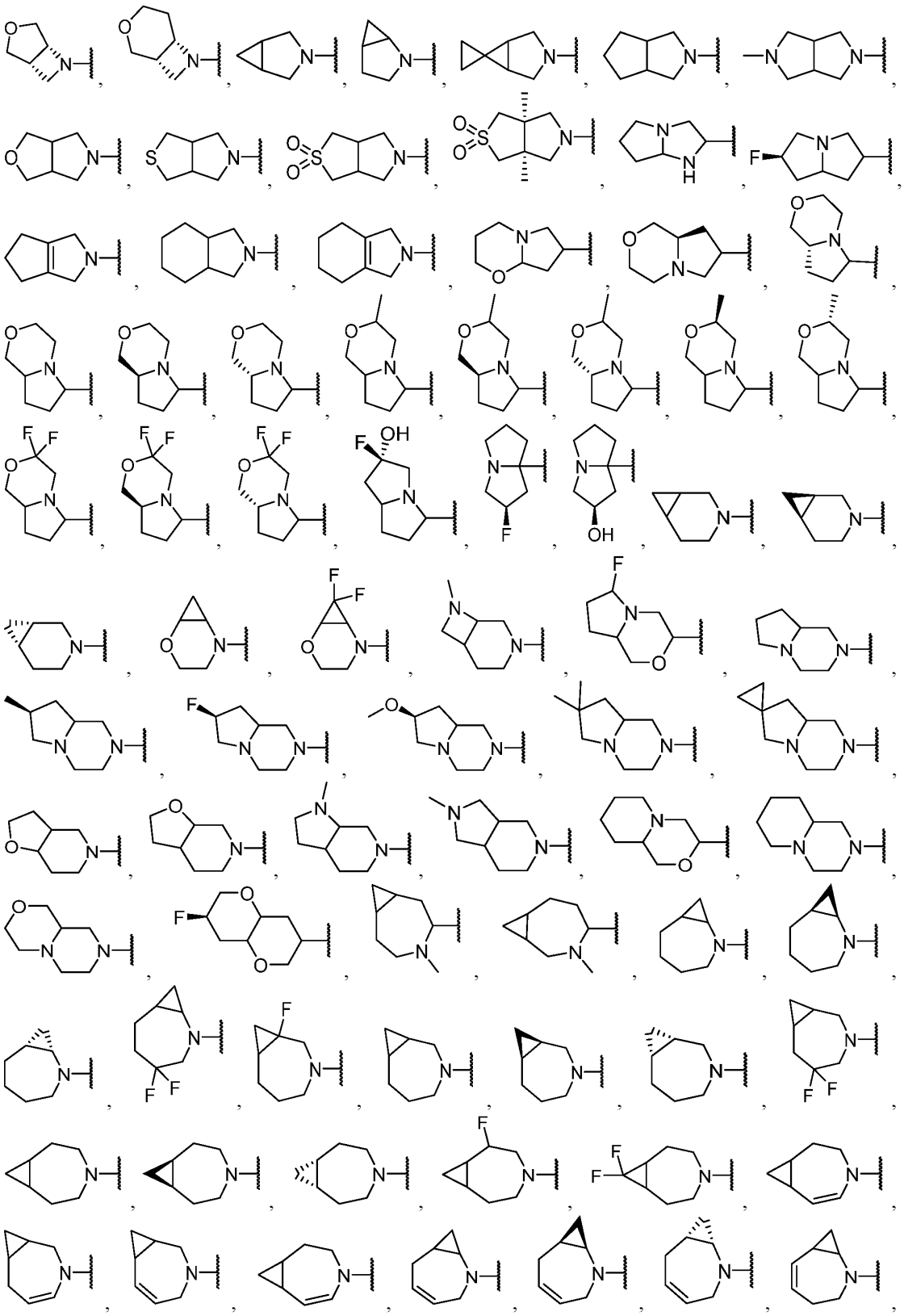
In some embodiments, $R^{1'}$ of formula (VII) is selected from: 

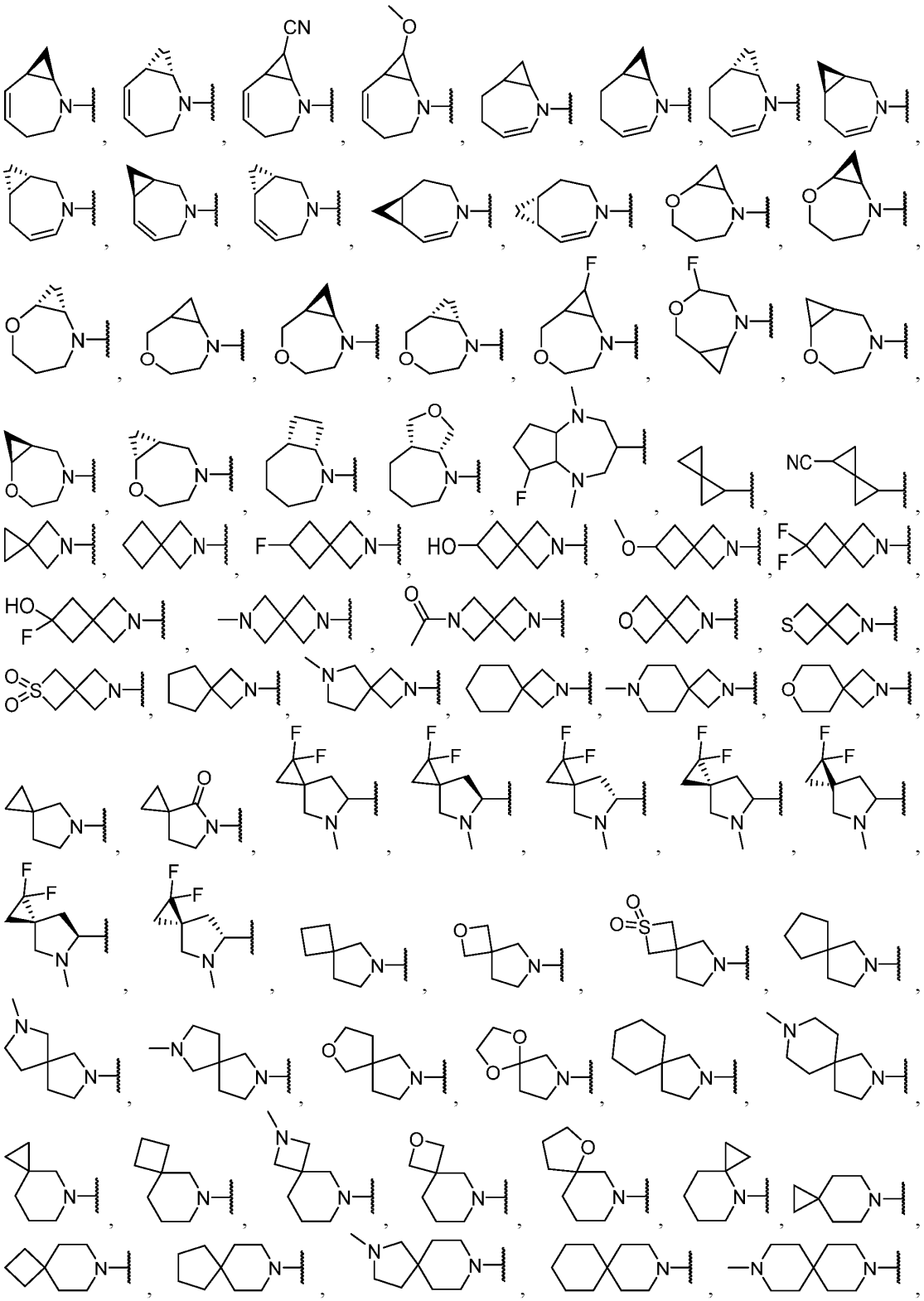


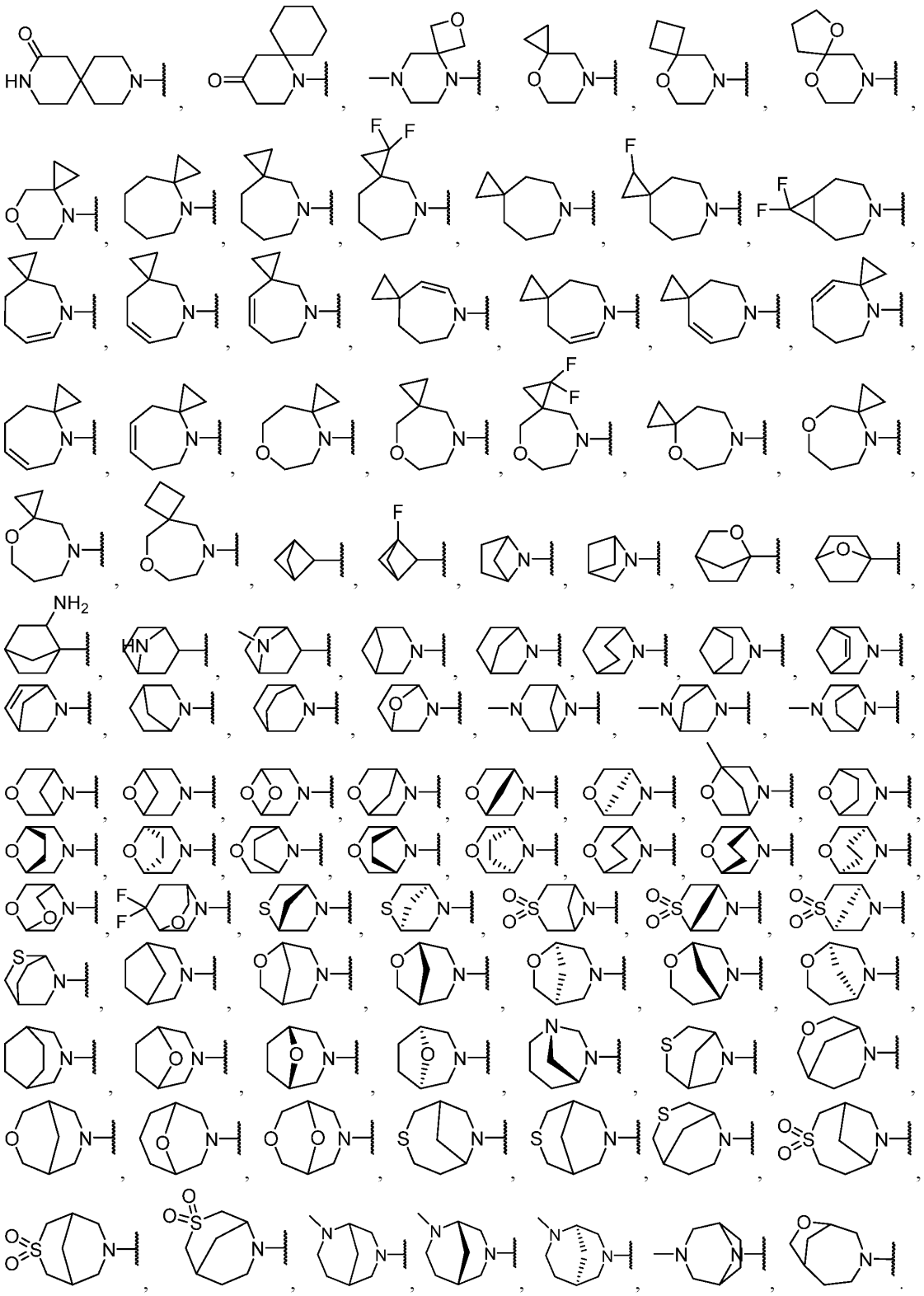




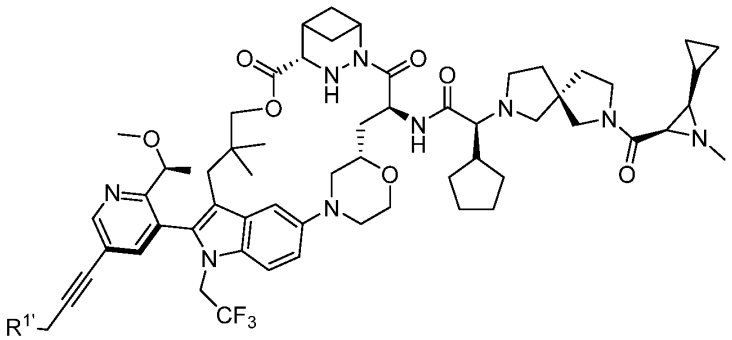






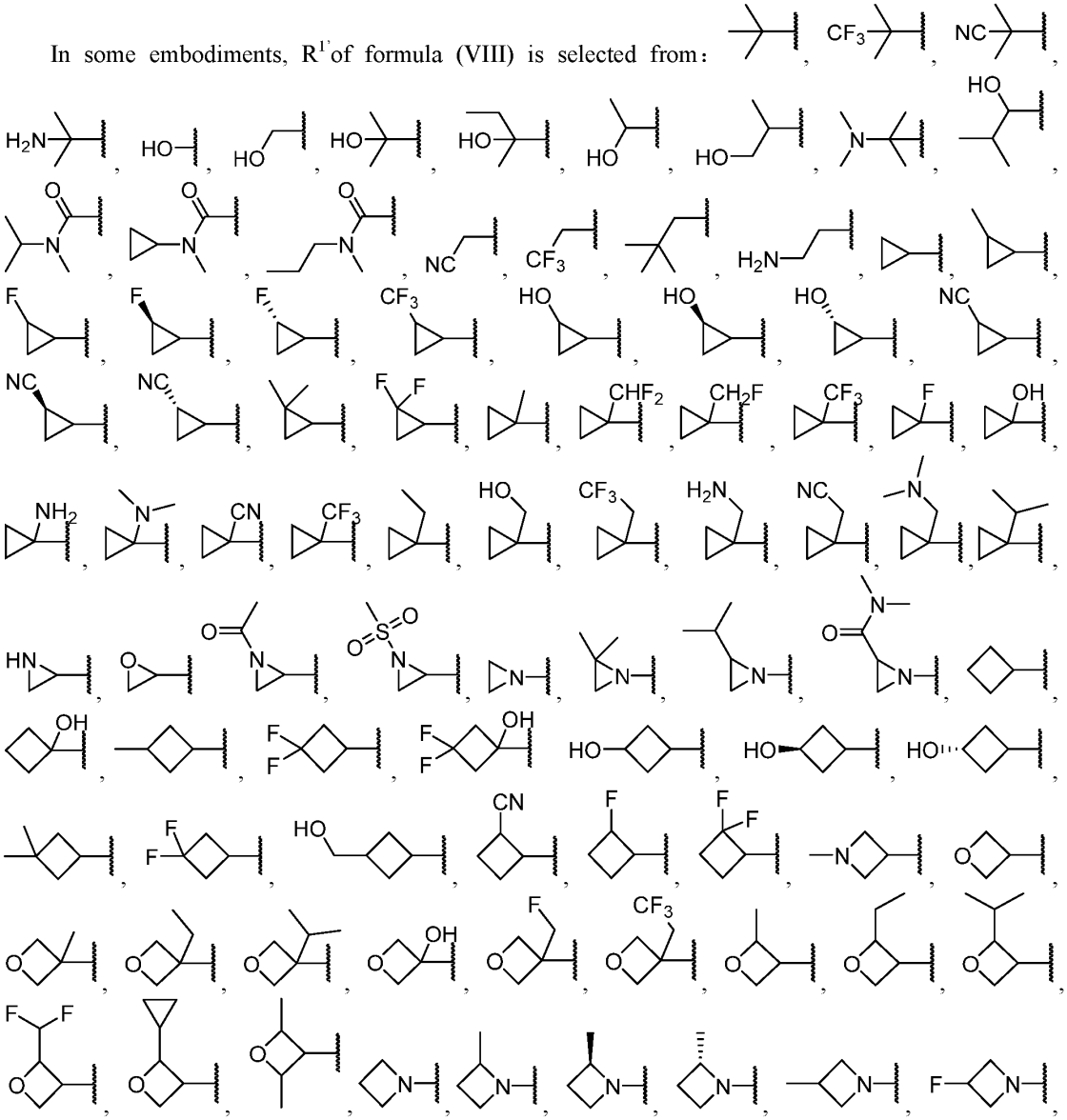


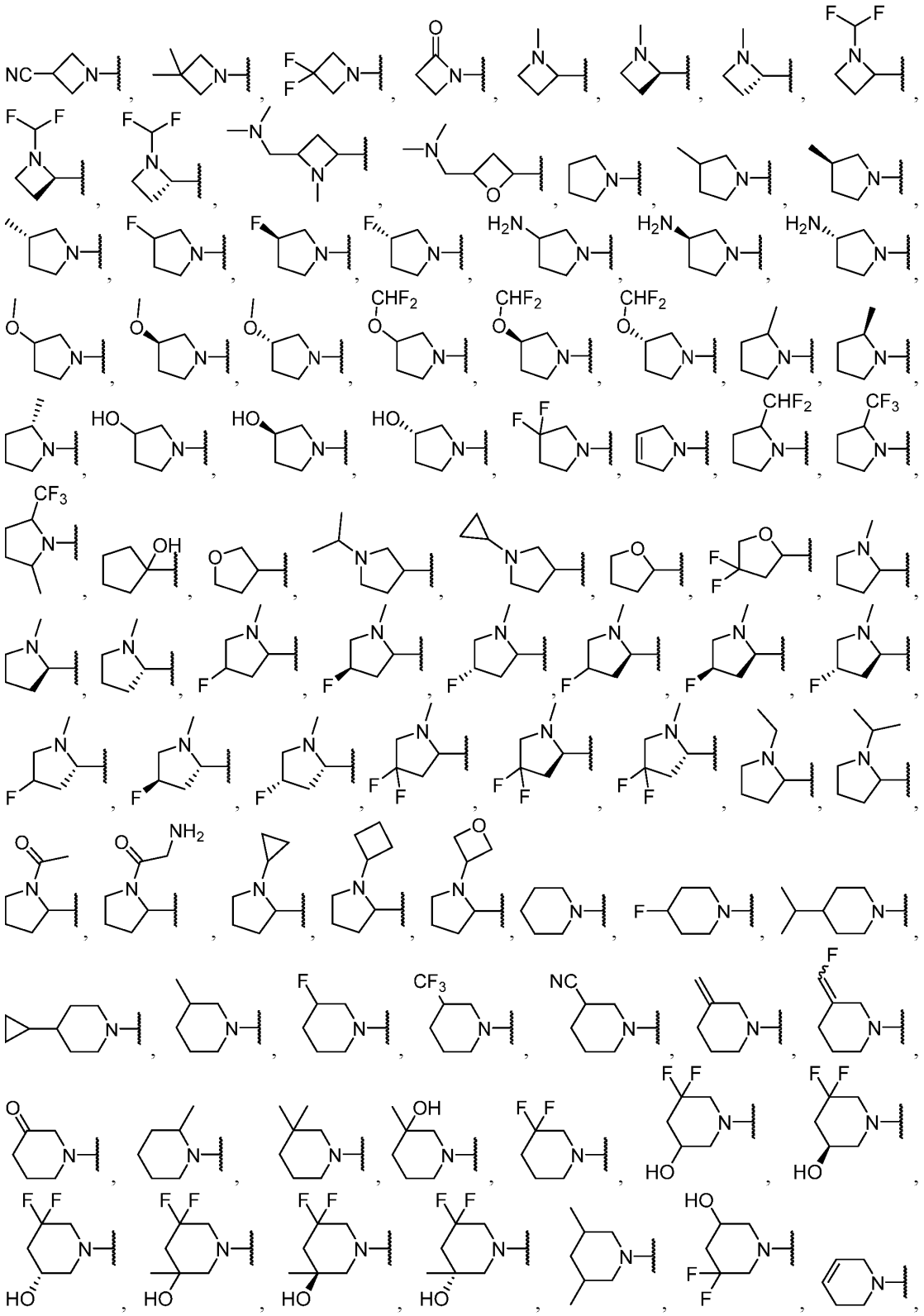
In some embodiments of the present disclosure, the compound of formula (IVa) is a compound of formula (VIII):

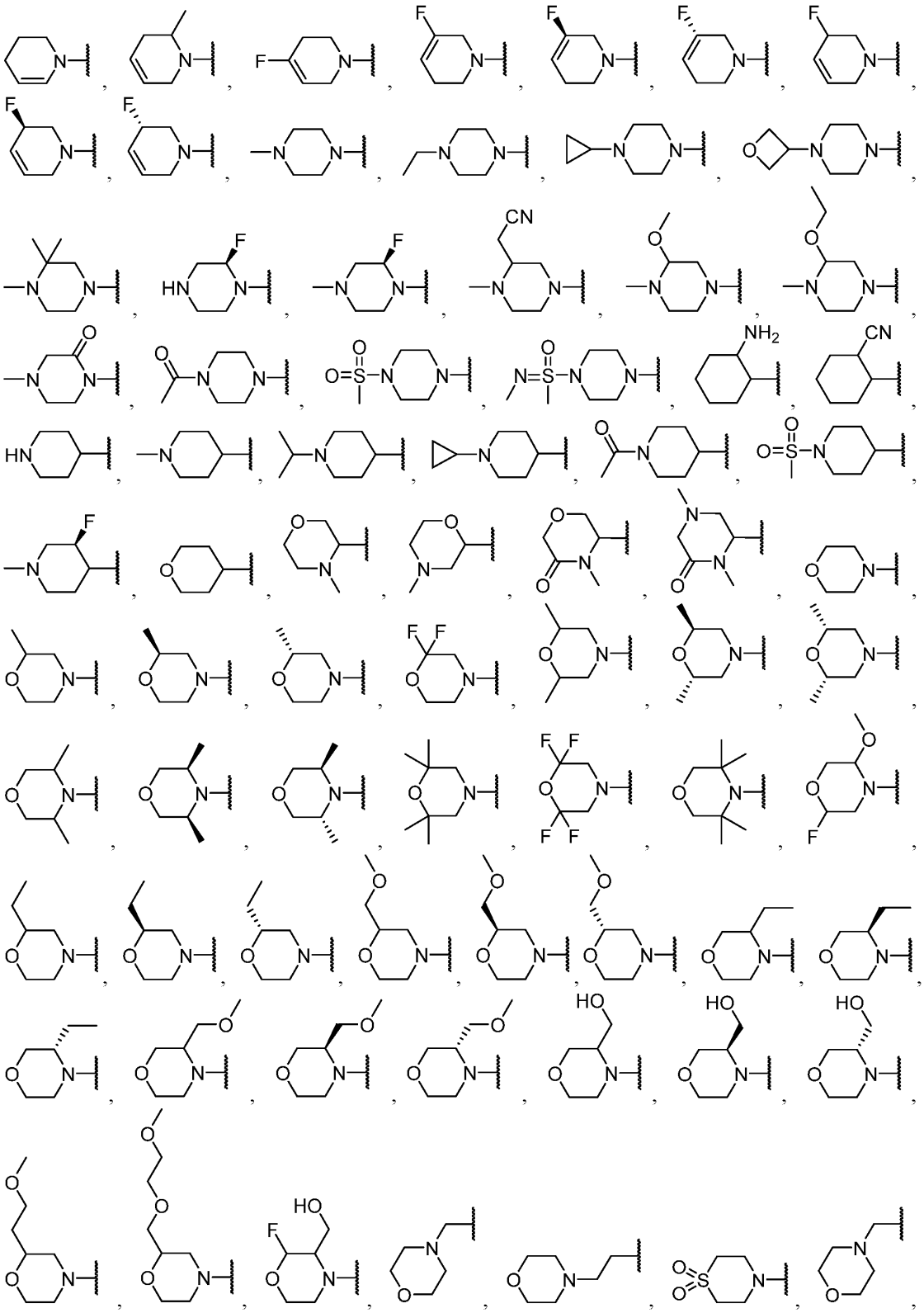


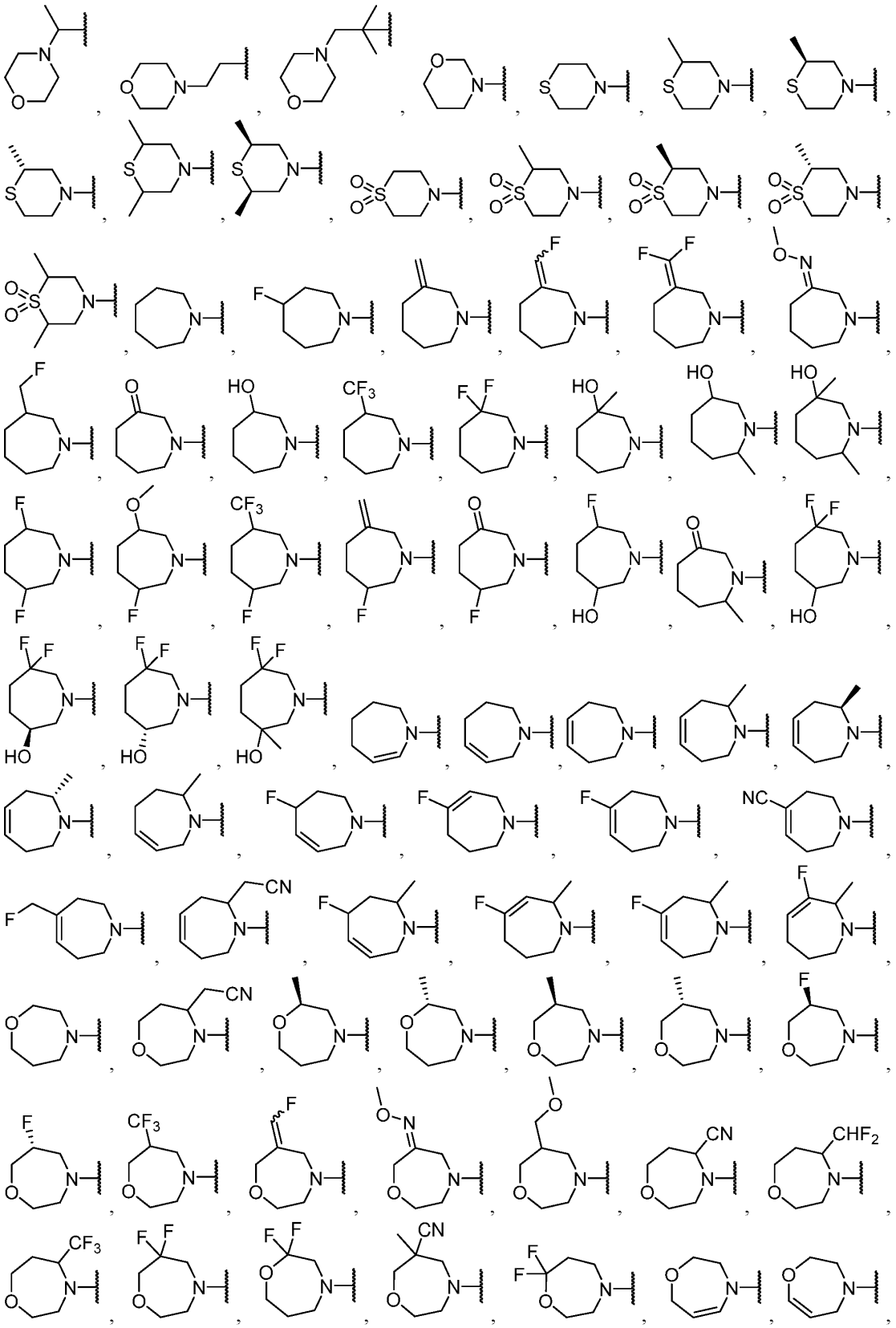
(VIII)

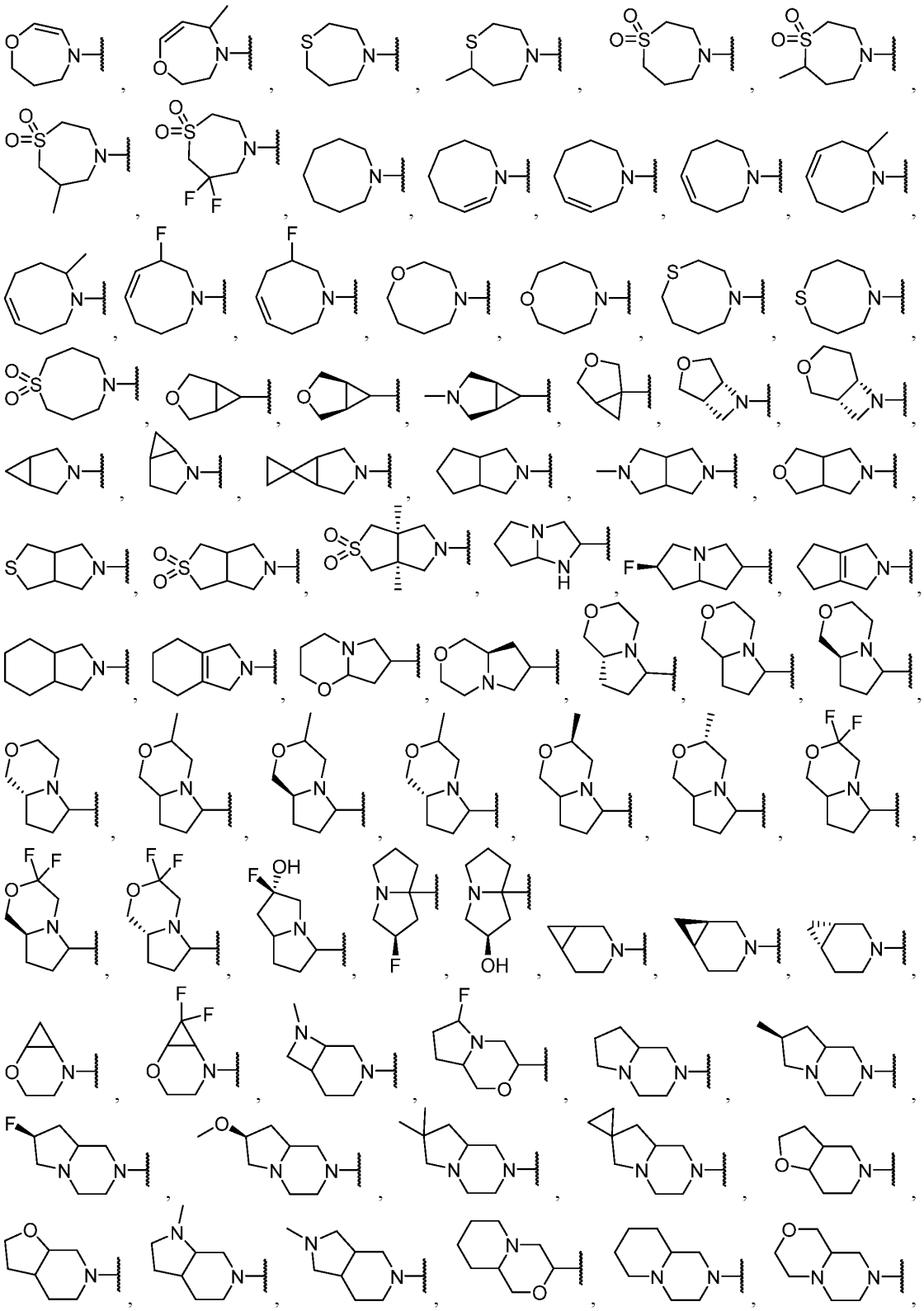
In some embodiments, $R^{1'}$ of formula (VIII) is selected from:

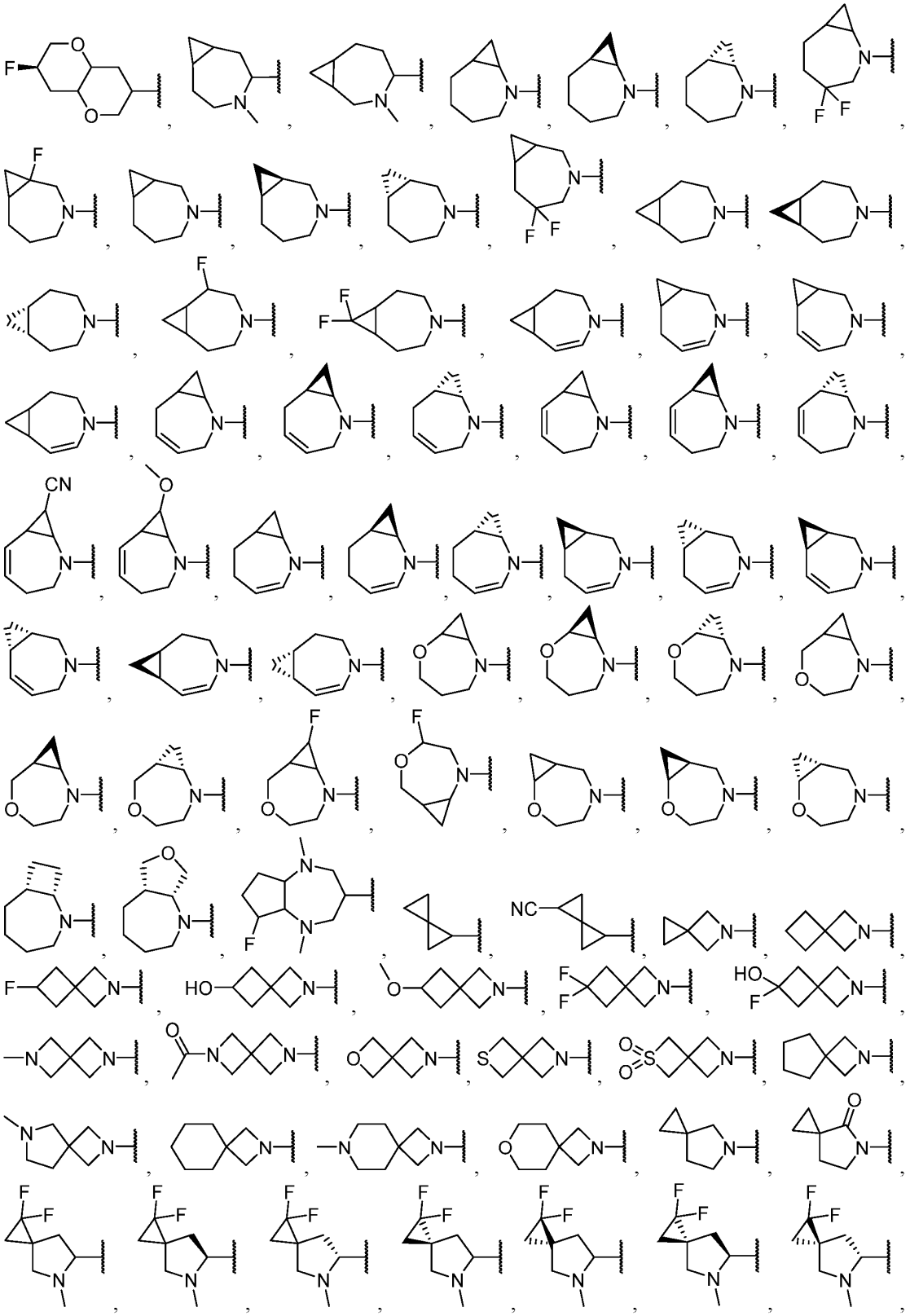


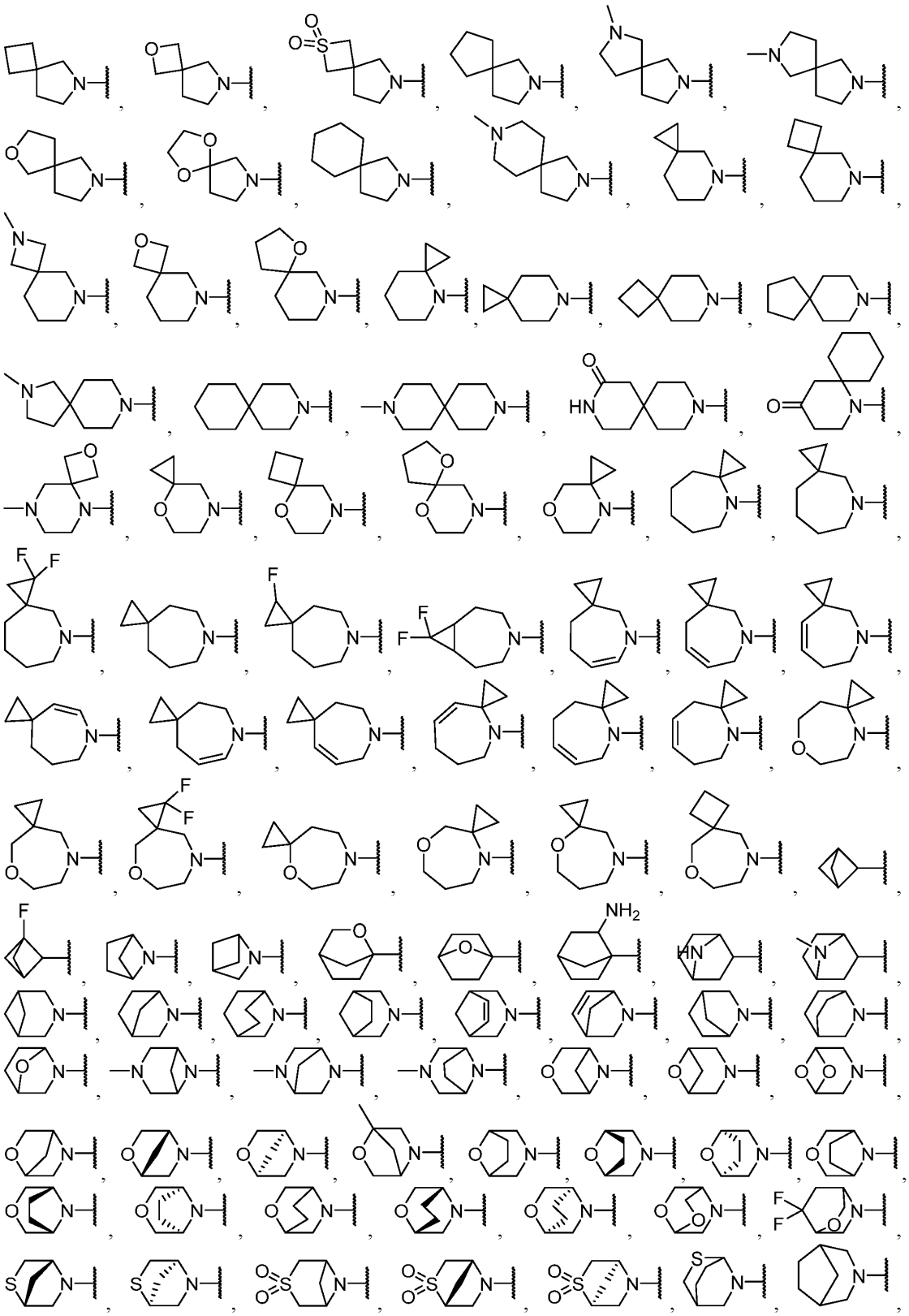


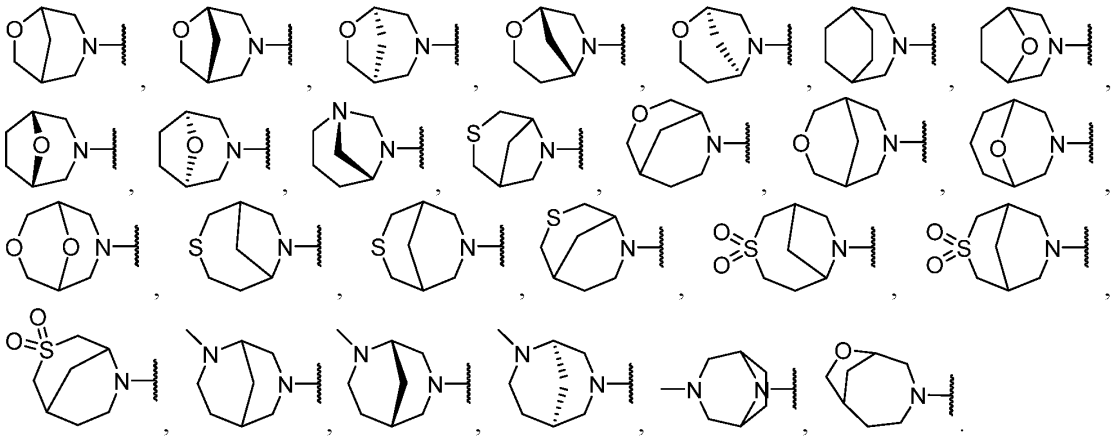










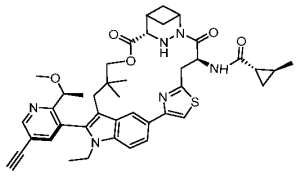
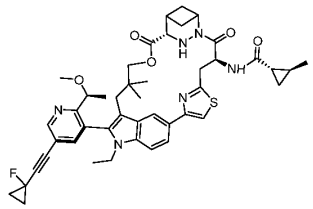
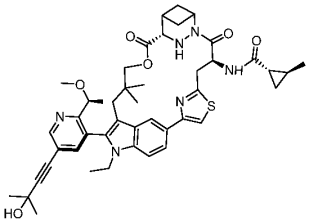
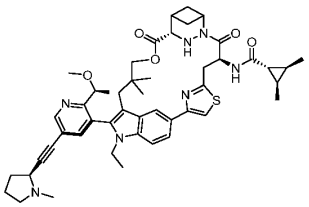
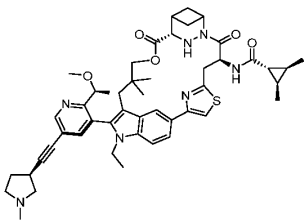
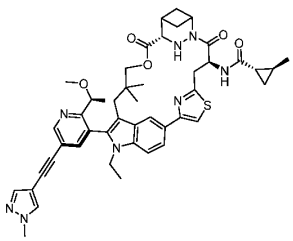


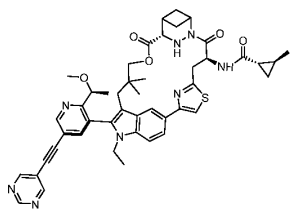
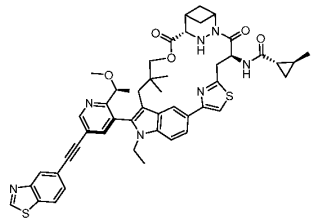
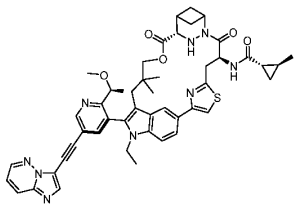
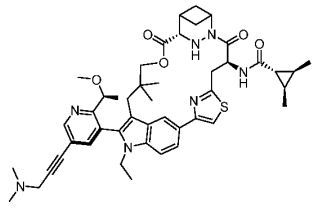
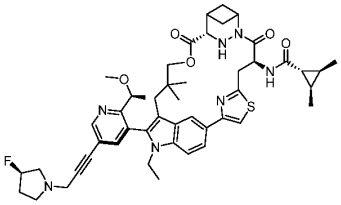
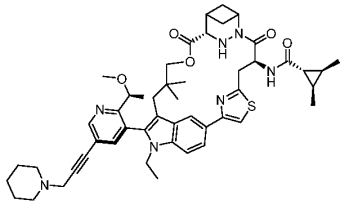
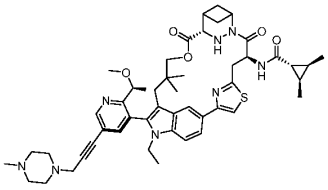
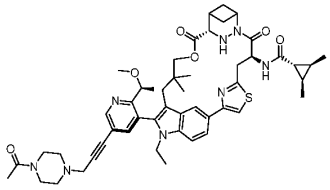
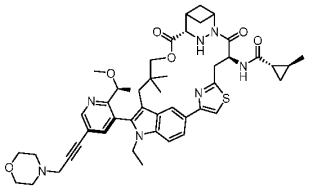
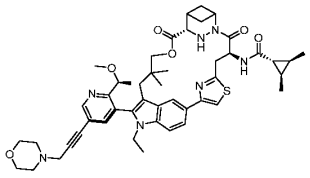
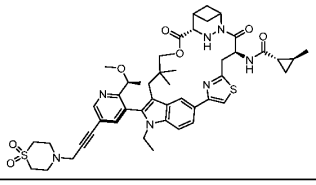
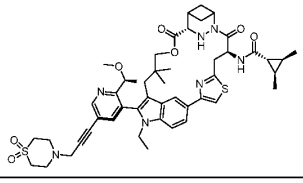
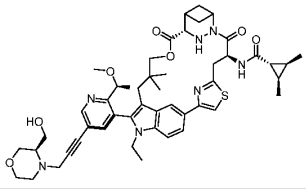
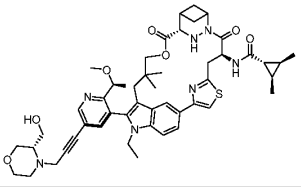
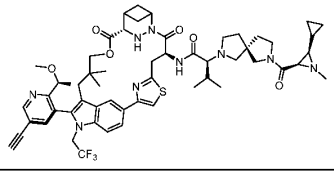
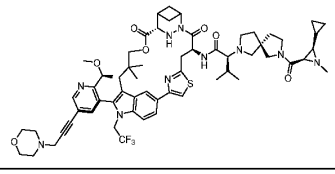
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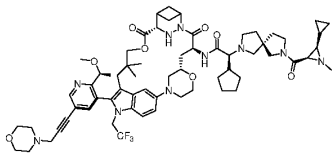
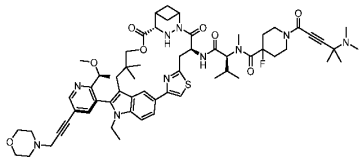
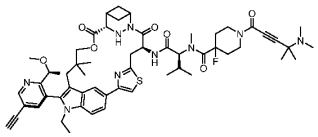
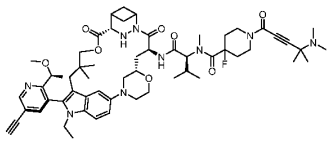
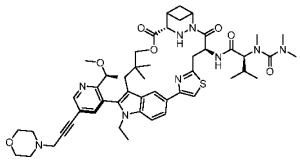
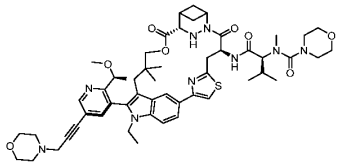
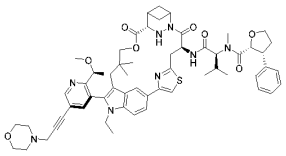
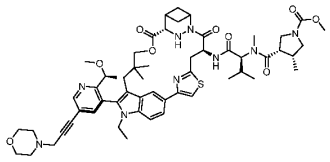
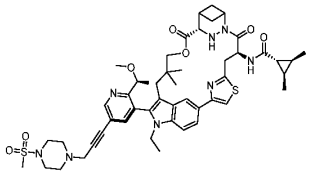
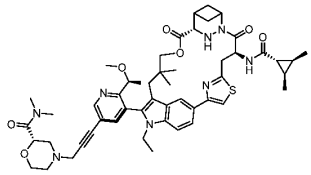
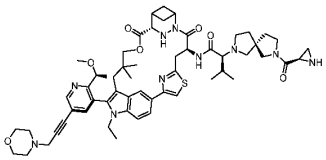
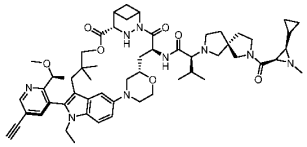
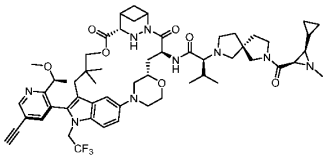
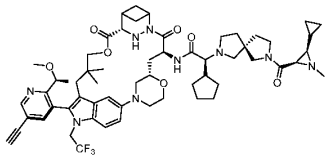
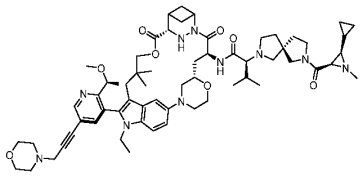
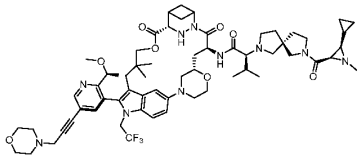
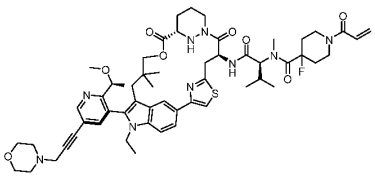
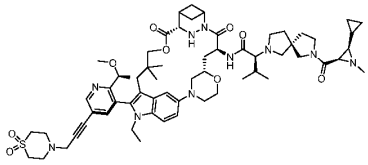
It is to be understood that the foregoing description of preferred embodiments is intended to be purely illustrative of the principles of the invention, rather than exhaustive thereof, and that changes and variations will be apparent to those skilled in the art, and that the present invention is not intended to be limited other than expressly set forth in the following claims.

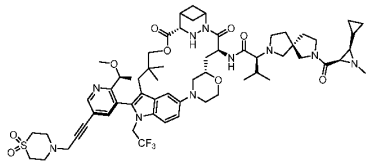
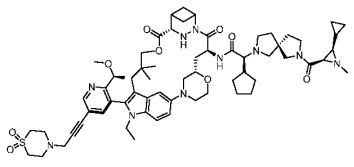
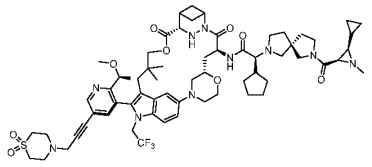
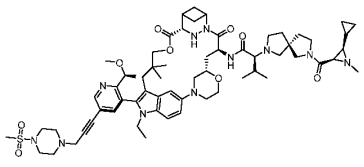
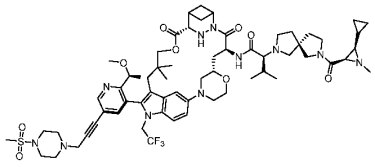
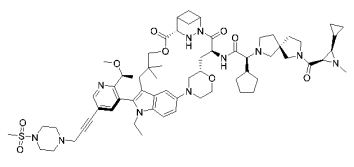
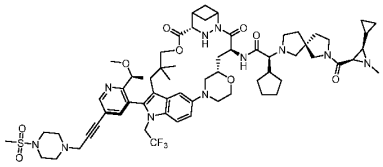
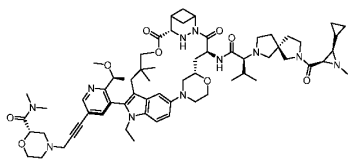
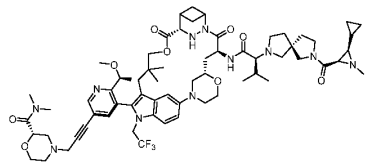
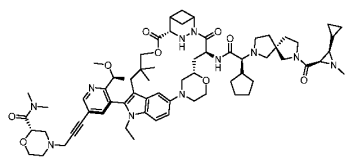
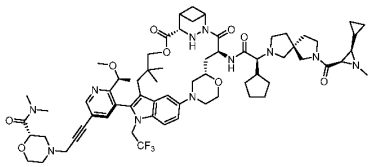
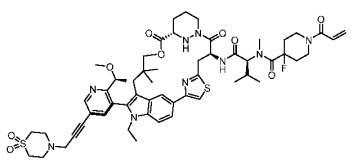
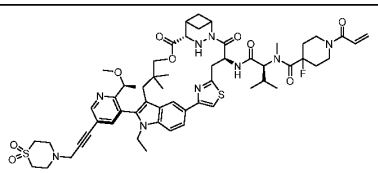
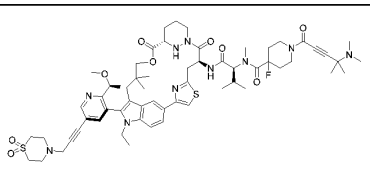
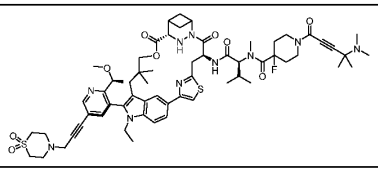
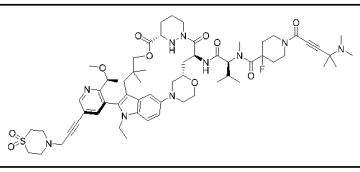
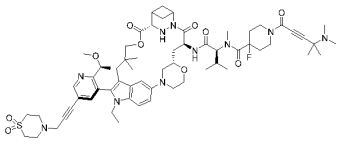
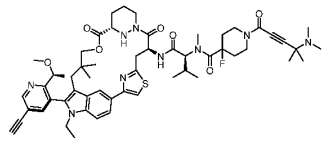
The present invention provides a Compound A, a pharmaceutically acceptable salt thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt, wherein, the Compound A is selected from any one of the following compounds in **Table 1**:

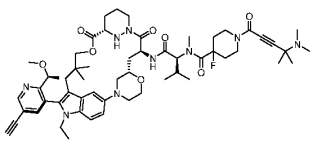
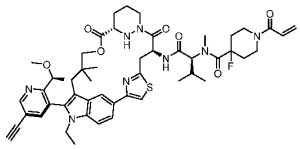
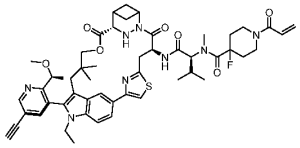
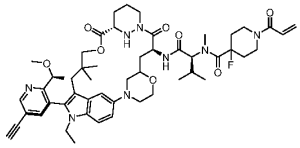
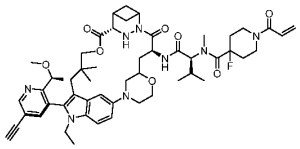
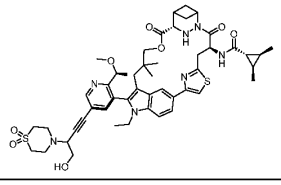
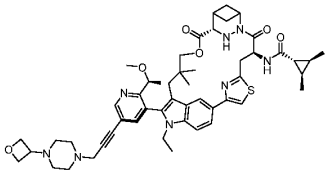
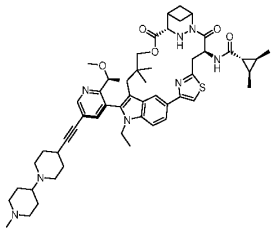
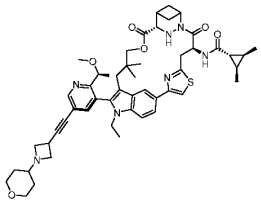
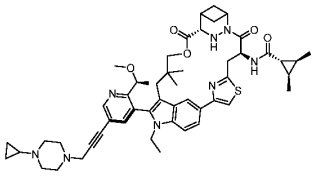
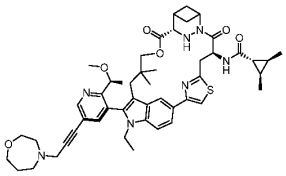
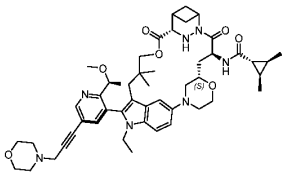
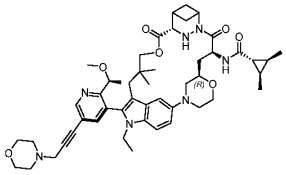
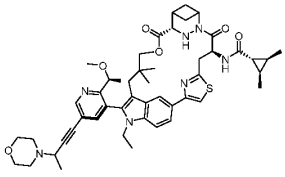
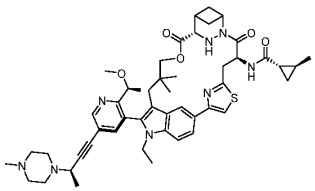
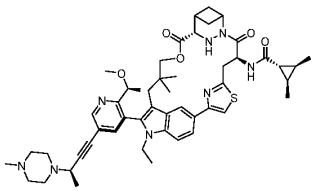
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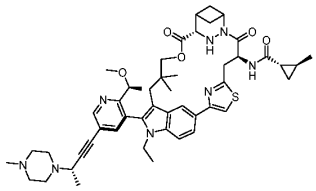
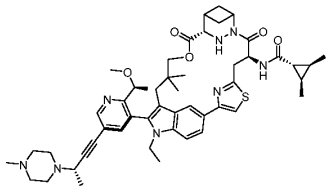
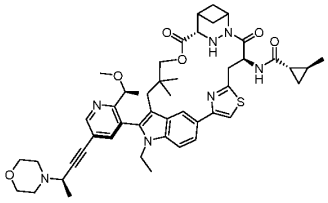
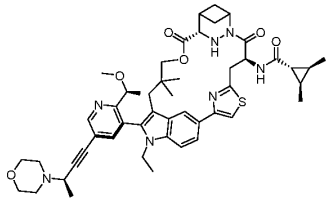
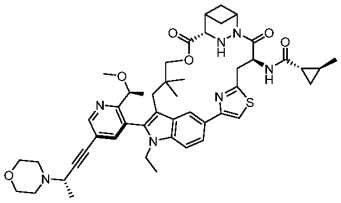
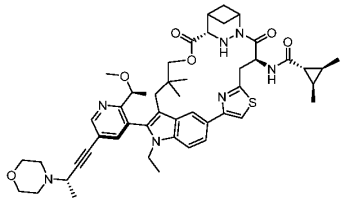
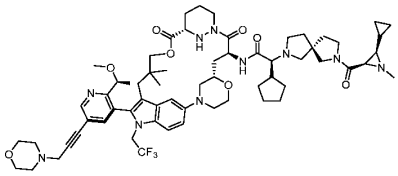
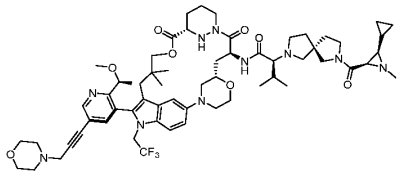
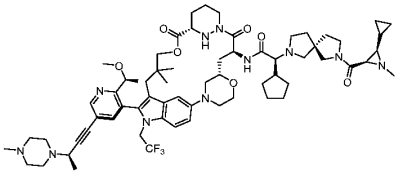
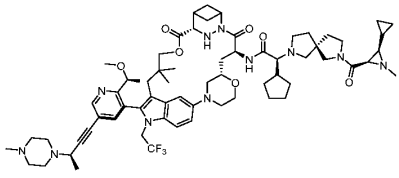
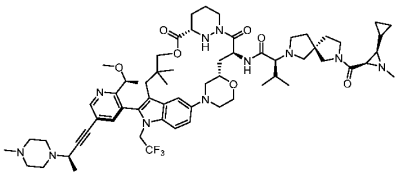
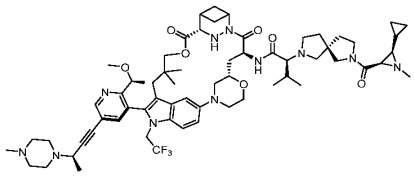
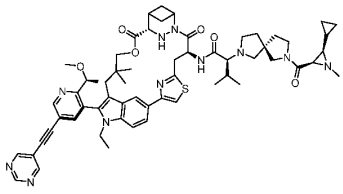
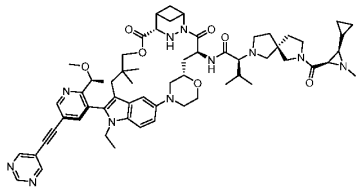
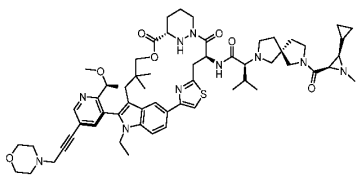
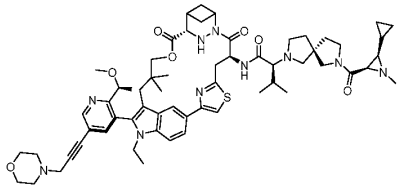
Code	Structure	Code	Structure
Example 1		Example 2	
Example 3		Example 4	
Example 5		Example 6	

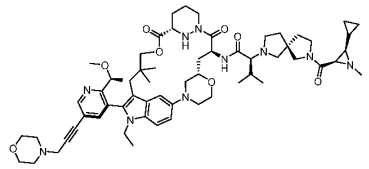
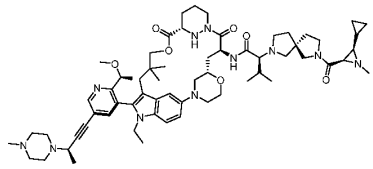
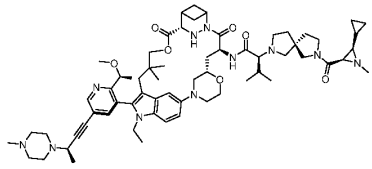
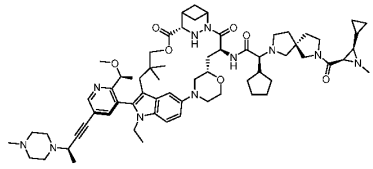
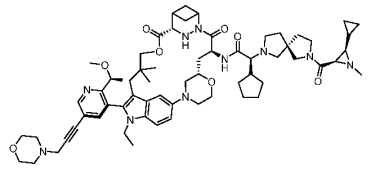
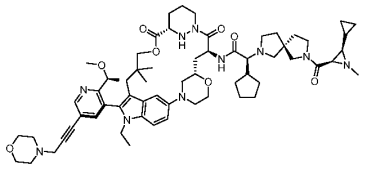
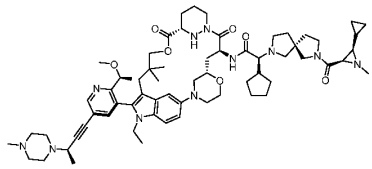
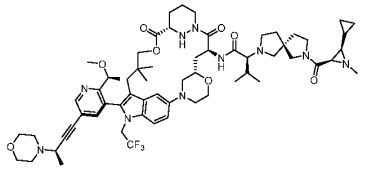
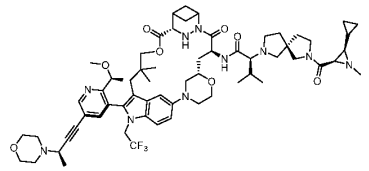
Example 7		Example 8	
Example 9		Example 10	
Example 11		Example 12	
Example 13		Example 14	
Example 15		Example 16	
Example 17		Example 18	
Example 19		Example 20	
Example 21		Example 22	

Example 23		Example 24	
Example 25		Example 26	
Example 27		Example 28	
Example 29		Example 30	
Example 31		Example 32	
Example 33		Example 34	
Example 35		Example 36	
Example 37		Example 38	
Example 39		Example 40	

Example 41		Example 42	
Example 43		Example 44	
Example 45		Example 46	
Example 47		Example 48	
Example 49		Example 50	
Example 51		Example 52	
Example 53		Example 54	
Example 55		Example 56	
Example 57		Example 58	

Example 59		Example 60	
Example 61		Example 62	
Example 63		Example 64	
Example 65		Example 66	
Example 67		Example 68	
Example 69		Example 70	
Example 71		Example 72	
Example 73		Example 74	

Example 75		Example 76	
Example 77		Example 78	
Example 79		Example 80	
Example 81		Example 82	
Example 83		Example 84	
Example 85		Example 86	
Example 87		Example 88	
Example 89		Example 90	

Example 91		Example 92	
Example 93		Example 94	
Example 95		Example 96	
Example 97		Example 98	
Example 99			

In another aspect, the present invention also provides a pharmaceutical composition comprising a compound, wherein a pharmaceutically acceptable salt thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt as defined above, and a pharmaceutically acceptable carrier, preferably, the compound is the Compound A as defined above.

In another aspect, the present invention also provides a use of a compound, wherein a pharmaceutically acceptable salt thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt, or the pharmaceutical composition as defined above in the preparation of a medicament used for the treatment of cancer, preferably, the compound is the Compound A as defined above.

In some embodiments of the present disclosure, wherein the cancer is a Ras-driven cancer.

In some embodiments of the present disclosure, wherein the cancer comprises a Ras mutation.

In some embodiments of the present disclosure, wherein the Ras mutation is a position 12, 13 or 61.

In some embodiments of the present disclosure, wherein the Ras mutation is at position 12.

In some embodiments of the present disclosure, wherein the Ras mutation is selected from the group consisting of G12C, G12D, G12V, G12A, G12R, G12S, G13C, G13D, Q61H, Q61R and Q61L, or a combination thereof.

In some embodiments of the present disclosure, wherein the Ras mutation is a position selected from the group consisting of G12D, G12V, and G12R, or a combination thereof.

In some embodiments of the present disclosure, wherein the cancer is pancreatic cancer, appendiceal cancer, small bowel cancer, colorectal cancer, ampullary cancer, non-small cell lung cancer, cervical cancer, lung cancer, endometrial cancer, acute myeloid leukemia, gastrointestinal neuroendocrine tumor, uterine endometrioid carcinoma, oesophagogastric cancer, bladder cancer, ovarian cancer, melanoma, multiple myeloma, thyroid gland adenocarcinoma, a myelodysplastic syndrome, or squamous cell lung carcinoma.

In some embodiments of the present disclosure, wherein the cancer is pancreatic cancer, lung cancer, or colorectal cancer.

In some embodiments of the present disclosure, wherein the Ras protein is KRAS.

In some embodiments, the compound can be used in combination with an additional anti-cancer therapy.

In some embodiments, the additional anti-cancer therapy is an EGFR inhibitor, a second Ras inhibitor, a SHP2 inhibitor, a SOS1 inhibitor, a Raf inhibitor, a MEK inhibitor, an ERK inhibitor, a Pl3K inhibitor, a PTEN inhibitor, an AKT inhibitor, an mTORC1 inhibitor, a BRAF inhibitor, a PD-L1 inhibitor, a PD-1 inhibitor, a CDK4/6 inhibitor, a HER2 inhibitor, or a combination thereof.

In another aspect, the present invention also provides a method for treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt as defined above, or the pharmaceutical composition as defined above, preferably the compound is the Compound A as defined above.

In some embodiments of the present disclosure, wherein the cancer is a Ras-driven cancer.

In some embodiments of the present disclosure, wherein the cancer comprises a Ras mutation.

In some embodiments of the present disclosure, wherein the Ras mutation is a position 12, 13 or 61.

In some embodiments of the present disclosure, wherein the Ras mutation is at position 12.

In some embodiments of the present disclosure, wherein the Ras mutation is at a position selected from the group consisting of G12C, G12D, G12V, G12A, G12R, G12S, G13C, G13D, Q61H, Q61R and Q61L, or a combination thereof.

In some embodiments of the present disclosure, wherein the Ras mutation is a position selected from the group consisting of G12D, G12V, and G12R, or a combination thereof.

In some embodiments of the present disclosure, wherein the cancer is pancreatic cancer, appendiceal cancer, small bowel cancer, colorectal cancer, ampullary cancer, non-small cell lung cancer, cervical cancer, lung cancer, endometrial cancer, acute myeloid leukemia, gastrointestinal neuroendocrine tumour, uterine endometrioid carcinoma, oesophagogastric cancer, bladder cancer, ovarian cancer, melanoma, multiple myeloma, thyroid gland adenocarcinoma, a myelodysplastic syndrome, or squamous cell lung carcinoma.

In some embodiments of the present disclosure, wherein the cancer is pancreatic cancer, lung cancer, or colorectal cancer.

In some embodiments of the present disclosure, wherein the Ras protein is KRAS.

In some embodiments, the method is provided of treating a Ras protein-related disorder in a subject in need thereof.

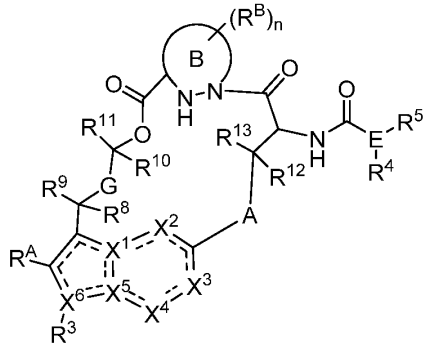
In some embodiments, the method further comprises administering an additional anti-cancer therapy.

In some embodiments, the additional anti-cancer therapy is an EGFR inhibitor, a second Ras inhibitor, a SHP2 inhibitor, a SOS1 inhibitor, a Raf inhibitor, a MEK inhibitor, an ERK inhibitor, a Pl3K inhibitor, a PTEN inhibitor, an AKT inhibitor, an mTORC1 inhibitor, a BRAF inhibitor, a PD-L1 inhibitor, a PD-1 inhibitor, a CDK4/6 inhibitor, a HER2 inhibitor, or a combination thereof.

It should be understood that each of the above technical features of the invention and each technical feature specifically described below (such as in Examples) can be combined with each other within the scope of the present invention so as to constitute new or preferred technical solutions.

EXEMPLARY EMBODIMENTS

Embodiment 1. The compound of any one of the preceding embodiments, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I);



(I)

wherein

n is 0, 1, 2, or 3;

A is optionally substituted 5 to 6-membered heterocycloalkylene, optionally substituted 5 to 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

B is selected from optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 3 to 6-membered heterocycloalkenylene, optionally substituted 4 to 11-membered bicyclic cycloalkylene, or optionally substituted 4 to 11-membered bicyclic heterocycloalkylene;

G is optionally substituted C_{1-6} alkylene;

R^8 and R^9 are each independently selected from hydrogen, deuterium, halogen, hydroxy, cyano, optionally substituted C_{1-3} alkyl, or R^8 and R^9 combine with the atoms to which they are attached to form an optionally substituted C_{3-6} cycloalkyl or a carbonyl;

R^{10} and R^{11} are each independently selected from hydrogen, deuterium, halogen, hydroxy, cyano, optionally substituted C_{1-3} alkyl, or R^{10} and R^{11} combine with the atoms to which they are attached to form an optionally substituted C_{3-6} cycloalkyl or a carbonyl;

R^{12} and R^{13} are each independently selected from hydrogen, deuterium, halogen, hydroxy, optionally substituted C_{1-3} alkyl, -O(C_{1-6} alkyl), -S(C_{1-6} alkyl) or -N(C_{1-6} alkyl)(C_{1-6} alkyl); furthermore, the C_{1-6} alkyl may be further optionally substituted;

R^A is optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl (or 4 to 7-membered heterocycloalkyl), optionally substituted 5 to 8-membered aryl, optionally substituted 5 to 8-membered heteroaryl, optionally substituted 8 to 10-membered fused bicyclic aryl or optionally substituted 8 to 10-membered fused bicyclic heteroaryl;

R^B is selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, optionally substituted C_{3-6} cycloalkyl, or optionally substituted C_{3-6} heterocycloalkyl (or 4 to 7- membered heterocycloalkyl); or provided that when n exceeds 1, any two of R^B combine with the atoms to which they are attached to form a 3 to 6-membered ring, wherein the ring can be optionally substituted with halogen, hydroxy, and C_{1-3} alkyl;

X^1 is N or C;

X^2 is N or $-CR^a-$;

X^3 is N or $-CR^b-$;

X^4 is N or $-CR^c-$;

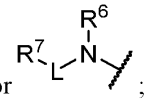
X^5 is N or C;

X^6 is S, O, N, or -CH-;

R^a, R^b, and R^c are each independently hydrogen, halogen, cyano, C_{1-3} alkyl, C_{1-3} alkoxyl, C_{1-3} haloalkyl, C_{1-3} haloalkoxyl, C_{3-6} cycloalkyl, or C_{3-6} heterocycloalkyl (or 4 to 7-membered heterocycloalkyl);

R^3 is absent, or selected from hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl, provided that when X^6 is O or S, R^3 is absent;

E is a bond, or selected from N, or $-CR^d-$, wherein R^d is selected from hydrogen, halogen, hydroxy, cyano, carboxyl, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkoxyl, C_{1-6} aminoalkyl, C_{1-6} hydroxyalkyl, or $-NR^eR^f$; wherein R^e and R^f are independently selected from hydrogen, or optionally substituted C_{1-6} alkyl;

R^4 is hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{3-10} cycloalkenyl, optionally substituted C_{3-10} heterocycloalkyl (or 4 to 12-membered heterocycloalkyl), optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or ;

R^5 is hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl, furthermore, the C_{1-6} alkyl or C_{3-6} cycloalkyl may be further optionally substituted;

or R^4 and R^5 combine with the atoms to which they are attached to form a ring, wherein the ring is selected from optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 4 to 11-membered bicyclic cycloalkyl, optionally substituted 4 to 11-membered bicyclic heterocycloalkyl;

wherein

L is absent, or selected from $-CH_2-$, -C(O)-, $-CHR^g-$ or $-C(R^g)_2-$, wherein R^g is optionally substituted C_{1-6} alkyl;

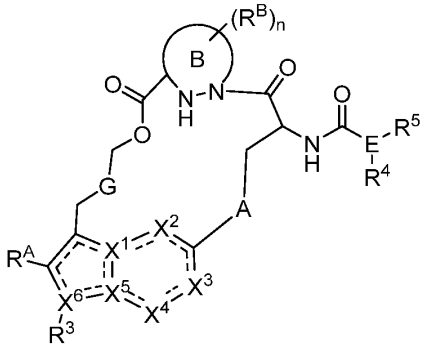
R^6 is hydrogen, or optionally substituted C_{1-6} alkyl;

R^7 is optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted

C_{3-10} cycloalkyl, optionally substituted C_{3-10} heterocycloalkyl (or 3 to 10-membered heterocycloalkyl), optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl;

or L, R^6 and R^7 combine with the atoms to which they are attached to form a ring, wherein the ring is selected from optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 4 to 11-membered bicyclic cycloalkyl, optionally substituted 4 to 11-membered bicyclic heterocycloalkyl.

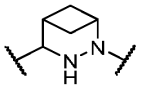
Embodiment 2. The compound of embodiment 1, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is a compound of formula (I-1)

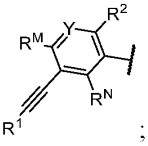


(I-1)

wherein X^1, X^2, X^3, X^4, X^5, X^6, A, B, E, G, R^A, R^B, R^3, R^4, R^5 and n are as defined in embodiment 1.

Embodiment 3. The compound of any one of embodiments 1 to 2, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein

B is optionally substituted  ; and

R^A is  ;

wherein

R^1 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl, optionally substituted 5 to 8-membered aryl, optionally substituted 5 to 8-membered heteroaryl, optionally substituted 8 to 10-membered fused bicyclic aryl, optionally substituted 8 to 10-membered fused bicyclic heteroaryl, optionally substituted -C_{1-2} alkylene-C_{3-6} cycloalkyl, optionally substituted -C_{1-2} alkylene-C_{3-6} heterocycloalkyl, optionally substituted -C_{1-2} alkylene-5 to 8-membered aryl, optionally substituted -C_{1-2} alkylene-5 to 8-membered heteroaryl, optionally substituted -C_{1-2} alkylene-8 to 10-membered fused bicyclic aryl, and optionally substituted -C_{1-2} alkylene-8 to 10-membered fused bicyclic heteroaryl; furthermore, the C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, C_{1-6} hydroxyalkyl may be further optionally substituted;

in R^1, when the C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, or C_{1-6} hydroxyalkyl is further substituted, the substituent is selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl, optionally substituted 5 to 8-membered aryl, optionally substituted 5 to 8-membered heteroaryl, optionally substituted 8 to 10-membered fused bicyclic aryl, optionally substituted 8 to 10-membered fused bicyclic heteroaryl; preferably, the substituent is selected from the group consisting of optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl, optionally substituted 5 to 8-membered aryl, optionally substituted 5 to 8-membered heteroaryl, optionally substituted 8 to 10-membered fused bicyclic aryl, optionally substituted 8 to 10-membered fused bicyclic heteroaryl; more preferably, the substituent is optionally substituted C_{3-6} heterocycloalkyl;

Y is -CH- or N;

R^2 is optionally substituted C_{1-6} alkoxy, or optionally substituted C_{1-6} alkyl; preferably, R^2 is optionally substituted C_{1-6} alkyl; and

R^M and R^N are each independently selected from hydrogen, halogen, hydroxy, cyano, carboxyl, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl; furthermore, the C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, C_{1-6} hydroxyalkyl may be further optionally substituted. In some embodiments, R^M and R^N are each independently selected from hydrogen, and C_{1-6} alkyl.

Embodiment 4. The compound of embodiment 3, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein

R^1 is optionally substituted C_{1-6} alkyl;

and, in R^1, the C_{1-6} alkyl is further substituted, and the substituent is selected from optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl, optionally substituted 5 to 8-membered aryl, optionally substituted 5 to 8-membered heteroaryl, optionally substituted 8 to 10-membered fused bicyclic aryl, optionally substituted 8 to 10-membered fused bicyclic heteroaryl.

Embodiment 5. The compound of any one of embodiments 3 to 4, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein

R^1 is optionally substituted C_{1-6} alkyl;

in R^1, the C_{1-6} alkyl is further substituted, and the substituent is optionally substituted C_{3-6} heterocycloalkyl.

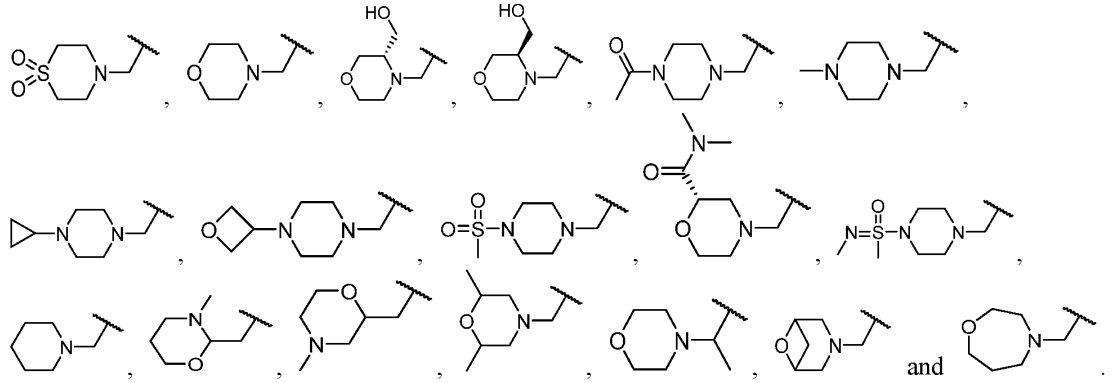
Embodiment 6. The compound of any one of embodiments 3 to 4, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein R^1 is C_1 alkyl; and the C_1 alkyl is further substituted with optionally substituted C_{3-6} heterocycloalkyl, wherein the heterocycloalkyl is saturated and the heterocycloalkyl is attached to the rest of the molecule via the N atom on the ring.

Embodiment 7. The compound of any one of embodiments 3 to 4, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate

of the pharmaceutically acceptable salt thereof, wherein R^1 is C_1 alkyl; and the C_1 alkyl is further substituted with optionally substituted C_{3-6} heterocycloalkyl, wherein the heterocycloalkyl is saturated and the heterocycloalkyl is attached to the rest of the molecule via the N atom on the ring.and the C_{3-6} heterocycloalkyl is 5 to 7 menbered heterocycloalkyl and has l to 2 heteroatoms.

Embodiment 8. The compound of any one of embodiments 3 to 7, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein

R^1 is selected from the group consisting of

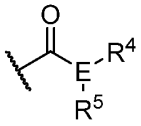


and

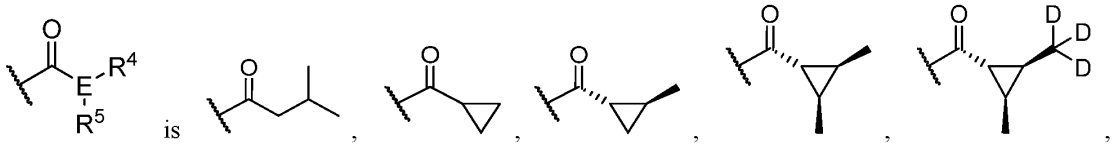
Embodiment 9. The compound according to any one of embodiments 3 to 8, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein R^1 is C_1 alkyl substituted by C_6 heterocycloalkyl, optionally wherein the C_6 heterocycloalkyl is piperazine or morpholine.

Embodiment 10. The compound of any one of embodiments 1 to 9, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein R^4 and R^5 combine with the atoms to which they are attached to form a ring, wherein the ring is optionally substituted 3 to 10-membered cycloalkyl; preferably, is optionally substituted 3 to 6-membered cycloalkyl; more preferably, optionally substituted cyclopropyl.

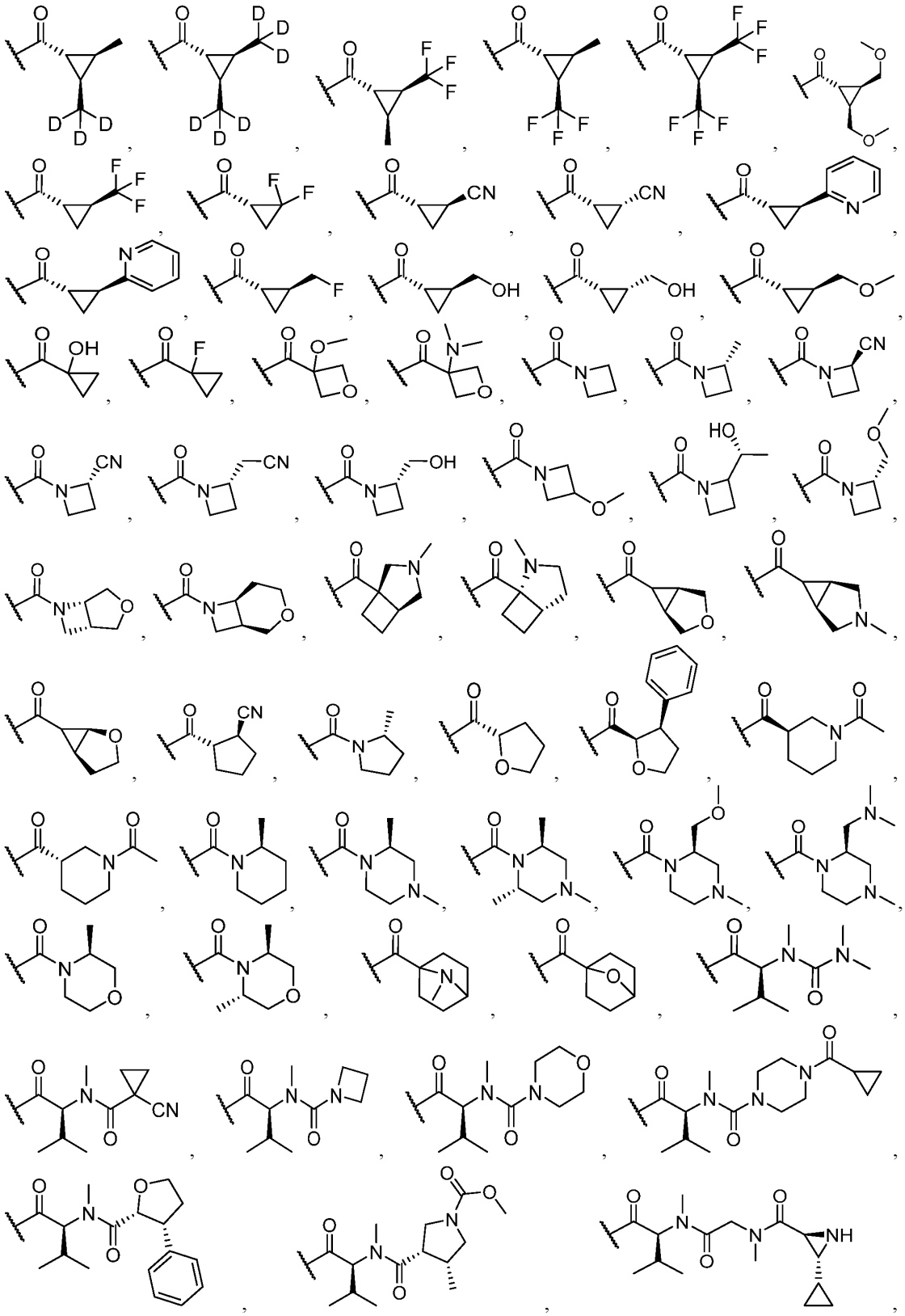
Embodiment 11. The compound of any one of embodiments 1 to 9, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein

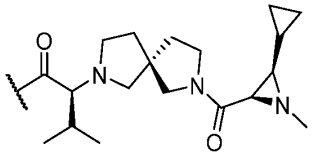
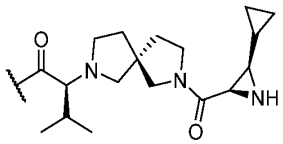
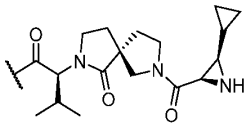
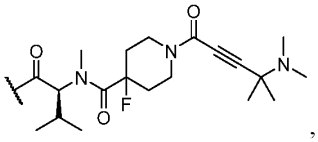
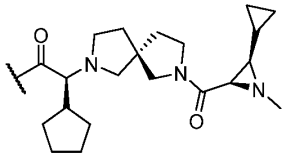


is selected from the group consisting of:



is



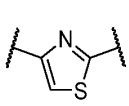
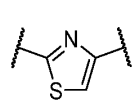
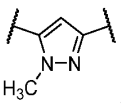
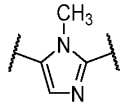
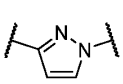
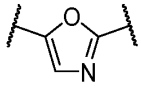
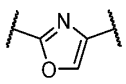
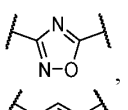
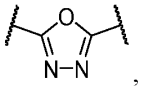
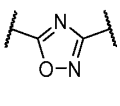
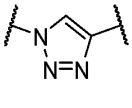
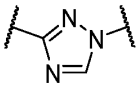
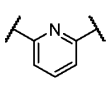
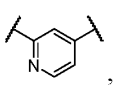
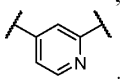

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or

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Embodiment 12. The compound of any one of embodiments 1 to 11, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein

A is optionally substituted 5 to 6-membered heteroarylene, the heteroatom is independently selected from one or two of N, O and S, and the number of the heteroatom is independently 1 to 3

preferably, A is optionally substituted 5-membered heteroarylene, the heteroatom is independently selected from N, O and S, and the number of the heteroatom is independently 1 to 2; preferably, one of the heteroatom is N, and the other, if present, is O or S;

more preferably, A is selected from the group consisting of


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Embodiment 13. The compound of any one of embodiments 1 to 12, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein

X^1 is C, and/or X^2 is -CR^a-, and/or X^3 is -CR^b, and/or X^4 is –CR^c-, and/or X^5 is -C-.

Embodiment 14. The compound of any one of embodiments 1 to 13, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, the metabolite thereof, the prodrug thereof, the solvate thereof or the solvate of the pharmaceutically acceptable salt thereof, wherein, the compound is selected from any one of the compounds in Table 1.

Embodiment 15. The compound of any one of embodiments 1 to 14, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, the metabolite thereof, the prodrug thereof, the solvate thereof or the solvate of the pharmaceutically acceptable salt thereof, wherein, the compound is selected from compounds of Examples 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 27, 28, 29, 30, 31, 32, 33, 37,38, 39, 40,41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 84, 86, 87, 88, and 90 in Table 1.

Embodiment 16. A pharmaceutical composition comprising: the compound of any one of embodiments 1 to 15, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, the metabolite

thereof, the prodrug thereof, the solvate thereof or the solvate of the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Embodiment 17. A use of the compound of any one of embodiments 1 to 15, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, the metabolite thereof, the prodrug thereof, the solvate thereof or the solvate of the pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to embodiment 16, or the pharmaceutical composition comprising the same in the preparation of a medicament used for the treatment of cancer.

Embodiment 18. The use of the compound of embodiment 17, wherein the cancer is selected from the group consisting of small cell lung cancer (SCLC), colorectal cancer (CRC), pancreatic cancer, and cholangiocarcinoma, pancreatic cancer, appendiceal cancer, small bowel cancer, colorectal cancer, ampullary cancer, non-small cell lung cancer, cervical cancer, lung cancer, endometrial cancer, acute myeloid leukemia, gastrointestinal neuroendocrine tumor, uterine endometrioid carcinoma, oesophagogastric cancer, bladder cancer, ovarian cancer, melanoma, multiple myeloma, thyroid gland adenocarcinoma, a myelodysplastic syndrome, and squamous cell lung carcinoma, or combinations thereof.

Embodiment 19. The use according to any one of embodiments 17 to 18, wherein the cancer is selected from the group consisting of non-small cell lung cancer, small cell lung cancer, colorectal cancer, pancreatic cancer, and cholangiocarcinoma.

Embodiment 20. The compound according to any one of embodiments 1 to 15, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, the metabolite thereof, the prodrug thereof, the solvate thereof or the solvate of the pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprising the same for use in treating cancer.

Embodiment 21. The compound for use according to embodiment 20, wherein the cancer is as defined in embodiment 18.

Embodiment 22. The compound for use according to any one of embodiments 20 to 21, wherein the cancer is as defined in embodiment 19.

Embodiment 23. A method for treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound of any one of the preceding embodiments, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, the metabolite thereof, the prodrug thereof, the solvate thereof or the solvate of the pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to embodiment 16, or the pharmaceutical composition comprising the same.

Embodiment 24. The method according to embodiment 23, wherein the cancer is as defined in embodiment 18.

Embodiment 25. The method according to any one of embodiments 23 to 24, wherein the cancer is as defined in embodiment 19.

TERM DEFINITION

Given below are definitions of terms used in this application. Any term not defined herein takes the normal meaning as the skilled person would understand the term.

As used herein, the term “pharmaceutically acceptable salts” refers to salts prepared from pharmaceu-

tically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids.

As used herein, the term "solvate" refers to solvent addition forms that contain either stoichiometric or non-stoichiometric amounts of solvent.

As used herein, excipient that is useful in preparing a pharmaceutical composition that is generally safe, nontoxic and neither biologically nor otherwise undesirable, and includes carrier that is acceptable for veterinary use as well as human pharmaceutical use.

A "pharmaceutically acceptable carrier" as used herein includes both one and more than one such carrier. The term "pharmaceutically acceptable carrier" also encompasses "pharmaceutically acceptable excipient" and "pharmaceutically acceptable diluent". The particular carrier used in the pharmaceutical compositions of the present disclosure will depend upon the means and purpose for which the compounds of the present disclosure are being applied.

As used herein, unless otherwise specified, the term "optionally substituted" refers to unsubtituted or being substituted with one or more (such as 1, 2, 3 or 4) substituents. Suitable substituents for each group can be found herein. Unless otherwise specified, exemplary substituents can be selected from the group consisting of D, halogen, -CN, $-NO_2$, R^i, $-C_{1-4}$ alkylene-R^i, $-C_{2-4}$ alkenylene-R^i, $-C_{2-4}$ alkynylene-R^i, $-OR^i$, $-OC(O)R^i$, $-C(O)R^i$, $-CO_2R^i$, $-CONR^iR^{ii}$, $-OC(O)NNR^iR^{ii}$, $-NR^{ii}C(O)R^i$, $-NR^i$-$C(O)NR^{ii}R^{iii}$, $-NR^{ii}C(O)_2R^i$, $-NH$-$C(NH_2)$=NH, $-NR^iC(NH_2)$=NH, $-NH$-$C(NH_2)$=NR^i, $-S(O)R^i$, $-S(O)_2R^i$, $-S(O)_2NR^iR^{ii}$, $-S(O)(=N\text{-}R^i)R^{ii}$ (e.g., ), $-NR^iS(O)_2R^{ii}$; wherein R^i, R^{ii} and R^{iii} are each independently selected from the group consisting of H, C_{1-6} alkyl, $-C_{2-6}$ alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3 to 10-membered heterocycloalkyl, 3 to 10-membered heterocycloalkenyl, C_{6-10} aryl, 5 to 10-membered heteroaryl, $-C_{1-4}$ alkylene-C_{3-10} cycloalkyl, $-C_{1-4}$ alkylene-C_{3-10} cycloalkenyl, $-C_{1-4}$ alkylene-3 to 10-membered heterocycloalkyl, $-C_{1-4}$ alkylene-3 to 10-membered heterocycloalkenyl, $-C_{1-4}$ alkylene-C_{6-10} aryl, and $-C_{1-4}$ alkylene-5 to 10-membered heteroaryl; or R^i and R^{ii}, R^{ii} and R^{iii} together with the atom to which they are attached to form C_{3-10} cycloalkenyl, 3 to 10-membered heterocycloalkyl, 3 to 10-membered heterocycloalkenyl, C_{6-10} aryl, 5 to 10-membered heteroaryl; wherein the alkylene, alkenylene, alkynylene, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl and heteroaryl can be unsubtituted or one or more (such as 1, 2, 3 or 4) or all of H atom in the group being substituted with substituents selected from the group consisting of D, halogen, -CN, -OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} deuteroalkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, amino, alkylamino, $-C(O)C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-OC(O)C_{1-6}$ alkyl, $-S(O)C_{1-6}$ alkyl, $-S(O)_2C_{1-6}$ alkyl, $-COOC_{1-6}$ alkyl, , oxo (=O), C_{1-6} alkylidene, C_{1-6} haloalkylidene, C_{1-6} deuteroalkylidene, C_{1-6} hydroxyalkylidene, C_{1-6} aminoalkylidene, C_{3-6} cycloalkyl optionally substituted with one or more of D, halogen, -CN, -OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} deuteroalkyl, C_{1-6} hydroxyalkyl, and C_{1-6} aminoalkyl, 3 to 6-membered heterocycloalkyl optionally substituted with one or more of D, halogen, -CN, -OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} deuteroalkyl, C_{1-6} hydroxyalkyl, and C_{1-6} aminoalkyl, 3 to

6-membered heterocycloalkenyl optionally substituted with one or more of D, halogen, -CN, -OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} deuteroalkyl, C_{1-6} hydroxyalkyl, and C_{1-6} aminoalkyl, phenyl, 5 to 6-membered heteroaryl optionally substituted with one or more of D, halogen, -CN, -OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} deuteroalkyl, C_{1-6} hydroxyalkyl, and C_{1-6} aminoalkyl. In some embodiments, said "optionally substituted" means that the group is substituted by one or more substituents selected from the group consisting of deuterium, halogen, amino, nitro, cyano, hydroxyl, oxo (=O), thio (=S), C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_2-C_4 alkenyl, C_2-C_4 alkyne, C_3-C_6 cycloalkyl, 3 to 6-membered heterocycloalkyl.

In addition, if an optionally substituted group can be further substituted means in addition to being substituted by the above-mentioned substituents for "optionally substituted", one or more hydrogen atoms in the group may also be substituted by other substituents specified (such as substituents for further substitution).

As used herein, the term "alkyl" refers to a saturated aliphatic hydrocarbon group including straight chain and branched chain groups having the number of carbon atoms designated (i.e., C_{1-20} means 1 to 20 carbon atoms). Preferably an alkyl group is an alkyl having 1 to 12 i.e., C_{1-12} alkyl. Sometimes preferably 1 to 6 i.e., C_{1-6} alkyl, sometimes more preferably 1 to 4, carbon atoms i.e., C_{1-4} alkyl. Representative examples include, but are not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, 1,1-dimethyl propyl, 1,2-dimethyl propyl, 2,2-dimethyl propyl, 1-ethylpropyl, 2-methylbutyl, 3-methylbutyl, n-hexyl, 1-ethyl-2-methylpropyl, 1,1,2-trimethylpropyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2-ethylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2,3-dimethylbutyl, n-heptyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylpentyl, 2,4-dimethylpentyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 2-ethylpentyl, 3-ethylpentyl, n-octyl, 2,3-dimethylhexyl, 2,4-dimethylhexyl, 2,5-dimethylhexyl, 2,2-dimethylhexyl, 3,3-dimethylhexyl, 4.4-dimethylhexyl, 2-ethylhexyl, 3-ethylhexyl, 4-ethylhexyl, 2-methyl-2-ethylpentyl, 2-methy1-3-ethylpentyl, n-nonyl, 2-methy1-2-ethylhexyl, 2-methy1-3-ethylhexyl, 2,2-diethylpentyl, n-decyl, 3,3-diethylhexyl, 2,2-diethylhexyl, and the isomers of branched chain thereof. More preferably an alkyl group is a lower alkyl having 1 to 6 carbon atoms. Representative examples include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, 2-methylbutyl, 3-methylbutyl, n-hexyl, 1-ethyl-2-methylpropyl, 1,1,2-trimethylpropyl, 1,1-dimethylbutyl, 1.2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2-ethylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2,3-dimethylbutyl, etc. The alkyl group can be substituted or unsubstituted. When substituted, the substituent group(s) can be substituted at any available connection point, preferably the substituent group(s) is one or more substituents independently selected from the group consisting of alkyl, halogen, alkoxy, alkenyl, alkynyl, alkylsulfo, alkylamino, thiol, hydroxy, nitro, cyano, amino, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkoxyl, heterocylic, cycloalkylthio, heterocylic alkylthio and oxo group.

The term "alkylene" refers to a saturated linear or branched aliphatic hydrocarbon group, wherein having 2 residues derived by removing two hydrogen atoms from the same carbon atom of the parent alkane or two different carbon atoms. The straight or branched chain group containing 1 to 20 carbon atoms,

preferably has 1 to 12 carbon atoms, more preferably 1 to 6 carbon atoms. Non-limiting examples of alkylene groups include, but are not limited to, methylene (-CH_2-), 1,1-ethylene (-$CH(CH_3)$-), 1,2-ethylene (-CH_2CH_2)-, 1,1-propylene (-$CH(CH_2CH_3)$-), 1,2-propylene (-$CH_2CH(CH_3)$-), 1,3-propylene (-$CH_2CH_2CH_2$-), 1,4-butylidene (-$CH_2CH_2CH_2CH_2$-) etc. The alkylene group can be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more, sometimes preferably one to five, sometimes more preferably one to three, group(s) independently selected from the group consisting of selected from alkyl, alkenyl, alkynyl, alkoxy, alkylsulfo, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclic alkyl, aryl, heteroaryl, cycloalkoxyl, heterocylic alkoxyl, cycloalkylthio and heterocylic alkylthio.

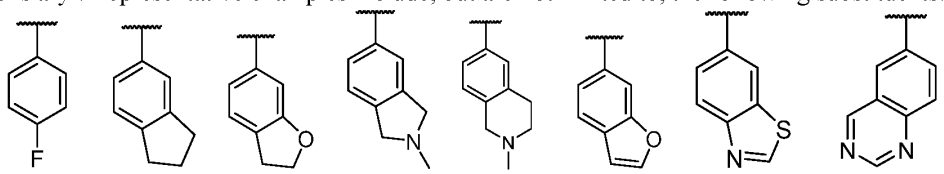
As used herein, the term "alkenyl" refers to an alkyl defined as above that has at least two carbon atoms and at least one carbon-carbon double bond, for example, vinyl, 1-propenyl, 2- propenyl, 1-2-, or 3-butenyl, etc., preferably C_{2-20} alkenyl, more preferably C_{2-12} alkenyl, and most preferably C_{2-6} alkenyl. The alkenyl group can be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more, sometimes preferably one to five, sometimes more preferably one to three, group(s) independently selected from the group consisting of alkyl, halogen, alkoxy, alkenyl, alkynyl, alkylsulfo, alkylamino, thiol, hydroxy, nitro, cyano, amino, cycloalkyl, heterocyclic alkyl, aryl, heteroaryl, cycloalkoxyl, heterocylic, cycloalkylthio, heterocylic alkylthio and oxo group.

The term "alkenylene" refers to an alkylene defined as above that has at least two carbon atomsand at least one carbon-carbon double bond, preferably C_{2-20} alkenylene, morepreferably C_{2-12} alkenylene, and most preferably C_{2-6} alkenylene. Non-limiting examples of alkenylene groups include, but are not limited to, -CH=CH-, -CH=$CHCH_2$, -CH=$CHCH_2CH_2$, -CH_2CH=$CHCH_2$- etc. The alkenylene group can be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more, sometimes preferably one to five, sometimes more preferably one to three, group(s) independently selected from the group consisting of selected from alkyl, alkenyl, alkynyl, alkoxy, alkylsulfo, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclic alkyl, aryl, heteroaryl, cycloalkoxyl, heterocylic alkoxyl, cycloalkylthio and heterocylic alkylthio.

As used herein, the term "alkynyl" refers to an alkyl defined as above that has at least two carbon atoms and at least one carbon-carbon triple bond, for example, ethynyl, 1-propynyl, 2-propynyl, 1-2-, or 3-butynyl etc., preferably C_{2-20} alkynyl, more preferably C_{2-12} alkynyl, and most preferably C_{2-6} alkynyl. The alkynyl group can be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more, sometimes preferably one to five, sometimes more preferably one to three, group(s) independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkylsulfo, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclic alkyl, aryl, heteroaryl, cycloalkoxyl, heterocylic alkoxyl, cycloalkylthio and heterocylic alkylthio.

As used herein, the term "aryl" refers to a 6 to 14-membered (or C_{6-14}) all-carbon monocyclic ring or a polycyclic fused ring (a "fused" ring system means that each ring in the system shares an adjacent pair of carbon atoms with another ring in the system) group, and has a completely conjugated pi-electron system. Preferably aryl is 6 to 10-membered (or C_{6-10}), such as phenyl and naphthyl, most preferably phenyl. The aryl can be fused to the ring of heteroaryl, heterocyclyl or cycloalkyl, wherein the ring bound to parent

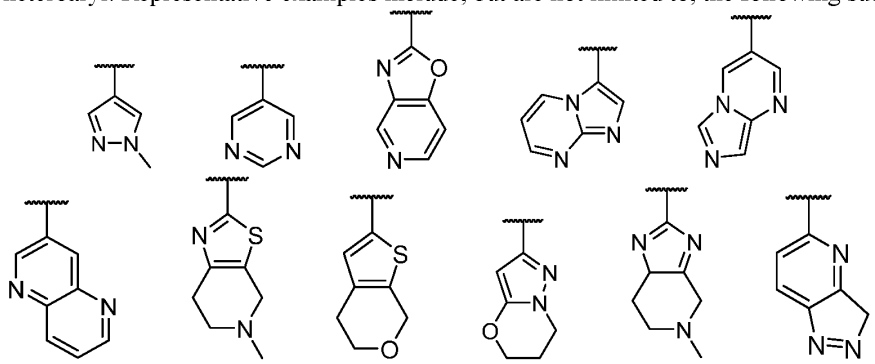
structure is aryl. Representative examples include, but are not limited to, the following substituents:



The aryl group can be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more, sometimes preferably one to five, sometimes more preferably one to three, substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkylsulfo, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclic alkyl, aryl, heteroaryl, cycloalkoxyl, heterocylicalkoxyl, cycloalkylthio and heterocylic alkylthio.

The term "arylene" is a divalent group which is connected to the rest of the molecule through two single bonds, and the rest definitions are the same as the term "aryl".

As used herein, the term "heteroaryl" refers to an aryl system having 1 to 4 heteroatoms selected from the group consisting of O, S and N as ring atoms and having 5 to 14 ring atoms (referred as 5 to 14-membered). Preferably a heteroaryl is 5 to 10-membered, more preferably 5 or 6-membered, for example, thiadiazolyl, pyrazolyl, oxazolyl, oxadiazolyl, imidazolyl, triazolyl, thiazolyl, thiazolylfuryl, thienyl, pyridyl, pyrrolyl, N-alkyl pyrrolyl, pyrimidinyl, pyrazinyl, imidazolyl, tetrazolyl, and the like. The heteroaryl can be fused with the ring of an aryl, heterocyclyl or cycloalkyl, wherein the ring bound to parent structure is heteroaryl. Representative examples include, but are not limited to, the following substituents:



The heteroaryl group can be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more, sometimes preferably one to five, sometimes more preferably one to three, substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkylsulfo, alkylamino, halogen, thiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclic alkyl, aryl, heteroaryl, cycloalkoxyl, heterocylic alkoxyl, cycloalkylthio, heterocylic alkylthio and $-NR^eR^f$.

The term "heteroarylene" is a divalent group which is connected to the rest of the molecule through two single bonds, and the rest definitions are the same as the term "heteroaryl".

The term "bicyclic" is intended to include spiro, fused-ring or bridged-ring.

As used herein, the term "spiro" refers to two rings that shares one ring atom (e.g., carbon).

As used herein, the term "fused" refers to two rings that share two adjacent ring atoms with one another.

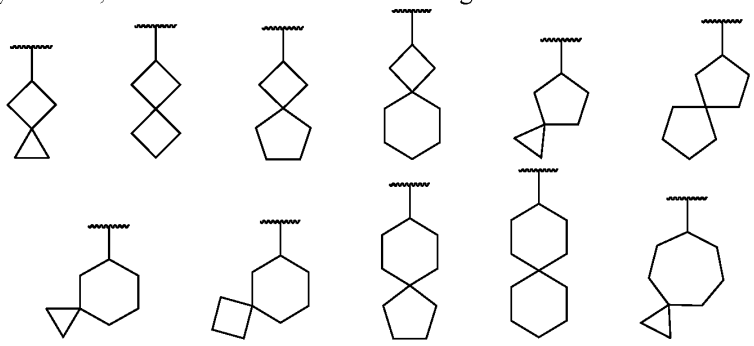
As used herein, the term "bridged" refers to two rings that share three adjacent ring atoms with one

another.

As used herein, the term "cycloalkyl" refers to a saturated and/or partially unsaturated monocyclic or polycyclic hydrocarbon group having 3 to 20 carbon atoms (refered as C_{3-20} or 3 to 20 membered), preferably 3 to 12 carbon atoms (refered as C_{3-12} or 3 to 12 membered), more preferably 3 to 10 carbon atoms (refered as C_{3-10} or 3 to 10 membered), and most preferably 3 to 8 carbon atoms (refered as C_{3-8} or 3 to 8 membered) or 3 to 6 carbon atoms (refered as C_{3-6} or 3 to 6 membered). In some embodiments, cycloalkyl is monocyclic cycloalkyl. Representative examples of monocyclic cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, cycloheptyl, cycloheptatrienyl, cyclooctyl, etc. In some embodiments, cycloalkyl is polycyclic cycloalkyl (such as bicyclic cycloalkyl). In some embodiments, cycloalkyl is a spiro cycloalkyl, a fused cycloalkyl or a bridged cycloalkyl. Polycyclic cycloalkyl includes a cycloalkyl having a spiro ring, fused ring or bridged ring. The cycloalkyl can be fused to the ring of an aryl, heteroaryl or heterocyclic alkyl, wherein the ring bound to the parent structure is cycloalkyl. Representative examples include, but are not limited to indanylacetic, tetrahydronaphthalene, benzocycloheptyl and so on. The cycloalkyl is optionally substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more, sometimes preferably one to five, sometimes more preferably one to three, substituents independently selected from the group consisting of alkyl, halogen, alkoxy, alkenyl, alkynyl, alkylsulfo, alkylamino, thiol, hydroxy, nitro, cyano, amino, cycloalkyl, heterocyclic alkyl, aryl, heteroaryl, cycloalkoxyl, heterocylic, cyeloalkylthio, heterocylic alkylthio and oxo group.

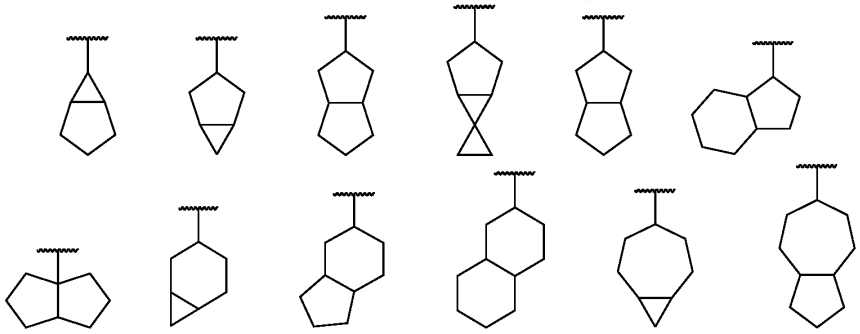
The term "cycloalkylene" is a divalent group which is connected to the rest of the molecule through two single bonds, and the rest definitions are the same as the term "cycloalkyl".

"Spiro Cycloalkyl" refers to a 5 to 20-membered polycyclic group with rings connected through one common carbon atom (called a spiro atom), wherein one or more rings can contain one or more double bonds, but none of the rings has a completely conjugated pi-electron system. Preferably a spiro cycloalkyl is 6 to 14-membered, and more preferably 7 to 10-membered. According to the number of common spiro atoms, a spiro cycloalkyl is divided into mono-spiro cycloalkyl, di-spiro cycloalkyl, or poly-spiro cycloalkyl, and preferably refers to a mono-spiro cycloalkyl or di-spiro cycloalkyl, more preferably 4-membered/4-membered, 4-membered/5-membered, 4-membered/6-membered, 5-membered/5-membered, or 5-membered/6-membered mono-spiro cycloalkyl. Representative examples of spiro cycloalkyl include, but are not limited to the following substituents:

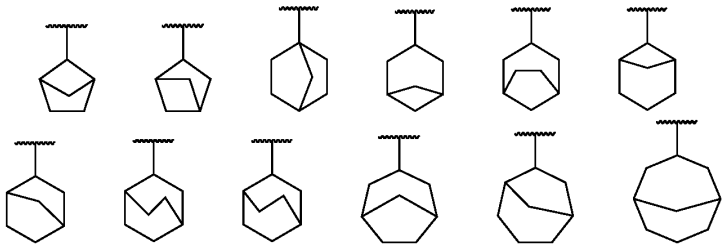


"Fused Cycloalkyl" refers to a 5 to 20-membered polycyclic hydrocarbon group, wherein each ring in

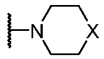
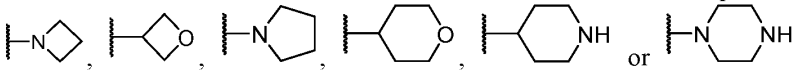
the system shares an adjacent pair of carbon atoms with another ring, wherein one or more rings can contain one or more double bonds, but none of the rings has a completely conjugated pi-electron system. Preferably, a fused cycloalkyl group is 6 to 14-membered, more preferably 7 to 10-membered. According to the number of membered rings, fused cycloalkyl is divided into bicyclic, tricyclic, tetracyclic or polycyclic fused cycloalkyl, and preferably refers to a bicyclic or tricyclic fused cycloalkyl, more preferably 5-membered/5-membered, or 5-membered/6-membered bicyclic fused cycloalkyl. Representative examples of fused cycloalkyls include, but are not limited to, the following substituents:



"Bridged Cycloalkyl" refers to a 5 to 20-membered polycyclic hydrocarbon group. wherein every two rings in the system share two disconnected carbon atoms. The rings can have one or more double bonds, but have no completely conjugated pi-electron system. Preferably, a bridged cycloalkyl is 6 to 14-membered, and more preferably 7 to 10-membered. According to the number of membered rings, bridged cycloalkyl is divided into bicyclic, tricyclic, tetracyclic or polycyclic bridged cycloalkyl, and preferably refers to a bicyclic, tricyclic or tetracyclic bridged cycloalkyl, more preferably a bicyclic or tricyclic bridged cycloalkyl. Representative examples of bridged cycloalkyls include, but are not limited to, the following substituents:

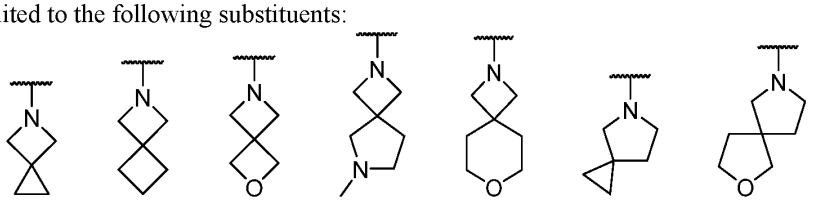


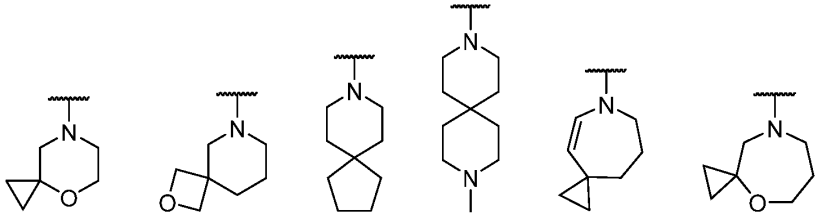
As used herein, the term "heterocyclyl" or "heterocycloalkyl" refers to a 3 to 20-membered saturated and/or partially unsaturated monocyclic or polycyclic hydrocarbon group having one or more, sometimes preferably one to five, sometimes more preferably one to three carbon ring atoms being replaced with heteroatoms selected from the group consisting of N, O, and $S(O)_m$ (wherein m is 0, l, or 2) as ring atoms, but excluding -O-O-, -O-S- or -S-S- in the ring, the remaining ring atoms being C. Preferably, heterocyclyl is a 3 to 12-membered ring having 1 to 4 heteroatoms (also referred as for example 3-12 membered heterocyclyl or heterocycloalkyl, or C_{2-11} heterocyclyl or heterocycloalkyl); more preferably a 4 to 12-membered ring having l to 3 heteroatoms (also referred as for example 4-12 membered heterocyclyl or heterocycloalkyl, or C_{3-10} heterocyclyl or heterocycloalkyl); more preferably a 3 to 10-membered ring having 1 to 3 heteroatoms (also referred as for example 3-10 membered heterocyclyl or heterocycloalkyl, or C_{2-9} heterocyclyl or heterocycloalkyl); more preferably a 4 to 8-membered ring having l to 3 heteroatoms (i.e., 4-8

membered heterocyclyl or heterocycloalkyl, or C_{2-7} heterocyclyl or heterocycloalkyl); most preferably a 5 to 7-membered ring having 1 to 2 heteroatoms (also referred as for example 5-7 membered heterocyclyl or heterocycloalkyl, or C_{3-6} heterocyclyl or heterocycloalkyl) or a 5 to 6-membered ring having 1 to 2 heteroatoms (also referred as for example 5-6 membered heterocyclyl or heterocycloalkyl, or C_{3-5} heterocyclyl or heterocycloalkyl). In some embodiments, heterocycloalkyl/heterocyclyl is monocyclic heterocycloalkyl/heterocyclyl. Representative examples of monocyclic heterocyclyls or heterocycloalkyl include, but arenot limited to, oxetanyl, azabutyl, pyrrolidyl, piperidyl, piperazinyl, morpholinyl,sulfo-morpholinyl, homopiperazinyl, and so on. In some embodiments, heterocycloalkyl/heterocyclyl is polycyclic heterocycloalkyl/heterocyclyl (such as bicyclic heterocycloalkyl/heterocyclyl). In some embodiments, heterocycloalkyl/heterocyclyl is a spiro heterocycloalkyl/heterocyclyl, a fused heterocycloalkyl/heterocyclyl or a bridged heterocycloalkyl/heterocyclyl. Polycyclic heterocyclyl or heterocycloalkyl includes the heterocyclyl having a spiro ring, fused ring or bridged ring. The "heterocyclyl" or "heterocycloalkyl" can be attached to the rest of the molecule via the N or C atom on the ring. In some embodiments, the "heterocyclyl" or "heterocycloalkyl" is attached to the rest of the molecule via the N atom on the ring. In some embodiments, specifically in the definition of R^1, the "heterocyclyl" or "heterocycloalkyl" is attached to the rest of the molecule via the C atom on the ring. In some embodiments, the "heterocyclyl" or "heterocycloalkyl" has a structure of ; wherein is a heteroatom or a carbon atom. Examples of such heterocyclyl groups are . When the heterocyclyl has substituents, the substituents may be attached to any atom in the ring, provided that a stable chemical structure results.

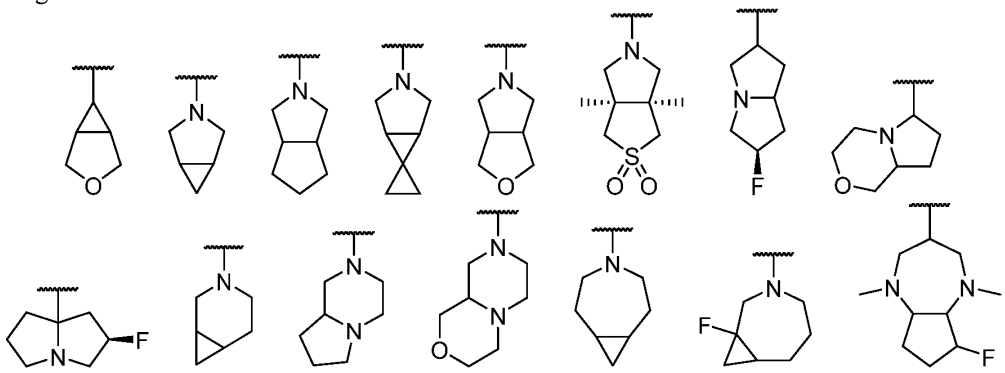
The term "heterocycloalkylene" is a divalent group which is connected to the rest of the molecule by two single bonds, and the rest definitions are the same as the term "heterocycloalkyl".

"Spiro heterocyclyl" refers to a 5 to 20-membered polycyclic heterocyclyl with rings connected through one common carbon atom (called a spiro atom), wherein said rings have one or more, sometimes preferably one to five, sometimes more preferably oneto three, heteroatoms selected from the group consisting of N, O, and $S(O)_m$. (wherein m is 0,1 or 2) as ring atoms, the remaining ring atoms being C, wherein one or more rings can contain one or more double bonds, but none of the rings has a completely conjugated pi-electron system. Preferably a spiro heterocyclyl is 6 to 14-membered, and more preferably 7 to 10-membered. According to the number of common spiroatoms, spiro heterocyclyl is divided into mono-spiro heterocyclyl, di-spiro heterocyclyl, or poly-spiro heterocyclyl, and preferably refers to mono-spiro heterocyclyl or di-spiro heterocyclyl, more preferably 4-membered/4-membered, 4-membered/5-membered, 4-membered/6-membered, 5-membered/5-membered, or 5-membered/6-membered mono-spiro heterocyclyl. Representative examples of spiro heterocyclyl include, but are not limited to the following substituents:

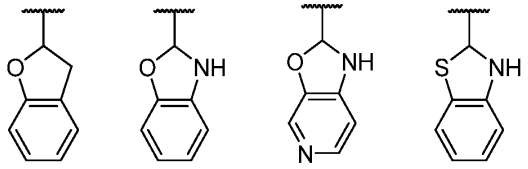




"Fused Heterocyclyl" refers to a 5 to 20-membered polycyclic heterocyclyl group,wherein each ring in the system shares an adjacent pair of carbon atoms with the other ring, wherein one or more rings can contain one or more double bonds, but none of the rings has a completely conjugated pi-electron system, and wherein said rings have one or more, sometimes preferably one to five, sometimes more preferably one to three, heteroatoms selected from the group consisting of N, O, and $S(O)_p$, (wherein p is 0,1,or 2) as ring atoms, the remaining ring atoms being C. Preferably a fused heterocyclyl is 6 to 14-membered, and more preferably 7 to 10-membered. According to the number of membered rings, fused heterocyclyl is divided into bicyclic, tricyclic, tetracyclic or polycyclic fused heterocyclyl, preferably refers to bicyclic or tricyclic fused heterocyclyl, more preferably 5-membered/5-membered, or 5-membered/6-membered bicyclic fused heterocyclyl. Representative examples of fused heterocyclyl include, but are not limited to, the following substituents:



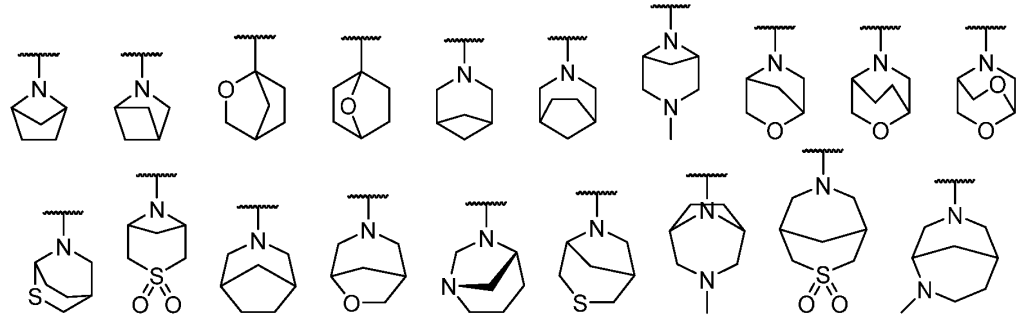
As used herein, the ring of said heterocyclyl can be fused to the ring of an aryl, heteroaryl orcycloalkyl,wherein the ringbound to the parent structure is heterocyclyl. Representative examples include, but are not limited to the following substituents:



The heterocyclyl is optionally substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more, sometimes preferably one to five, sometimes more preferably one to three, group(s) independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkylsulfo, alkylamino, halogenthiol, hydroxy, nitro, cyano, cycloalkyl, heterocyclic alkyl, aryl, heteroaryl, cycloalkoxyl, heterocylic alkoxyl, cycloalkylthio, heterocylic alkylthio.

"Bridged Heterocyclyl" refers to a 5 to l4-membered polycyclic heterocyclic alkyl group, wherein every two rings in the system share two disconnected atoms, the rings can have one or more double bonds, but have no completely conjugated pi-electron system, and the rings have one or more heteroatoms select-

ed from the group consisting of N, O, and $S(O)_m$ (wherein m is 0, 1, or 2) as ring atoms, the remaining ring atoms being C. Preferably a bridged heterocyclyl is 6 to 14-membered, and more preferably 7 to 10-membered. According to the number of membered rings, bridged heterocyclyl is divided into bicyclic, tricyclic, tetracyclic or polycyclic bridged heterocyclyl, and preferably refers to bicyclic, tricyclic or tetracyclic bridged heterocyclyl, more preferably bicyclic or tricyclic bridged heterocyclyl. Representative examples of bridged heterocyclyl include, but are not limited to, the following substituents:



As used herein, the term "C_{1-6} haloalkoxyl" refers to an alkoxyl group in which one or more hydrogen atoms are replaced by a halogen, for example, $-OCF_3$.

As used herein, the term "haloalkyl" refers to an alkyl group in which one or more hydrogen atoms are replaced by a halogen, for example, $-CF_3$.

As used herein, the term "C_{1-6} alkoxyC_{1-6} alkyl" refers to a C_{1-6} alkyl group in which one or more hydrogen atoms are replaced by C_{1-6} alkoxy or a C_{1-6} alkoxy group in which one or more hydrogen atoms are replaced by C_{1-6} alkyl.

As used herein, the term "alkoxy" refers to a straight or branched alkoxy group containing the specified number of carbon atoms. For example, C_{1-6} alkoxy means a straight or branched alkoxy group containing at least 1, and at most 6, carbon atoms. Examples of "alkoxy" as used herein include, but not limited to, methoxy, ethoxy, prop-1-oxy, pro-2-oxy, pentoxy, hexyloxy, and the like.

As used herein, the term "aminoalkyl" refers to an alkyl moiety substituted by one or more amino moieties. Such as $-CH_2(NH_2)$.

As used herein, the term "alkylamino" refers to an amino group substituted by one or more alkyl such as $-NH(C_{1-6}$ alkyl) or $-N(C_{1-6}$ alkyl)$_2$. Examples of alkylamino include, but not limited to, $-NH(CH_3)$, $-N(CH_3)_2$.

As used herein, the term "halogen" or "halo" refers to fluorine (F), chlorine (Cl), bromine (Br) or iodine (I).

As used herein, the term "oxo" means that =O, oxygen atoms replace two hydrogens on the same carbon atom, that is, carbonyl groups replace methylene groups.

As used herein, the term "Bond" refers to a covalent bond using a sign of "—". In some embodiments, ⚌ represents a double bond or single bond.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

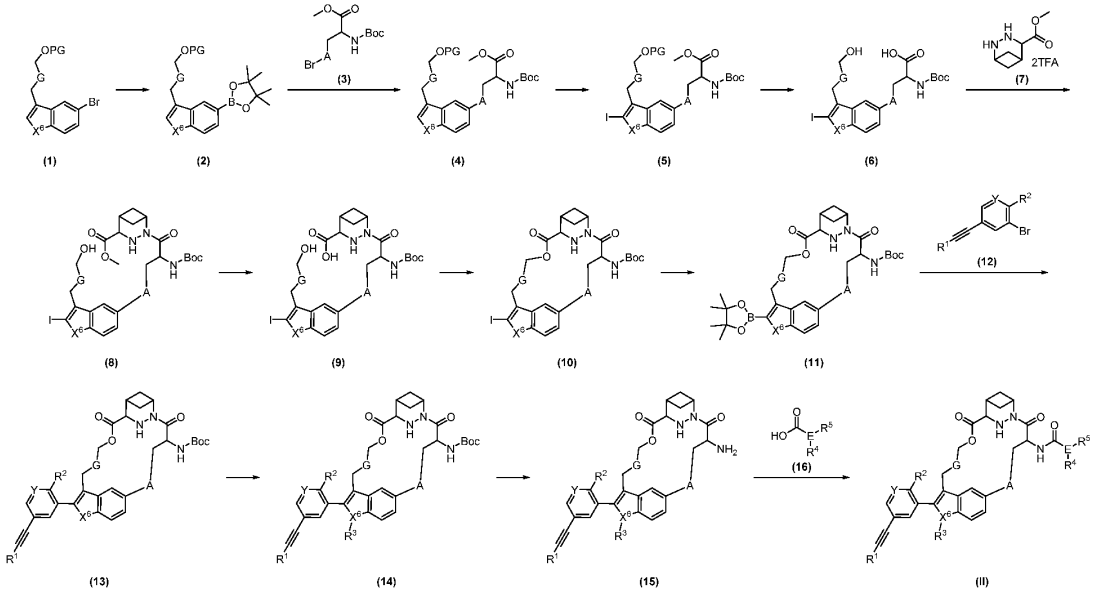
Methods of Synthesis

The compounds of the present invention can be prepared by any conventional means. Suitable processes for synthesizing these compounds as well as their starting materials are provided in the schemes be-

low and in the examples. All substituents are as defined above unless otherwise indicated. Furthermore, and unless explicitly otherwise stated, all reactions, reaction conditions, abbreviations and symbols have the meanings well known to a person of ordinary skill in organic chemistry.

General synthetic procedure for preparing compounds as formula (II) are shown in **Scheme 1**:

Scheme 1

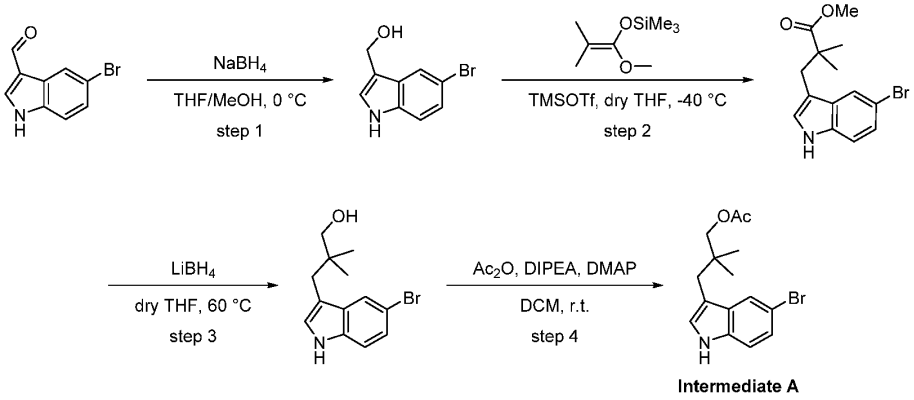


Scheme 1 illustrates the preparation of compound of formula (II). At first the coupling of compounds of formula (1) can be obtained through standard Suzuki coupling conditions (for example $Pd(dppf)Cl_2$ and K_2CO_3) to provide compound of formula (2). Compound of formula (2) was coupled with compound of formula (3) under Suzuki coupling conditions (for example $Pd(dppf)Cl_2$ and K_2CO_3) to give compound of formula (4), which was converted to compound of formula (5) in the presence of iodization reagents, such I_2 or NIS. Deprotection of compound of formula (5) to provide compound of formula (6), such as hydrolysis of the ester with LiOH·OH, or with TBAF deprotecting silicon protective group on hydroxyl group. Compound of formula (8) was attained by a routine coupling condition between compound of formula (6) and amine of formula (7) with coupling reagents, such as HATU, EDCI/HOBt or PyBOP etc, in the presence of an organic base, such as Et_3N, DIPEA or pyridine, which was hydrolyzed to provide acid of formula (9) under a base, such as LiOH·OH. The intramolecular coupling of compound of formula (9) with coupling reagents, such as EDCI/HOBt and HATU, to give compound of formula (10). Then the coupling of compounds of formula (10) can be obtained through standard Suzuki coupling conditions (for example $Pd(dppf)Cl_2$ and K_2CO_3) to provide compound of formula (11). Compound of formula (11) was coupled with compound of formula (12) under Suzuki coupling conditions (for example $Pd(dppf)Cl_2$ and K_2CO_3) to give compound of formula (13), which was converted to compound of formula (14) with alkylate reagents, such iodomethane or iodoethane, in the presence of an inorganic base, such as Cs_2CO_3. Deprotection of compound (14) can afford compound of formula (15) in the presence of an acid, such as TFA. Compound of formula (II) can be obtained by a coupling reaction between acid of formula (16) and compound of formula (15) with coupling reagents, such as HATU, EDCI/HOBy, PyBOP or COMU, in the presence of a

base, such as TEA, DIPEA, pyridine or 2,6-lutidine.

Preparation of Intermediate

Intermediate A: 3-(5-bromo-1H-indol-3-yl)-2,2-dimethylpropyl acetate



Intermediate A

Step 1. Preparation of (5-bromo-1H-indol-3-yl)methanol

To a solution of 5-bromo-1H-indole-3-carbaldehyde (100.0 g, 0.45 mol) in premixed solvents THF/MeOH (1 L, V: V = 4:1) was stirred at 0°C for 5 mins, then $NaBH_4$ (20.0g, 0.53 mol) was added into the above solution at room temperature. The resulting mixture was stirred at 0°C for 2h. The reaction was monitored by LCMS. After completion, the reaction mixture was quenched with H_2O (300 mL) dropwise and diluted with EtOAc (100 mL), then the resulting mixture was extracted with EtOAc (100 mL x 4). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated to give the crude product (5-bromo-1H-indol-3-yl)methanol (107.5g, 98%) as a white solid. The crude product was proceeded to the next reaction without purification.

LCMS (ESI) calcd. for C_9H_8BrNO $[M-H]^+$ m/z 224.07, found: 224.10

Step 2. Preparation of methyl 3-(5-bromo-1H-indol-3-yl)-2,2-dimethylpropanoate

To a solution of ((1-methoxy-2-methylprop-1-en-1-yl)oxy)trimethylsilane (157.3 g, 0.90 mol) in dry THF (150 mL) under N_2 atmosphere, the reaction mixture was stirred at -40°C for 5 mins, then (5-bromo-1H-indol-3-yl)methanol (107.5 g, 0.48 mol) in dry THF (50 mL) was added under N_2 atmosphere, After 10 mins, TMSOTf (90.0 g, 0.40 mol) in dry THF (50 mL) was added into the above solution by dropwise at nitrogen atmosphere. The reaction mixture was stirred at this temperature for 2h. The reaction was monitored by LCMS. After completion, the reaction mixture was warmed to room temperature and diluted with $NaHCO_3$ solution (100 mL), then the resulting mixture was extracted with EtOAc (100 mL x 4). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated to give the crude product, which was further purified by silica gel chromatography eluting with petroleum ether/EtOAc (from 0% to 20%) to obtain methyl 3-(5-bromo-1H-indol-3-yl)-2,2-dimethylpropanoate (98g, 70%) as a yellow solid.

LCMS (ESI) calcd. for $C_{14}H_{16}BrNO_2$ $[M+H]^+$ m/z 310.19, found: 310.20

Step 3. Preparation of 3-(5-bromo-1H-indol-3-yl)-2,2-dimethylpropan-1-ol

To a solution of methyl 3-(5-bromo-1H-indol-3-yl)-2,2-dimethylpropanoate (98g, 0.32 mol) and $LiBH_4$ (40g, 1.82 mol) was added in dry THF (300 mL) at room temperature, the reaction mixture was stirred at 80°C for 12h. The reaction was monitored by LCMS. After completion, the reaction mixture was

cooled to room temperature, quenched with NH_4Cl solution (150 mL) and diluted with EtOAc (100 mL), then the resulting mixture was extracted with EtOAc (100 mL x 4). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated to give the crude product 3-(5-bromo-1H-indol-3-yl)-2,2-dimethylpropan-1-ol (91.3g, 99%) as a light-yellow solid. The crude product was proceeded to the next reaction without purification.

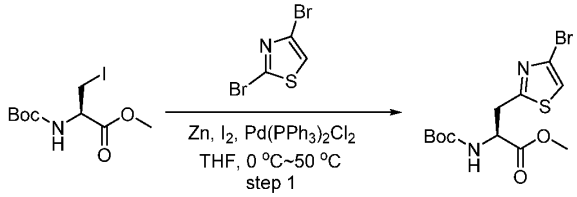
LCMS (ESI) calcd. for $C_{13}H_{16}BrNO$ $[M+H]^+$ m/z 282.18, found: 282.40

Step 4. Preparation of 3-(5-bromo-1H-indol-3-yl)-2,2-dimethylpropyl acetate

To a solution of 3-(5-bromo-1H-indol-3-yl)-2,2-dimethylpropan-1-ol (91.3g, 0.31 mol) in dry DCM (150 mL) at room temperature under N_2 atmosphere, then DIPEA (62.7g, 0.49 mol), DMAP (4.0g, 0.03 mol) and AC_2O (24.0 g, 0.31 mol) was added into the above solution under N_2 atmosphere. The reaction mixture was stirred at room temperature for 3h. The reaction was monitored by LCMS. After completion, The reaction mixture was diluted with $NaHCO_3$ solution (100 mL), then the resulting mixture was extracted with DCM (100 mL x 4), the combined organic phase was washed with saturated NaCl (50 mL), then died over with Na_2SO_4, following with concentration under reduced pressure to obtain crude one, which was purified by silica gel column eluting with petroleum ether/EtOAc (from 0% to 20%) to afford 3-(5-bromo-1H-indol-3-yl)-2,2-dimethylpropyl acetate (82.0 g, 79%) as a white solid.

LCMS (ESI) calcd. for $C_{15}H_{18}BrNO_2$ $[M+H]^+$ m/z 324.22, found: 324.60

Intermediate B: methyl (S)-3-(4-bromothiazol-2-yl)-2-((tert-butoxycarbonyl)amino)propanoate



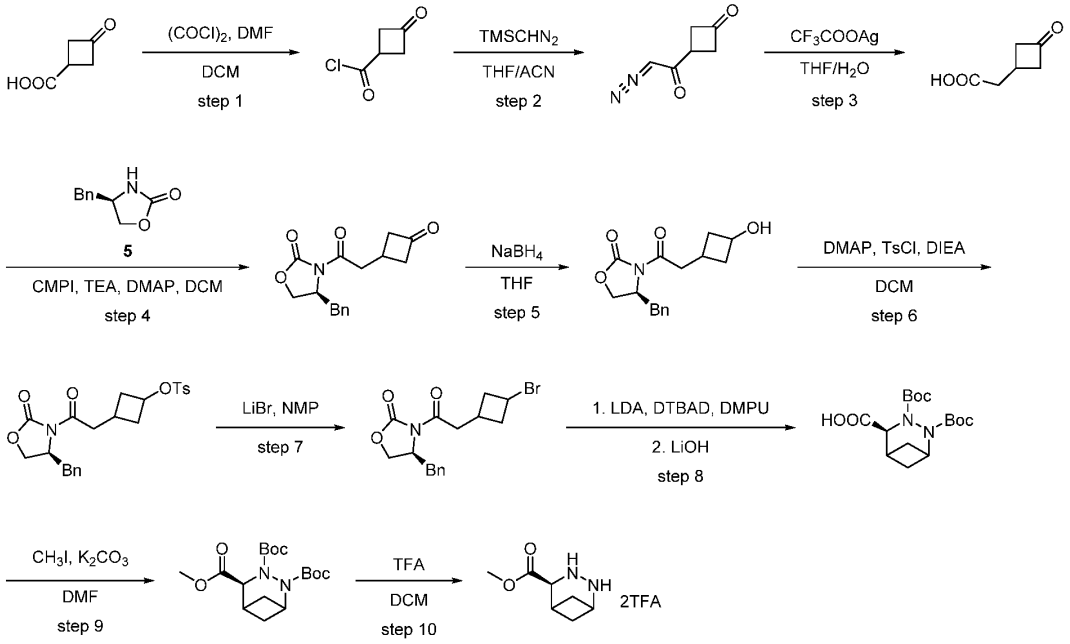
Intermediate B

Step 1. Preparation of methyl (S)-3-(4-bromothiazol-2-yl)-2-((tert-butoxycarbonyl)amino)propanoate

To a solution of activated Zn dust (22 g, 334 mmol) and DMF (100 mL) was added to a 250 mL three-necked round-bottomed flask and purged with N_2, then a solution of I_2 (1.5 g, 6.08 mmol) in DMF (5 mL) was added to the above solution. The mixture was stirred for 10 min at rt, then a solution of methyl (R)-2-((tert-butoxycarbonyl)amino)-3-iodopropanoate (20 g, 60.79 mmol) in DMF (200 mL) was added dropwise over a period of 10 min. The mixture was heated at 35°C and stirred for 2 h, then the reaction was cooled to rt. Transfer the liquid to another 500 mL three-necked round-bottomed flask and purged with N_2, and a solution of $Pd(PPh_3)Cl_2$ (2.1 g, 3.04 mmol) and 2,4-dibromothiazole 2 (17.7 g, 72.95 mmol) in DMF (100 mL) was added dropwise over a period of 10 min. The reaction was stirred at 50°C for 16 h under N_2 atmosphere, the reaction was monitored by LCMS. After completion, the reaction mixture was diluted with brine and extracted with EtOAc (2 x 500 mL). The organic layers were combined, washed with saturated NaCl (2 x 500 mL), dried over anhydrous Na_2SO_4 and concentrated to give the crude product. The crude product was purified by silica gel column chromatography purified by silica gel column eluting with EtOAc/PE from 0% to 25% to afford methyl (S)-3-(4-bromothiazol-2-yl)-2-((tert-butoxycarbonyl)amino)propanoate (10 g, 45.2 %) as a yellow solid.

LCMS (ESI) calcd. for $C_{12}H_{17}BrN_2O_4S$ $[M+H]^+$ m/z 365.01, found: 367.3

Intermediate C: (S)-4-(methoxycarbonyl)-2,3-diazabicyclo[3.1.1]heptan-2-ium 2,2,2-trifluoroacetate



Intermediate C

Step 1. Preparation of 3-oxocyclobutane-1-carbonyl chloride

To a stirred solution of 3-oxocyclobutane-1-carboxylic acid (50 g, 438.60 mmol) in DCM (500 mL) and DMF (321 mg, 4.39 mmol) was added $(COCl)_2$ (83.51 g, 657.89 mmol), the resulting mixture was stirred at rt for 3 h. The reaction mixture was concentrated under reduced pressure to give the crude product. The crude product was used to next step without purification.

LCMS (ESI) calcd. for $C_5H_5ClO_2$ $[M+H]^+$ m/z 133.00, found: 133.4

Step 2. Preparation of 3-(2-diazoacetyl)cyclobutan-1-one

To a stirred solution of crude 3-oxocyclobutane-1-carbonyl chloride in THF (250 mL) and CH_3CN (250 mL) was added $TMSCHN_2$ (2M in hexanes, 285 mL, 570.18 mmol) dropwisely at 0°C. The resulting mixture was stirred at rt for 18 h. After completion, the reaction solution was concentrated under reduced pressure to give the residual, the residual was purified by silica gel column (eluting with EtOAc/PE from 0% to 50%) to afford 3-(2-diazoacetyl)cyclobutan-1-one (60.2 g, 99.5 %) as a yellow oil.

LCMS (ESI) calcd. for $C_6H_6N_2O_2$ $[M+H]^+$ m/z 139.04, found: 139.4

Step 3. Preparation of 2-(3-oxocyclobutyl)acetic acid

To a stirred solution of CF_3COOAg (4.82 g, 21.81 mmol) in THF (300 mL), H_2O (30 mL) and TEA (181.91 mL, 1.31 mol) was added a solution of 3-(2-diazoacetyl)cyclobutan-1-one (60.20 g, 436.23 mmol) in THF (300 mL) and H_2O (30 mL) at 0°C, the reaction mixture was stirred at rt for 18 h. After completion, the reaction solution was concentrated under reduced pressure to give the residual, the residual was diluted with H_2O and acidified with HCl (2N) to pH = 2. The resuliting mixture was extracted with EtOAc (5*300 mL). The organic layers were combined and dried over Na_2SO_4, following with concentration under reduced pressure to afford crude 2-(3-oxocyclobutyl)acetic acid (55. 8g, 99.9 %) as a brown oil.

LCMS (ESI) calcd. for $C_6H_8O_3$ $[M+H]^+$ m/z 129.13, found: 129.4

Step 4. Preparation of (S)-4-benzyl-3-(2-(3-oxocyclobutyl)acetyl)oxazolidin-2-one

To a stirred solution of 2-(3-oxocyclobutyl)acetic acid (52.0 g, 406.3 mmol), (*S*)-4-benzyloxazolidin-2-one (71.9 g, 406.3 mmol), 4-Dimethylaminopyridine (5.0 g, 40.6 mmol) and triethylamine (141.2 mL, 1015.6 mmol) in DCM (1 L) was added 2-Chloro-1-methylpyridinium iodide (135.0 g, 528.1 mmol) in portions at 0°C . The reaction mixture was stirred at R.T. for 4 h. After completion, the reaction solution was diluted with H_2O and extracted with DCM, the combined organic phase was washed with H_2O dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column (eluting with EA/PE from 0% to 20%) to give (*S*)-4-benzyl-3-(2-(3-oxocyclobutyl)acetyl)oxazolidin-2-one (68 g 58.3 %) as a yellow oil.

LCMS (ESI) calcd. for $C_{16}H_{17}NO_4$ $[M+H]^+$ m/z 288.1, found: 288.5

Step 5. Preparation of (S)-4-benzyl-3-(2-(3-hydroxycyclobutyl)acetyl)oxazolidin-2-one

To a stirred solution of (S)-4-benzyl-3-(2-(3-oxocyclobutyl)acetyl)oxazolidin-2-one (45.0 g, 156.8 mmol) in THF (500 mL) was added AcOH (17.9 mL, 313.6 mmol) and $NaBH_4$ (6.5 g, 172.5 mmol) in portions at 0°C. The reaction mixture was stirred at r.t. for 2 h. After completion, the reaction solution was diluted with H_2O then concentrated under reduced pressure to remove THF. The residual was extracted with EtOAc, the combined organic phase was dried over Na_2SO_4, following with concentration under reduced pressure to obtain (*S*)-4-benzyl-3-(2-(3-hydroxycyclobutyl)acetyl)oxazolidin-2-one (45 g, 99.3 %) as a light yellow oil.

LCMS (ESI) calcd. for $C_{16}H_{19}NO_4$ $[M+H]^+$ m/z 290.1, found: 290.5

Step 6. Preparation of (S)-3-(2-(4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)cyclobutyl 4-methylbenzenesulfonate

To a stirred solution of (*S*)-4-benzyl-3-(2-(3-hydroxycyclobutyl)acetyl)oxazolidin-2-one (48.0 g, 156.8 mmol) and DIEA (43.3 g, 249.1 mmol) in DCM (500 mL) was added 4-Dimethylaminopyridine (16.2 g, 132.9 mmol) and Tosyl chloride (34.8 g, 182.7 mmol) at 0°C. The reaction mixture was stirred at r.t. for 14 h. After completion, the reaction solution was diluted with H_2O and extracted with DCM, the combined organic phase was washed with H_2O dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column (eluting with EA/PE from 0% to 30%) to give (*S*)-3-(2-(4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)cyclobutyl 4-methylbenzenesulfonate (62.0 g, 84.3 %) as a yellow oil.

LCMS (ESI) calcd. for $C_{23}H_{25}NO_6S$ $[M+H]^+$ m/z 444.1, found: 444.6

Step 7. Preparation of (S)-4-benzyl-3-(2-(3-bromocyclobutyl)acetyl)oxazolidin-2-one

To a stirred solution of (*S*)-3-(2-(4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)cyclobutyl 4-methylbenzenesulfonate (62.0 g, 139.8 mmol) in N-Methyl-2-pyrrolidone (650 mL) was added Lithium bromide (24.3 g, 279.6 mmol), the resulting mixture was stirred at 65°C for 13 h. The reaction was monitored by LCMS. After completion, the reaction solution was diluted with H_2O and extracted with EtOAc, the combined organic phase was washed with NaCl (aq.) dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column (eluting with EA/PE from 0% to 20%) to give (*S*)-4-benzyl-3-(2-(3-bromocyclobutyl)acetyl)oxazolidin-2-one (42 g, 85.3 %) as a light yellow oil.

LCMS (ESI) calcd. for $C_{16}H_{18}BrNO_3$ $[M+H]^+$ m/z 352.0, found: 352.5

Step 8. Preparation of (S)-2,3-bis(tert-butoxycarbonyl)-2,3-diazabicyclo[3.1.1]heptane-4-carboxylic acid

To a stirred solution of (*S*)-4-benzyl-3-(2-(3-bromocyclobutyl)acetyl)oxazolidin-2-one (30.0 g, 85.5 mmol) in THF (300 mL) was added LDA (2M in THF, 111.0 mmol) was added dropwise over a period of 15 minutes at -78°C under N_2 condition. The reaction mixture was stirred at -78°C for 30 mins, then a solution of Di-tert-Butyl azodicarboxylate (23.6 g, 102.6 mmol) in DCM (50 mL) was added rapidly. The reaction mixture was stirred at -78°C for 30 mins, then 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (310 mL, 2565.0 mmol) was added dropwise at -78°C. The reaction mixture was stirred at r.t. for 14 h. After completion, the reaction solution was quenched with water (200 mL), then $LiOH·H_2O$ (10.8 g, 256.5 mmol) was added and the reaction solution was stirred at r.t. for 2 h. After completion, the reaction solution was diluted with brine (200 mL) and washed with tert-Butyl methyl ether 2 times, the aqueous phase was acidified to pH = 3-4 with 2 N HCl. The resulting mixture was extracted with EtOAc, washed with water and brine, then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product (*S*)-2,3-bis(tert-butoxycarbonyl)-2,3-diazabicyclo[3.1.1]heptane-4-carboxylic acid, which was used directly for the next step.

LCMS (ESI) calcd. for $C_{16}H_{26}N_2O_6$ $[M+H]^+$ m/z 343.39, found: 343.5

Step 9. Preparation of 2,3-di-tert-butyl 4-methyl (S)-2,3-diazabicyclo[3.1.1]heptane-2,3,4-tricarboxylate

To a stirred solution of crude product (*S*)-2,3-bis(tert-butoxycarbonyl)-2,3-diazabicyclo[3.1.1]heptane-4-carboxylic acid (27.0 g, 78.9 mmol) in DMF (300 mL) was added K_2CO_3 (27.3 g, 197.4 mmol) and Iodomethane (10 mL, 157.8 mmol) at r.t.. The reaction mixture was stirred at r.t. for 2 h. After completion, the reaction solution was concentration under reduced pressure to obtain crude product which was purified by silica gel column (eluting with EA/PE from 0% to 23%) to give 2,3-di-tert-butyl 4-methyl (*S*)-2,3-diazabicyclo[3.1.1]heptane-2,3,4-tricarboxylate (5.6 g, 18.45 % in two-steps) as a light yellow oil.

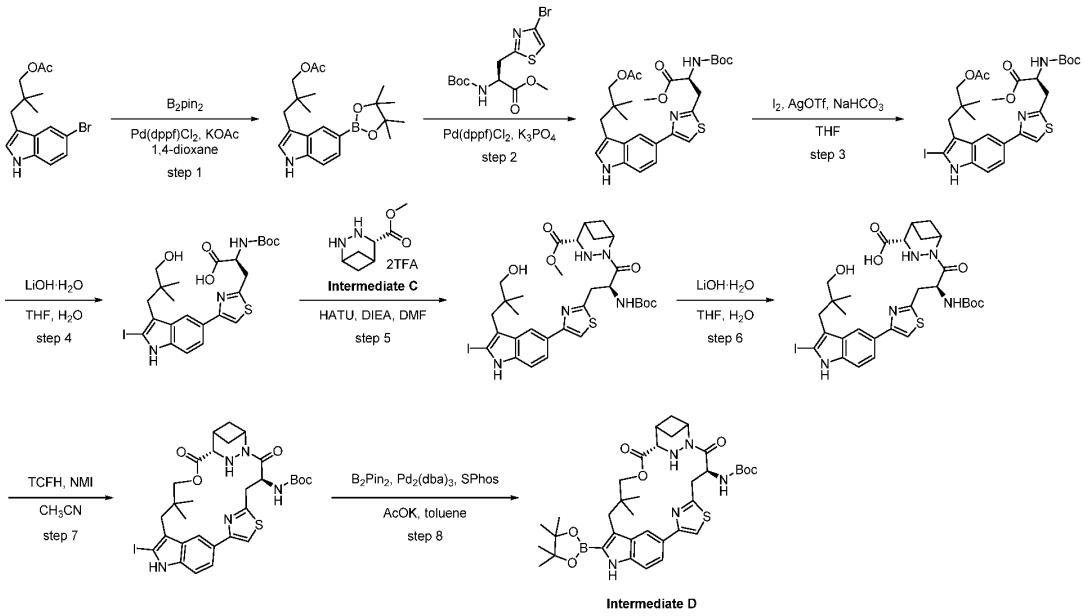
LCMS (ESI) calcd. for $C_{17}H_{28}N_2O_6$ $[M-H]^-$ m/z 357.2, found: 357.6

Step 10. Preparation of (S)-4-(methoxycarbonyl)-2,3-diazabicyclo[3.1.1]heptan-2-ium 2,2,2-trifluoroacetate

To a stirred solution of 2,3-di-tert-butyl 4-methyl (*S*)-2,3-diazabicyclo[3.1.1]heptane-2,3,4-tricarboxylate (7.3 g, 0.18 mmol) in DCM (100 mL) was added TFA (40 mL), the resulting mixture was stirred at rt for 2 h. The reaction mixture was concentrated to give the crude product (*S*)-4-(methoxycarbonyl)-2,3-diazabicyclo[3.1.1]heptan-2-ium 2,2,2-trifluoroacetate (7.2 g) as a yellow solid.

LCMS (ESI) calcd. for $C_{15}H_{23}BO_4$ $[M+H]^+$ m/z 157.09, found: 157.4

Intermediate D: tert-butyl ((6^{3}S,4S,Z)-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)carbamate



Step 1. Preparation of 2,2-dimethyl-3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3-yl)propyl acetate

To a stirred solution of 3-(5-bromo-1H-indol-3-yl)-2,2-dimethylpropyl acetate (20 g, 61.92 mmol) in 1,4-dioxane (400 mL) was added Pd(dppf)Cl_2 (2.2 g, 3.10 mmol) and KOAc (18.4 g, 185.76 mmol). The reaction was stirred at 90°C for 16 h under N_2 atmosphere, the reaction was monitored by LCMS. After completion, the reaction solution was concentrated under reduced pressure to remove 1,4-dioxane, the residual was diluted with H_2O and extracted with EtOAc (500 mL x 3), the combined organic phase was washed with saturated NaCl (500 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column eluting with EtOAc/PE from 0% to 27% to afford 2,2-dimethyl-3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3-yl)propyl acetate (18.7 g, 81.4 %) as a light yellow solid.

LCMS (ESI) calcd. for $C_{21}H_{30}BNO_4$ $[M+H]^+$ m/z 372.23, found: 372.5

Step 2. Preparation of methyl (S)-3-(4-(3-(3-acetoxy-2,2-dimethylpropyl)-1H-indol-5-yl)thiazol-2-yl)-2-((tert-butoxycarbonyl)amino)propanoate

To a stirred solution of 2,2-dimethyl-3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3-yl)propyl acetate (18.7 g, 50.40 mmol), methyl (S)-3-(4-bromothiazol-2-yl)-2-((tert-butoxycarbonyl)amino)propanoate (27.5 g, 75.61 mmol) and K_3PO_4 (26.7 g, 126.01 mmol) in toluene/1,4-dioxane/H_2O (300 mL, V:V:V = 4:1:1) was added Pd(dppf)Cl_2 (1.6 g, 2.52 mmol) at rt. The reaction mixture was stirred at 70°C under N_2 for 16 h. After completion, the reaction solution was concentrated under reduced pressure to remove 1,4-dioxane and toluene, the residual was diluted with H_2O and extracted with EtOAc (500 mL x 3), the combined organic phase was washed with saturated NaCl (500 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column eluting with

EtOAc/PE from 0% to 36% to afford methyl (S)-3-(4-(3-(3-acetoxy-2,2-dimethylpropyl)-1H-indol-5-yl)thiazol-2-yl)-2-((tert-butoxycarbonyl)amino)propanoate (20.7 g, 77.6 %) as a light yellow solid.

LCMS (ESI) calcd. for $C_{27}H_{35}N_3O_6S$ $[M+H]^+$ m/z 530.22, found: 530.6

Step 3. Preparation of methyl (S)-3-(4-(3-(3-acetoxy-2,2-dimethylpropyl)-2-iodo-1H-indol-5-yl)thiazol-2-yl)-2-((tert-butoxycarbonyl)amino)propanoate

To a stirred solution of methyl (S)-3-(4-(3-(3-acetoxy-2,2-dimethylpropyl)-1H-indol-5-yl)thiazol-2-yl)-2-((tert-butoxycarbonyl)amino)propanoate (12.3 g, 23.25 mmol) and $NaHCO_3$ (2.3 g, 27.90 mmol) in THF (150 mL) under ice-water bath was added $AgSO_3CF_3$ (7.2 g, 27.90 mmol) in THF (50 mL) and I_2 (5.0 g, 19.76 mmol) in THF (50 mL) by dropwise to the reaction mixture. The reaction was stirred at -20°C for 1 h, the reaction was monitored by LCMS. After completion, The reaction was quenched with saturated $Na_2S_2O_3$ (200 mL) and was extracted with EtOAc (500 mL x 2), the combined organic phase was washed with saturated NaCl (500 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column eluting with EtOAc/PE from 0% to 40% to afford methyl (S)-3-(4-(3-(3-acetoxy-2,2-dimethylpropyl)-2-iodo-1H-indol-5-yl)thiazol-2-yl)-2-((tert-butoxycarbonyl)amino)propanoate (12.0 g, 78.8 %) as a light yellow solid.

LCMS (ESI) calcd. for $C_{27}H_{34}IN_3O_6S$ $[M+H]^+$ m/z 656.12, found: 656.5

Step 4. Preparation of (S)-2-((tert-butoxycarbonyl)amino)-3-(4-(3-(3-hydroxy-2,2-dimethylpropyl)-2-iodo-1H-indol-5-yl)thiazol-2-yl)propanoic acid

To a solution of methyl (S)-3-(4-(3-(3-acetoxy-2,2-dimethylpropyl)-2-iodo-1H-indol-5-yl)thiazol-2-yl)-2-((tert-butoxycarbonyl)amino)propanoate (25 g, 38.17 mmol) in THF (500 mL) and H_2O (100 mL) was added $LiOH·H_2O$ (4.6 g, 190.84 mmol) at 0-10°C, the resulting mixture was stirred at 0-10°C for 16 h. The reaction was monitored by LCMS. After completion, the reaction mixture was acidified to pH = 3-4 with 2 N HCl. The resulting mixture was extracted with EtOAc (300 mL x 2), the combined organic phase was washed with saturated NaCl (500 mL), then dried over Na_2SO_4 and concentrated to give the (S)-2-((tert-butoxycarbonyl)amino)-3-(4-(3-(3-hydroxy-2,2-dimethylpropyl)-2-iodo-1H-indol-5-yl)thiazol-2-yl)propanoic acid (22.8 g, 100 %) as a light yellow solid.

LCMS (ESI) calcd. for $C_{24}H_{30}IN_3O_5S$ $[M+H]^+$ m/z 599.10, found: 600.6

Step 5. Preparation of (S)-2-((S)-2-((tert-butoxycarbonyl)amino)-3-(4-(3-(3-hydroxy-2,2-dimethylpropyl)-2-iodo-1H-indol-5-yl)thiazol-2-yl)propanoyl)-2,3-diazabicyclo[3.1.1]heptane-4-carboxylate

To a solution of (S)-2-((tert-butoxycarbonyl)amino)-3-(4-(3-(3-hydroxy-2,2-dimethylpropyl)-2-iodo-1H-indol-5-yl)thiazol-2-yl)propanoic acid (1.10 g, 1.84 mmol) in DMF (15 mL) were added HATU (1.04 g, 2.75 mmol) and DIEA (1.30 mL, 7.35 mmol) at 0-10°C. The resulting mixture was stirred at 0-10°C for 10 min. Then me-

thyl (*S*)-2,3-diazabicyclo[3.1.1]heptane-4-carboxylate (472 mg, 1.84 mmol) was added into the reaction mixture, the resulting mixture was stirred at rt for 2 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with brine and extracted with EtOAc (2 x 400 mL), the combined organic phase was washed with saturated NaCl (500 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column eluting with EtOAc/PE from 0% to 60% to afford methyl (S)-2-((S)-2-((tert-butoxycarbonyl)amino)-3-(4-(3-(3-hydroxy-2,2-dimethylpropyl)-2-iodo-1H-indol-5-yl)thiazol-2-yl)propanoyl)-2,3-diazabicyclo[3.1.1]heptane-4-carboxylate (1.23 g, 90.7 %) as a light yellow solid.

LCMS (ESI) calcd. for $C_{31}H_{40}IN_5O_6S$ $[M+H]^+$ m/z 738.2, found: 738.6

Step 6. Preparation of (S)-2-((S)-2-((tert-butoxycarbonyl)amino)-3-(4-(3-(3-hydroxy-2,2-dimethylpropyl)-2-iodo-1H-indol-5-yl)thiazol-2-yl)propanoyl)-2,3-diazabicyclo[3.1.1]heptane-4-carboxylic acid

To a solution of methyl (S)-2-((S)-2-((tert-butoxycarbonyl)amino)-3-(4-(3-(3-hydroxy-2,2-dimethylpropyl)-2-iodo-1H-indol-5-yl)thiazol-2-yl)propanoyl)-2,3-diazabicyclo[3.1.1]heptane-4-carboxylate (1.23 g, 24.53 mmol) in THF (1.23 g, 24.53 mmol) and H_2O (6 mL) was added $LiOH·H_2O$ (210 mg, 5.01 mmol) at 0-10°C, the resulting mixture was stirred at 0-10°C for 2 h. The reaction was monitored by LCMS. After completion, the reaction mixture was acidified to pH = 3-4 with 2 N HCl. The resulting mixture was extracted with EtOAc (300 mL x 2), the combined organic phase was washed with saturated NaCl (500 mL), then dried over Na_2SO_4 and concentrated to give the (S)-2-((S)-2-((tert-butoxycarbonyl)amino)-3-(4-(3-(3-hydroxy-2,2-dimethylpropyl)-2-iodo-1H-indol-5-yl)thiazol-2-yl)propanoyl)-2,3-diazabicyclo[3.1.1]heptane-4-carboxylic acid (1.03 g, 85.3 %) as a light yellow solid.

LCMS (ESI) calcd. for $C_{30}H_{38}IN_5O_6S$ $[M+H]^+$ m/z 724.1, found: 724.9

Step 7. Preparation of tert-butyl ((6^{4}S,4S,Z)-1^2-iodo-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

To a solution of TCFH (994 mg, 3.54 mmol) in ACN (80 mL) was added a solution of (S)-2-((S)-2-((tert-butoxycarbonyl)amino)-3-(4-(3-(3-hydroxy-2,2-dimethylpropyl)-2-iodo-1H-indol-5-yl)thiazol-2-yl)propanoyl)-2,3-diazabicyclo[3.1.1]heptane-4-carboxylic acid 22 (640 mg, 0.89 mmol) and NMI (582 mg, 7.08 mmol) in ACN (48 mL), the reaction was gradually improved temperature to room temperature and stirred for 2 h. The reaction was monitored by LCMS. After completion, the reaction was concentrated under reduced pressure to give crude product which was purified by silica gel column (eluting with EtOAc/PE from 0% to 65% to afford tert-butyl ((64S,4S,Z)-12-iodo-10,10-dimethyl-5,7-dioxo-11H-8-oxa-62,63-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate 23 (199 mg, 31.7 %) as a light yellow solid.

LCMS (ESI) calcd. for C30H36IN5O5S [M+H]+ m/z 706.2, found: 706.8

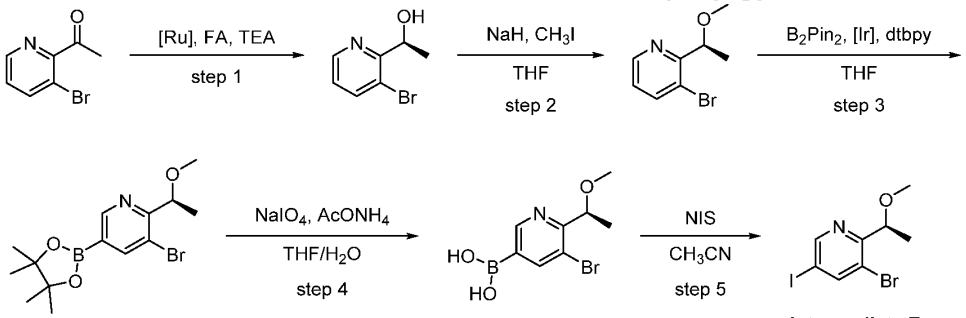
Step 8. Preparation of tert-butyl

((6⁴S,4S,Z)-10,10-dimethyl-5,7-dioxo-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

To a stirred solution of tert-butyl ((6⁴S,4S,Z)-1²-iodo-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (790 mg, 1.12 mmol), $Pd_2(dba)_3$ (154 mg, 0.17 mmol), SPhos (154 mg, 0.17 mmol) and AcOK (495 mg, 5.04 mmol) in toluene was added B_2Pin_2 (1.08 g, 8.40 mmol) at 0°C under N_2 atmosphere. The reaction mixture was stirred at 60°C under N_2 for 3h. After completion, the reaction mixture was concentrated under reduced pressure to give the crude product which was purified by silica gel column (eluting with EtOAc/PE from 0% to 60%) to give crude tert-butyl ((6⁴S,4S,Z)-10,10-dimethyl-5,7-dioxo-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (810 mg) as a pale yellow solid.

LCMS (ESI) calcd. for $C_{36}H_{48}BN_5O_7S$ $[M+H]^+$ m/z 706.3, found: 707.0

Intermediate E: (S)-3-bromo-5-iodo-2-(1-methoxyethyl)pyridine



Intermediate E

Step 1. Preparation of (S)-1-(3-bromopyridin-2-yl)ethan-1-ol

To a stirred solution of TEA (151.76 g, 1.50 mol) was added FA (13.81 g, 299.96 mmol) at 0°C. Then (S,S)-N-(p-Toluenesulfonyl)-1,2-diphenylethanediamine(chloro)(p-cymene)ruthenium(II) (800 mg, 1.25 mmol) was added into the reaction mixture, the resulting mixture was stirred at 40°C under N_2 for 0.5 h. 1-(3-bromopyridin-2-yl)ethan-1-one (25.00 g, 124.98 mmol) was added into the reaction mixture, the resulitng mixture was stirred at 40°C under N_2 for 1 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with EtOAc (500 mL), washed with saturated NH_4Cl (300 x 3 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column (eluting with EtOAc/PE from 0% to 25%) to give (S)-1-(3-bromopyridin-2-yl)ethan-1-ol (28.80 g, 95.0 %) as a yellow oil.

LCMS (ESI) calcd. for C_7H_6BrNO $[M+H]^+$ m/z 200.98, found: 202.1

Step 2. Preparation of (S)-3-bromo-2-(1-methoxyethyl)pyridine

To a stirred solution of (S)-1-(3-bromopyridin-2-yl)ethan-1-ol (23.80 g, 117.82 mmol) in THF (240 mL) was added NaH (60% in oil, 7.07 g, 176.73 mmol) portion wisely at 0°C, the resulting mixture was stirred at 0°C for 1 h. CH_3I (33.45 g, 235.64 mmol) was added into the reaction mixture at 0°C, the resulting mixture was stirred at rt for 15 h. The reaction mixture was quenched with H_2O (50 mL) at 0°C and extracted with EtOAc (2*200 mL). The organic layers were combined, washed with brine, dried over

Na_2SO_4 and concentrated to give the crude product which was purified by silica gel column (eluting with EtOAc/PE from 0% to 25%) to give (S)-3-bromo-2-(1-methoxyethyl)pyridine (23.39 g, 91.9 %) as a light yellow oil.

LCMS (ESI) calcd. for $C_8H_{10}BrNO$ $[M+H]^+$ m/z 214.99, found: 216.3

Step 3. Preparation of (S)-3-bromo-2-(1-methoxyethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine

To a stirred solution of (S)-3-bromo-2-(1-methoxyethyl)pyridine (12.00 g, 55.56 mmol) B_2Pin_2 (15.53 g, 61.11 mmol) in THF (180 mL) was added $[Ir(COD)(OMe)]_2$ (737 mg, 1.11 mmol) and dtbpy (895 mg, 3.33 mmol) at rt , the resulting mixture was stirred at 75°C under N_2 for 23 h. The reaction was monitored by LCMS. After completion, the reaction mixture was concentrated to give the crude product which was purified by silica gel column (eluting with EtOAc/PE from 0% to 80%) to give crude (S)-3-bromo-2-(1-methoxyethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (20.9 g) as an orange oil.

LCMS (ESI) calcd. for $C_{14}H_{21}BBrNO_3$ $[M+H]^+$ m/z 341.08, found: 342.4

Step 4. Preparation of (S)-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)boronic acid

To a stirred solution of crude (S)-3-bromo-2-(1-methoxyethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (16.20 g, 47.51 mmol) in THF (150 mL) and H_2O (150 mL) were added NH_4OAc (14.60 g, 190.03 mmol) and $NaIO_4$ (40.60 g, 190.03 mmol) at 0°C, the resulting mixture was stirred at rt for 3h. The reaction was monitored by LCMS. After completion, the reaction mixture was extracted with EtOAc (2*300 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated to give the crude product which was purified by silica gel column (eluting with EtOAc/PE from 0% to 80%) to give (S)-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)boronic acid (10.98 g, 89.2%) as a yellow solid.

LCMS (ESI) calcd. for $C_8H_{11}BBrNO_3$ $[M+H]^+$ m/z 259.00, found: 260.3

Step 5. Preparation of (S)-3-bromo-5-iodo-2-(1-methoxyethyl)pyridine

To a stirred solution of (S)-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)boronic acid (3.00 g, 11.58 mmol) in CH_3CN (45 mL) was added NIS (3.13 g, 13.90 mmol) at rt, the resulting mixture was stirred at 75°C for 20h. The reaction was monitored by LCMS. After completion, the reaction mixture was quenched with sat. aq. Na_2SO_3 and concentrated to give the residue. The residue was extracted with EtOAc (2*30 mL). The organic layers were combined and washed with brine, then dried over Na_2SO_4 and concentrated to give the crude product which was purified by silica gel column (eluting with EtOAc/PE from 0% to 20%) to give (S)-3-bromo-5-iodo-2-(1-methoxyethyl)pyridine (2.65 g, 67.1%) as a brown solid.

LCMS (ESI) calcd. for $C_8H_9BrINO_3$ $[M+H]^+$ m/z 340.89, found: 342.3

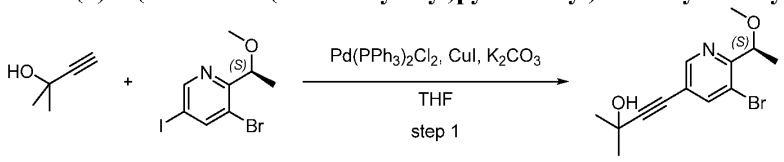
Preparation of compounds

Unless otherwise defined, all technical and scientific terms in the present invention have the same meanings as generally understood by a person skilled in the art to which the invention belongs. In accordance with the general technical knowledge and customary means in the art, under the premise of not departing from the above-mentioned basic technical ideas of the present invention, other forms of modification, replacement or change can also be made.

Unless otherwise stated, the raw materials and reagents used in the following embodiments are commercially available or may be prepared by known methods.

Intermediate of Example 3:

Synthesis of (S)-4-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)-2-methylbut-3-yn-2-ol



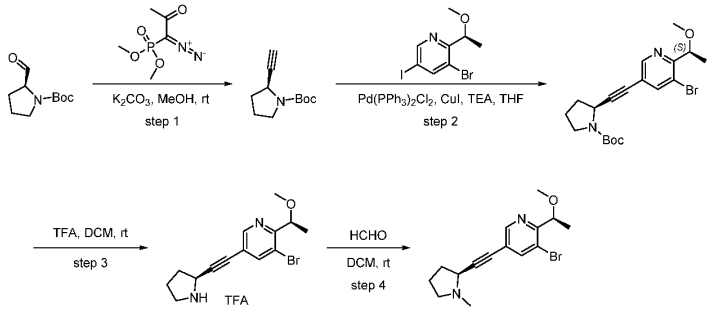
Step 1. Preparation of (S)-4-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)-2-methylbut-3-yn-2-ol

A mixture of (S)-3-bromo-5-iodo-2-(1-methoxyethyl)pyridine (200 mg, 0.59 mmol), 2-methylbut-3-yn-2-ol (99 mg, 1.17 mmol), K_2CO_3 (243 mg, 1.76 mmol), $Pd(PPh_3)_2Cl_2$ (41 mg, 0.059 mmol) and CuI (11 mg, 0.059 mmol) in THF (4.5 mL) was stirred at 65°C under N_2 for 23 h. The reaction was monitored by LCMS. After completion, the reaction mixture was concentrated to give the crude product which was purified by silica gel column (eluting with EtOAc/PE from 0% to 40%) to give (S)-4-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)-2-methylbut-3-yn-2-ol (160 mg, 91.3%) as a brown solid.

LCMS (ESI) calcd. for $C_{13}H_{16}BrNO_2$ $[M+H]^+$ m/z 297.04, found: 298.4

Intermediate of Example 4:

Synthesis of 3-bromo-2-((S)-1-methoxyethyl)-5-(((S)-1-methylpyrrolidin-2-yl)ethynyl)pyridine



Step 1: Synthesis of tert-butyl (S)-2-ethynylpyrrolidine-1-carboxylate

To a stirred solution of tert-butyl (S)-2-formylpyrrolidine-1-carboxylate (2.0 g, 10.05 mmol) in MeOH (40 mL) was added K_2CO_3 (3.5 g, 25.13 mmol) and Dimethyl (1-Diazo-2-oxopropyl)phosphonate (2.3 g, 12.06 mmol) at r.t.. The reaction mixture was stirred at r.t. for overnight. After completion, the reaction solution was concentrated under reduced pressure to remove MeOH, the residual was diluted with H_2O and extracted with EtOAc, the combined organic phase was dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column (eluting with EA/PE from 0% to 20%) to give tert-butyl (S)-2-ethynylpyrrolidine-1-carboxylate (1.7 g, 86.7 %) as a colourless oil.

LCMS (ESI) calcd. for $C_{11}H_{17}NO_2$ $[M+H]^+$ m/z 195.1, found: 196.3.

Step 2: Synthesis of tert-butyl (S)-2-((5-bromo-6-((S)-1-methoxyethyl)pyridin-3-yl)ethynyl)pyrrolidine-1-carboxylate

To a stirred solution of tert-butyl (S)-2-ethynylpyrrolidine-1-carboxylate (1.7 g, 8.72 mmol), (S)-3-bromo-5-iodo-2-(1-methoxyethyl)pyridine (2.5 g, 7.26 mmol), $Pd(PPh_3)_2Cl_2$ (509 mg, 0.73 mmol)

and CuI (277 mg, 1.45 mmol) in 1,4-dioxane (40 mL) was added TEA (4 mL, 29.04 mmol) at r.t.. The reaction mixture was stirred at 35°C under N_2 for 8 h. After completion, the reaction solution was concentrated under reduced pressure to remove 1,4-dioxane, the residual was diluted with H_2O and extracted with EtOAc, the combined organic phase was dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column (eluting with EA/PE from 0% to 30%) to give tert-butyl (S)-2-((5-bromo-6-((S)-1-methoxyethyl)pyridin-3-yl)ethynyl)pyrrolidine-1-carboxylate (2.8 g, 93.6 %) as a light yellow oil.

LCMS (ESI) calcd. for $C_{19}H_{25}BrN_2O_3$ $[M+H]^+$ m/z 409.1, found: 310.9.

Step 3: Synthesis of 3-bromo-2-((S)-1-methoxyethyl)-5-(((S)-pyrrolidin-2-yl)ethynyl)pyridine

To a stirred solution of tert-butyl (S)-2-((5-bromo-6-((S)-1-methoxyethyl)pyridin-3-yl)ethynyl)pyrrolidine-1-carboxylate (2.8 g, 6.84 mmol) in dichloromethane (30 mL) was added TFA (10 mL) slowly at r.t., the resulting mixture was stirred at rt for 3 h. The reaction mixture was concentrated to give the crude product 3-bromo-2-((S)-1-methoxyethyl)-5-(((S)-pyrrolidin-2-yl)ethynyl)pyridine (2.8 g, crude) as a yellow oil.

LCMS (ESI) calcd. for $C_{14}H_{17}BrN_2O$ $[M+H]^+$ m/z 309.2, found: 310.6.

Step 4: Synthesis of 3-bromo-2-((S)-1-methoxyethyl)-5-(((S)-1-methylpyrrolidin-2-yl)ethynyl)pyridine

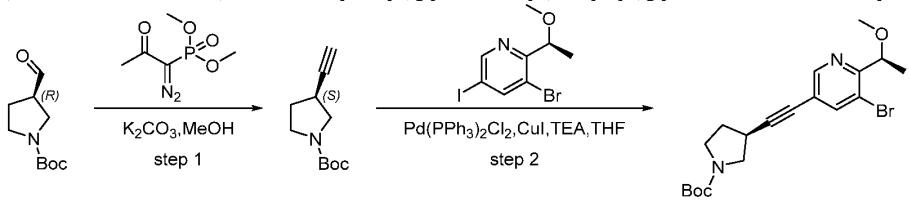
To a stirred solution of (S)-4-(benzyloxy)-1-bromo-2-(1-methoxyethyl)benzene (2.12 g, 6.84 mmol) in DCM/MeOH (55 mL, V:V = 5:1) was added Formaldehyde (2.9 g, 37% in water , 35.9 mmol) and AcOH (0.5 mL) at r.t.. The reaction mixture was stirred at r.t. for 5 h, then NaBH3CN (734 mg, 11.7 mmol) was added. The reaction mixture was stirred at r.t. for 2 h. After completion, the reaction solution was diluted with H_2O and extracted with DCM, the combined organic phase was dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column (eluting with DCM/MeOH from 0% to 10%) to give 3-bromo-2-((S)-1-methoxyethyl)-5-(((S)-1-methylpyrrolidin-2-yl)ethynyl)pyridine (2.13 g, 96.1 %) as a light yellow oil.

LCMS (ESI) calcd. for $C_{15}H_{19}BrN_2O$ $[M+H]^+$ m/z 323.1, found: 323.4.

Intermediate of Example 5:

Synthesis of tert-butyl

(S)-3-((5-bromo-6-((S)-1-methoxyethyl)pyridin-3-yl)ethynyl)pyrrolidine-1-carboxylate



Step 1. Preparation of tert-butyl (S)-3-ethynylpyrrolidine-1-carboxylate

To a stirred solution of tert-butyl (R)-3-formylpyrrolidine-1-carboxylate (1 g, 5.0 mmol) and K_2CO_3 (1.4 g, 10.0 mmol) in MeOH (15 mL) was added dimethyl (1-diazo-2-oxopropyl)phosphonate (1.2 g, 6.0 mmol) at RT. The reaction mixture was stirred at RT for 2 h. After completion, the reaction mixture was diluted with EtOAc (50 mL), washed with brine (30 mL), then dried over Na_2SO_4, following with concen-

tration under reduced pressure to obtain crude product tert-butyl (S)-3-ethynylpyrrolidine-1-carboxylate (980 mg) as a yellow oil.

LCMS (ESI) calcd. for $C_{11}H_{17}NO_2$ $[M+H-56]^+$ m/z 140.1, found: 140.4

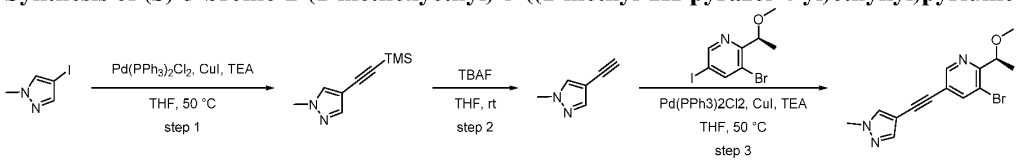
Step 2. Preparation of tert-butyl (S)-3-((5-bromo-6-((S)-1-methoxyethyl)pyridin-3-yl)ethynyl)pyrrolidine-1-carboxylate

A mixture of tert-butyl (S)-3-ethynylpyrrolidine-1-carboxylate (980 mg, 5.0 mmol), (S)-3-bromo-5-iodo-2-(1-methoxyethyl)pyridine (1.7 g, 5.0 mmol), CuI (96 mg, 0.5 mmol) TEA (1.0 g, 10.0 mmol) and $Pd(PPh_3)_2Cl_2$ (352 mg, 0.5 mmol) in THF (20 mL) was stirred at 50°C under N_2 for 2 h. After completion, the reaction mixture was concentrated to give the crude product which was purified by silica gel column (eluting with EA/PE from 0% to 25%) to give tert-butyl (S)-3-((5-bromo-6-((S)-1-methoxyethyl)pyridin-3-yl)ethynyl)pyrrolidine-1-carboxylate (1.8 g, 90 % in 2 steps) as a brown oil.

LCMS (ESI) calcd. for $C_{19}H_{25}BrN_2O_3$ $[M+H]^+$ m/z 409.1, found: 409.6

Intermediate of Example 6:

Synthesis of (S)-3-bromo-2-(1-methoxyethyl)-5-((1-methyl-1H-pyrazol-4-yl)ethynyl)pyridine



Step 1: Synthesis of 1-methyl-4-((trimethylsilyl)ethynyl)-1H-pyrazole

A mixture of 4-iodo-1-methyl-1H-pyrazole (1 g, 4.81 mmol), ethynyltrimethylsilane (708 mg, 7.21 mmol), TEA (1.46 g, 14.42 mmol), $Pd(PPh_3)_2Cl_2$ (337 mg, 0.48 mmol) and CuI (92 mg, 0.48 mmol) in THF (15 mL) was stirred at 50°C under N_2 for 1 h. After completion, the reaction mixture was concentrated to give the crude product which was purified by silica gel column (eluting with EtOAc/PE from 0% to 50%) to give 1-methyl-4-((trimethylsilyl)ethynyl)-1H-pyrazole (500 mg, 58.4%) as a brown solid.

LCMS (ESI) calcd. for $C_9H_{14}N_2Si$ $[M+H]+$ m/z 179.1, found: 179.4.

Step 2: Synthesis of 4-ethynyl-1-methyl-1H-pyrazole

To a stirred solution of 1-methyl-4-((trimethylsilyl)ethynyl)-1H-pyrazole (500 mg, 2.81 mmol)in THF (5mL) was added TBAF (1M in THF, 4.2 mL, 4.2 mmol) dropwisely at rt, the resulting mixture was stirred at rt for 1 h. After completion, the reaction mixture was used to next step without purification.

LCMS (ESI) calcd. for $C_6H_6N_2$ $[M+H]+$ m/z 106.1, found: 107.4.

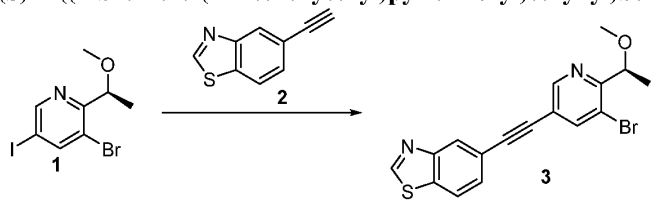
Step 3: Synthesis of (S)-3-bromo-2-(1-methoxyethyl)-5-((1-methyl-1H-pyrazol-4-yl)ethynyl)pyridine

A mixture of (S)-3-bromo-5-iodo-2-(1-methoxyethyl)pyridine (735 mg, 2.16 mmol), 4-ethynyl-1-methyl-1H-pyrazole 3 (300 mg, 2.80 mmol), TEA (654 mg, 6.47 mmol), $Pd(PPh_3)_2Cl_2$ (151 mg, 0.22 mmol) and CuI (41 mg, 0.22 mmol) in THF (6 mL) was stirred at 50°C under N_2 for 2 h. The reaction was monitored by LCMS. After completion, the reaction mixture was concentrated to give the crude product which was purified by silica gel column (eluting with EtOAc/PE from 0% to 50%) to give (S)-3-bromo-2-(1-methoxyethyl)-5-((1-methyl-1H-pyrazol-4-yl)ethynyl)pyridine (379 mg, 55.0%) as a yellow solid.

LCMS (ESI) calcd. for $C_{13}H_{16}BrNO_2$ $[M+H]+$ m/z 320.0, found: 320.5.

Intermediate of Example 8:

Synthesis of (S)-5-((5-bromo-6-(1-methoxyethyl)pyridin-3-yl)ethynyl)benzo[d]thiazole



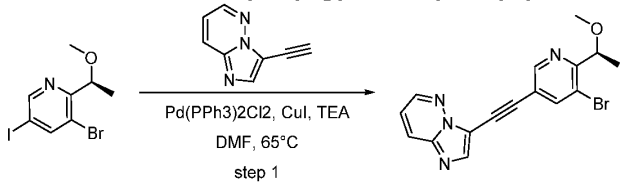
Synthesis of (S)-5-((5-bromo-6-(1-methoxyethyl)pyridin-3-yl)ethynyl)benzo[d]thiazole

To a stirred solution of 5-ethynylbenzo[d]thiazole (100 mg, 0.63 mmol), (S)-3-bromo-5-iodo-2-(1-methoxyethyl)pyridine (178 mg, 0.52 mmol), $Pd(PPh_3)_2Cl_2$ (37 mg, 0.05 mmol) and CuI (20 mg, 0.10 mmol) in 1,4-dioxane (3 mL) was added TEA (0.3 mL, 2.09 mmol) at r.t.. The reaction mixture was stirred at 50°C under N_2 for 4 h. After completion, the reaction solution was concentrated under reduced pressure to remove 1,4-dioxane, the residual was diluted with H_2O and extracted with EtOAc , the combined organic phase was dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column (eluting with EA/PE from 0% to 95%) to give (S)-5-((5-bromo-6-(1-methoxyethyl)pyridin-3-yl)ethynyl)benzo[d]thiazole (190 mg, 80.9%) as a light yellow solid.

LCMS (ESI) calcd. for $C_{17}H_{13}BrN_2OS$ $[M+H]^+$ m/z 373.0, found: 373.4.

Intermediate of Example 9:

Synthesis of (S)-3-((5-bromo-6-(1-methoxyethyl)pyridin-3-yl)ethynyl)imidazo[1,2-b]pyridazine



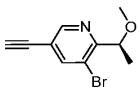
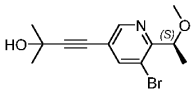
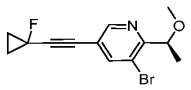
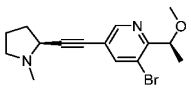
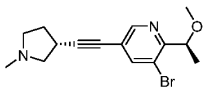
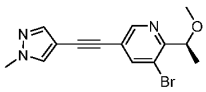
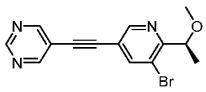
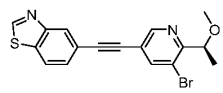
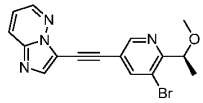
Step 1: Synthesis of (S)-3-((5-bromo-6-(1-methoxyethyl)pyridin-3-yl)ethynyl)imidazo[1,2-b]pyridazine

A mixture of (S)-3-bromo-5-iodo-2-(1-methoxyethyl)pyridine (200 mg, 0.59 mmol), 3-ethynylimidazo[1,2-b]pyridazine 2 (126 mg, 0.88 mmol), CuI (11 mg, 0.059 mmol), TEA (227 mg, 1.76 mmol) and $Pd(PPh_3)_2Cl_2$ (41 mg, 0.059 mmol) in DMF (3 mL) was stirred at 65°C for 1 h under N_2 atmosphere, the reaction was monitored by LCMS. After completion, the mixture was filtered and the filtrate was concentrated, the residue was purified by silica gel column chromatography (eluting with EtOAc/PE from 0% to 100%) to obtain (S)-3-((5-bromo-6-(1-methoxyethyl)pyridin-3-yl)ethynyl)imidazo[1,2-b]pyridazine (200 mg, 95.2%) as a yellow oil.

LCMS (ESI) calcd. for $C_{16}H_{13}BrN_4O$ [M+H]+ m/z 357.0, found 357.4.

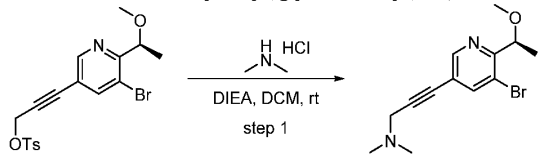
The following intermediates in **Table 2** were prepared using the method described above in step for the preparation of (S)-4-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)-2-methylbut-3-yn-2-ol or tert-butyl (S)-3-((5-bromo-6-((S)-1-methoxyethyl)pyridin-3-yl)ethynyl)pyrrolidine-1-carboxylate and utilizing the appropriate starting materials and modifications.

Table 2. Certain Intermediates containing alkynyl group of the Present invention

Name	Structure	LCMS
(S)-3-bromo-5-ethynyl-2-(1-methoxyethyl)pyridine		$[M+H]^+$ 240.1/242.1
(S)-4-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)-2-methylbut-3-yn-2-ol		$[M+H]^+$ 297.1/299.1
(S)-3-bromo-5-((1-fluorocyclopropyl)ethynyl)-2-(1-methoxyethyl)pyridine		$[M+H]^+$ 298.2/300.2
3-bromo-2-((S)-1-methoxyethyl)-5-(((S)-1-methylpyrrolidin-2-yl)ethynyl)pyridine		$[M+H]^+$ 323.2/325.2
(S)-2-((5-bromo-6-(1-methoxyethyl)pyridin-3-yl)ethynyl)-5-methyl-1,3,4-thiadiazole		$[M+H]^+$ 323.2/325.2
(S)-3-bromo-2-(1-methoxyethyl)-5-((1-methyl-1H-pyrazol-4-yl)ethynyl)pyridine		$[M+H]^+$ 320.2/322.2
(S)-5-((5-bromo-6-(1-methoxyethyl)pyridin-3-yl)ethynyl)pyrimidine		$[M+H]^+$ 318.2/320.2
(S)-5-((5-bromo-6-(1-methoxyethyl)pyridin-3-yl)ethynyl)benzo[d]thiazole		$[M+H]^+$ 373.3/375.3
(S)-3-((5-bromo-6-(1-methoxyethyl)pyridin-3-yl)ethynyl)imidazo[1,2-b]pyrimidine		$[M+H]^+$ 357.2/359.2

Intermediate of Example 10:

Synthesis of (S)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)-N,N-dimethylprop-2-yn-1-amine



Step 1: Synthesis of (S)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)-N,N-dimethylprop-2-yn-1-amine (2)

To a solution of (R)-morpholin-3-ylmethanol (58 mg, 0.71 mmol) in DCM (2 mL) were added DIEA (244 mg, 1.89 mmol) and a solution of (S)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl 4-methylbenzenesulfonate (200 mg, 0.47 mmol) in DCM (2 mL) at rt, the resulting mixture was stirred at rt for 15 h. The reaction was monitored by LCMS. After completion, the mixture was concentrated under reduced pressure to give the residual which was purified by silica gel column chromatography (eluting with MeOH/DCM from 0% to 10%) to give (S)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)-N,N-dimethylprop-2-yn-1-amine (73 mg, yield: 52.5%)

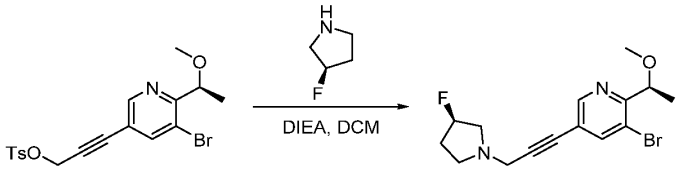
as a brown oil.

LCMS (ESI) calcd. for $C_{13}H_{17}BrN_2O$ [M+H]+ m/z 297.1, found 297.5.

Intermediate of Example 11:

Synthesis of

3-bromo-5-(3-((R)-3-fluoropyrrolidin-1-yl)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridine



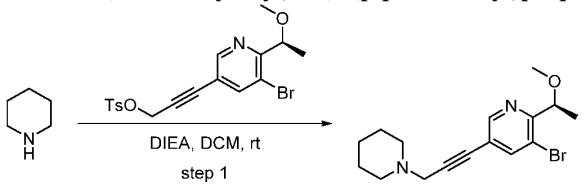
Step 1: Synthesis of 3-bromo-5-(3-((R)-3-fluoropyrrolidin-1-yl)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridine

To a stirred solution of (S)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl 4-methylbenzenesulfonate (350 mg, 0.83 mmol) in DCM (10 mL) was added (R)-3-fluoropyrrolidine (81 mg, 0.91 mmol) and DIEA (170 mg, 1.32 mmol) at r.t. , the resulting mixture was stirred at r.t. for 8 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with DCM/MeOH (30 mL, V:V = 10:1), washed with water (10 mL x 3) and saturated NaCl (10 x 2 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column (eluting with MeOH/DCM from 0% to 5%) to give 3-bromo-5-(3-((R)-3-fluoropyrrolidin-1-yl)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridine (230 mg, 81.5 %) as a lihgt yellow oil.

LCMS (ESI) calcd. for $C_{15}H_{18}BrFN_2O$ $[M+H]^+$ m/z 341.1, found: 341.53.

Intermediate of Example 12:

Synthesis of (S)-3-bromo-2-(1-methoxyethyl)-5-(3-(piperidin-1-yl)prop-1-yn-1-yl)pyridine



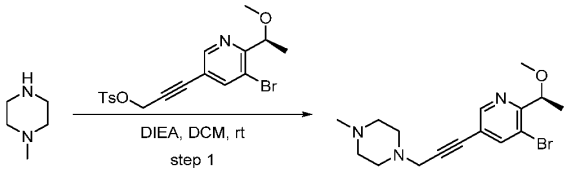
Step 1: Preparation of (S)-3-bromo-2-(1-methoxyethyl)-5-(3-(piperidin-1-yl)prop-1-yn-1-yl)pyridine

A mixture of piperidine (66.2 mg, 0.78 mmol), (S)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl 4-methylbenzenesulfonate (300 mg, 0.71 mmol) in DCM (5 mL) was added DIEA (182.7 mg, 1.4 mmol). The reaction mixture was stirred at rt for 3h. After completion, the mixture was was concentrated under reduced pressure. The residue was purified by FCC with EtOAc/PE = 0-30% to afford the (S)-3-bromo-2-(1-methoxyethyl)-5-(3-(piperidin-1-yl)prop-1-yn-1-yl)pyridine (206 mg, 86%) as a yellow oil.

LCMS (ESI) calcd. for $C_{16}H_{21}BrN_2O$ $[M+H]^+$ m/z 337.1, found 337.6

Intermediate of Example 13:

Synthesis of (S)-1-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)-4-methylpiperazine



Step 1: Preparation of (S)-1-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)-4-methylpiperazine

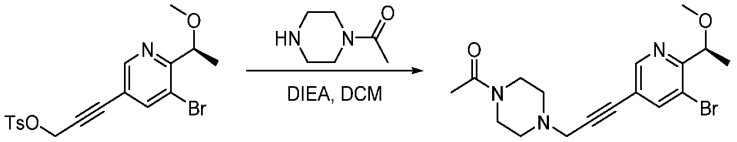
A mixture of 1-methylpiperazine (52 mg, 0.52 mmol), (S)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl 4-methylbenzenesulfonate (200 mg, 0.47 mmol) in DCM (5 mL) was added DIEA (121.5 mg, 0.94 mmol). The reaction mixture was stirred at rt for 3h. After completion, the mixture was was concentrated under reduced pressure. The residue was purified by FCC with MeOH/DCM = 0-6% to afford the (S)-1-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)-4-methylpiperazine (130 mg, 79%) as a yellow oil.

LCMS (ESI) calcd. for $C_{16}H_{22}BrN_3O$ $[M+H]^+$ m/z 352.1, found 352.6.

Intermediate of Example 14:

Synthesis of

(S)-1-(4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)piperazin-1-yl)ethan-1-one



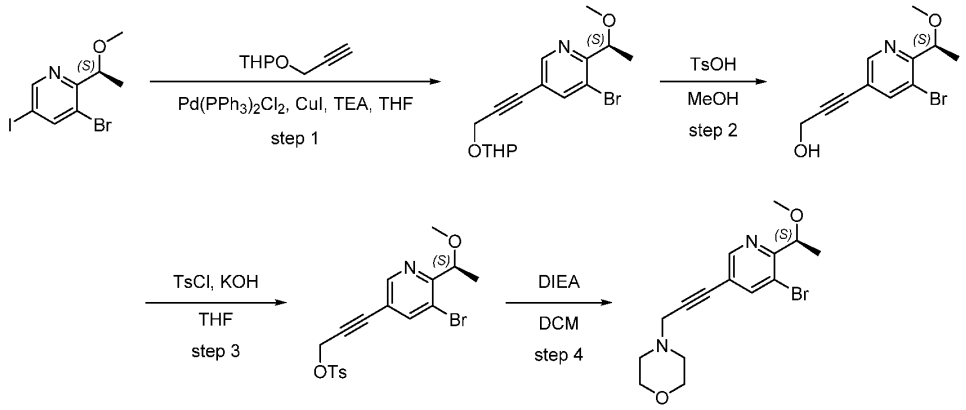
Step 1: Synthesis of (S)-1-(4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)piperazin-1-yl)ethan-1-one

To a stirred solution of (S)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl 4-methylbenzenesulfonate (350 mg, 0.83 mmol) in DCM (10 mL) was added 1-(piperazin-1-yl)ethan-1-one (120 mg, 0.91 mmol) and DIEA (170 mg, 1.32 mmol) at r.t. , the resulting mixture was stirred at r.t. for 8 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with DCM/MeOH (30 mL, V:V = 10:1), washed with water (10 mL x 3) and saturated NaCl (10 x 2 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column (eluting with MeOH/DCM from 0% to 5%) to give (S)-1-(4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)piperazin-1-yl)ethan-1-one (190 mg, 60.4 %) as a lihgt yellow oil.

LCMS (ESI) calcd. for $C_{17}H_{22}BrN_3O_2$ $[M+H]^+$ m/z 380.1, found: 380.5.

Intermediate of Example 15:

Synthesis of (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholine



Step 1. Preparation of 3-bromo-2-((S)-1-methoxyethyl)-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridine

A mixture of (*S*)-3-bromo-5-iodo-2-(1-methoxyethyl)pyridine (10.00 g, 29.24 mmol), 2-(prop-2-yn-1-yloxy)tetrahydro-2H-pyran (4.92 g, 35.09 mmol), CuI (0.45 g, 2.34 mmol), TEA (8.88 g, 8.73 mmol) and $Pd(PPh_3)_2Cl_2$ (1.64 g, 2.34 mmol) in THF (120.00 mL) was stirred at 50°C for 4h under N_2 atmosphere, the reaction was monitored by LCMS. After completion, the mixture was filtered and the filtrate was concentrated, the residue was purified by silica gel column chromatography (eluting with EtOAc/PE, from 0% to 3% in 20 min) to obtain 3-bromo-2-((*S*)-1-methoxyethyl)-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridine (10.10 g, yield: 97.5%) as a yellow oil.

LCMS (ESI) calcd. for $C_{16}H_{20}BrNO_3$ $[M+H]^+$ m/z 354.1, found 354.5.

Step 2. Preparation of (S)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-ol

To a solution of 3-bromo-2-((*S*)-1-methoxyethyl)-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridine (10.10 g, 28.51 mmol) in MeOH (100.00 mL) was added TsOH (19.64 g, 114.05 mmol) at 0°C, the mixture was stirred at room temperature for 5 h under N_2 atmosphere, the reaction was monitored by LCMS. After completion, the mixture was diluted with DCM (50.00 mL) and H_2O (150.00 mL) and extracted with DCM (50 mL x 3), the combined layers were washed with saturated NaCl (150.00 mL), dried over Na_2SO_4, concentrated to obtain (*S*)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-ol (7.10 g, yield: 92.2%) as a yellow oil.

LCMS (ESI) calcd. for $C_{11}H_{12}BrNO_2$ $[M+H]^+$ m/z 270.0, found 270.3.

Step 3. Preparation of (S)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl 4-methylbenzenesulfonate

To a solution of (*S*)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-ol (7.10 g, 26.28 mmol) in THF (100.00 mL) were added TsCl (10.02 g, 52.57 mmol) and KOH (2.95 g, 52.57 mmol) at 0°C, the mixture was stirred at 0°C for 2 h under N_2 atmosphere, the reaction was monitored by LCMS. After completion, the mixture was diluted with EtOAc (50.00 mL) and water (100.00 mL), then extracted with EA (50.00 mL x 3). The combined organic phase was washed with brine (100.00 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residual was purified by silica gel column chromatography (eluting with EtOAc/PE, from 0% to 30% in 30 min) to obtain

(*S*)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl 4-methylbenzenesulfonate (10.50 g, yield: 94.2%) as a brown solid.

LCMS (ESI) calcd. for $C_{18}H_{18}BrNO_4S$ $[M+H]^+$ m/z 424.0, found 424.8.

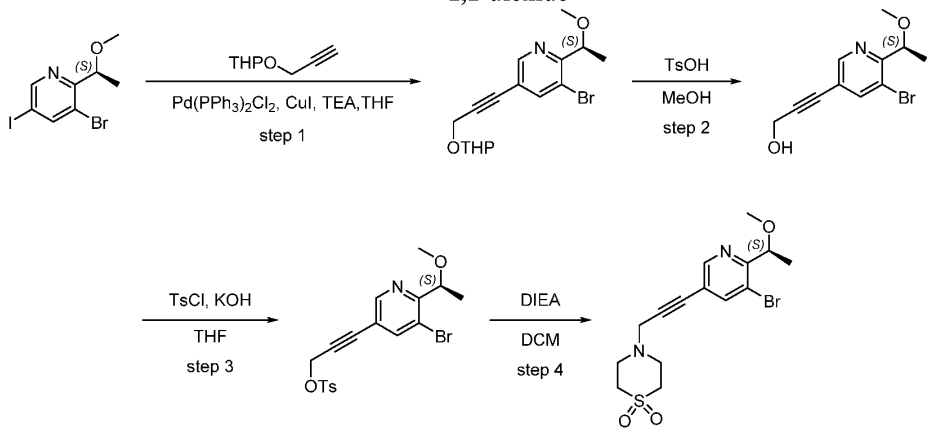
Step 4. Preparation of (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholine

To a solution of morpholine (358 mg, 4.11 mmol) in DCM (10 mL) were added DIEA (1.21 g, 9.34 mmol) and a solution of (*S*)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl 4-methylbenzenesulfonate (1.58 g, 3.74 mmol) in DCM (10 mL) at rt, the resulting mixture was stirred at rt for 16 h. The reaction was monitored by LCMS. After completion, the mixture was concentrated under reduced pressureto give the residual which was purified by silica gel column chromatography (eluting with EtOAc/PE from 0% to 40%) to obtain (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholine (980 mg, yield: 77.5%) as a brown oil.

LCMS (ESI) calcd. for $C_{15}H_{19}BrNO_2$ $[M+H]^+$ m/z 339.1, found 339.6

Intermediate of Example 17:

Synthesis of (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)thiomorpholine 1,1-dioxide



Step 1. Preparation of 3-bromo-2-((S)-1-methoxyethyl)-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridine

A mixture of (S)-3-bromo-5-iodo-2-(1-methoxyethyl)pyridine (10.00 g, 29.24 mmol), 2-(prop-2-yn-1-yloxy)tetrahydro-2H-pyran (4.92 g, 35.09 mmol), CuI (0.45 g, 2.34 mmol), TEA (8.88 g, 8.73 mmol) and $Pd(PPh_3)_2Cl_2$ (1.64 g, 2.34 mmol) in THF (120.00 mL) was stirred at 50oC for 4h under N_2 atmosphere, the reaction was monitored by LCMS. After completion, the mixture was filtered and the filtrate was concentrated, the residue was purified by silica gel column chromatography (eluting with EtOAc/PE, from 0% to 3% in 20 min) to obtain 3-bromo-2-((S)-1-methoxyethyl)-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridine 32 (10.10 g, yield: 97.5%) as a yellow oil.

LCMS (ESI) calcd. for $C_{16}H_{20}BrNO_3$ $[M+H]+$ m/z 354.1, found 354.5.

Step 2. Preparation of (S)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-ol

To a solution of

3-bromo-2-((*S*)-1-methoxyethyl)-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridine (10.10 g, 28.51 mmol) in MeOH (100.00 mL) was added TsOH (19.64 g, 114.05 mmol) at 0°C, the mixture was stirred at room temperature for 5 h under N_2 atmosphere, the reaction was monitored by LCMS. After completion, the mixture was diluted with DCM (50.00 mL) and H_2O (150.00 mL) and extracted with DCM (50 mL x 3), the combined layers were washed with saturated NaCl (150.00 mL), dried over Na_2SO_4, concentrated to obtain (*S*)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-ol (7.10 g, yield: 92.2%) as a yellow oil.

LCMS (ESI) calcd. for $C_{11}H_{12}BrNO_2$ $[M+H]^+$ m/z 270.0, found 270.3.

Step 3. Preparation of (S)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl 4-methylbenzenesulfonate

To a solution of (*S*)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-ol (7.10 g, 26.28 mmol) in THF (100.00 mL) were added TsCl (10.02 g, 52.57 mmol) and KOH (2.95 g, 52.57 mmol) at 0°C, the mixture was stirred at 0°C for 2 h under N_2 atmosphere, the reaction was monitored by LCMS. After completion, the mixture was diluted with EtOAc (50.00 mL) and water (100.00 mL), then extracted with EA (50.00 mL x 3). The combined organic phase was washed with brine (100.00 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residual was purified by silica gel column chromatography (eluting with EtOAc/PE, from 0% to 30% in 30 min) to obtain (*S*)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl 4-methylbenzenesulfonate (10.50 g, yield: 94.2%) as a brown solid.

LCMS (ESI) calcd. for $C_{18}H_{18}BrNO_4S$ $[M+H]^+$ m/z 424.0, found 424.8.

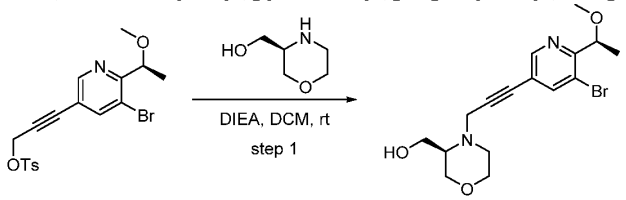
Step 4. Preparation of (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)thiomorpholine 1,1-dioxide

To a solution of thiomorpholine 1,1-dioxide (160 mg, 1.18 mmol) in DCM (2.5 mL) were added DIEA (229 mg, 1.77 mmol) and a solution of (S)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl 4-methylbenzenesulfonate (250 mg, 0.59 mmol) in DCM (2.5 mL) at rt, the resulting mixture was stirred at rt for 20 h. The reaction was monitored by LCMS. After completion, the mixture was concentrated under reduced pressure to give the residual which was purified by silica gel column chromatography (eluting with EtOAc/PE from 0% to 60%) to obtain (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)thiomorpholine 1,1-dioxide (186 mg, yield: 81.7%) as a brown oil. LCMS (ESI) calcd. for $C_{15}H_{19}BrN_2O_3S$ [M+H]+ m/z 387.0, found 387.5.

Intermediate of Example 19:

Synthesis of

((R)-4-(3-(5-bromo-6-((S)-1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholin-3-yl)methanol



Step 1: Synthesis of ((R)-4-(3-(5-bromo-6-((S)-1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholin-3-yl)methanol

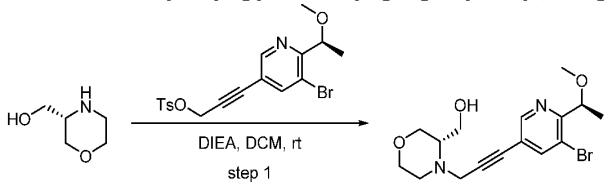
To a solution of (R)-morpholin-3-ylmethanol (500 mg, 4.27 mmol) in DCM (10 mL) were added DIEA (1.10 g, 8.51 mmol) and a solution of (S)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl 4-methylbenzenesulfonate (1.80 g, 4.24 mmol) in DCM (15 mL) at rt, the resulting mixture was stirred at rt for 16 h. The reaction was monitored by LCMS. After completion, the mixture was concentrated under reduced pressure to give the residual which was purified by silica gel column chromatography (eluting with MeOH/DCM from 0% to 15%) to give ((R)-4-(3-(5-bromo-6-((S)-1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholin-3-yl)methanol (1.1 g, yield: 70.0%) as a brown oil.

LCMS (ESI) calcd. for $C_{16}H_{21}BrN_2O_3$ [M+H]+ m/z 369.1, found 369.5.

Intermediate of Example 20:

Synthesis of

((S)-4-(3-(5-bromo-6-((S)-1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholin-3-yl)methanol



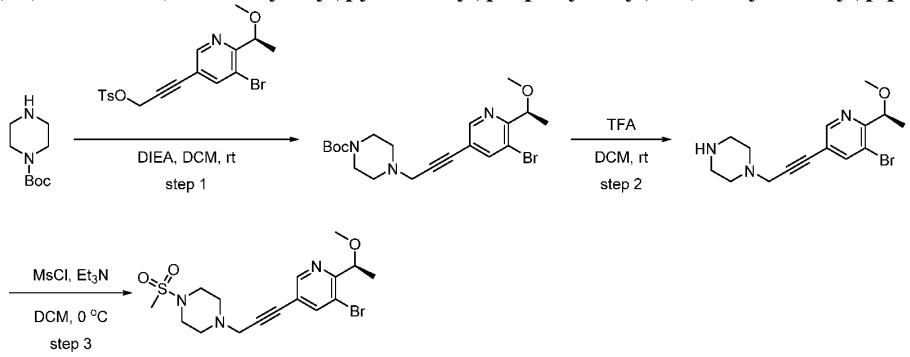
Step 1: Preparation of ((S)-4-(3-(5-bromo-6-((S)-1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholin-3-yl)methanol

A mixture of (S)-morpholin-3-ylmethanol (61 mg, 0.52 mmol), (S)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl 4-methylbenzenesulfonate (200 mg, 0.47 mmol) in DCM (5 mL) was added DIEA (121.5 mg, 0.94 mmol). The reaction mixture was stirred at rt for 3h. After completion, the mixture was was concentrated under reduced pressure. The residue was purified by FCC with EtOAc/PE = 0-30% to afford the ((S)-4-(3-(5-bromo-6-((S)-1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholin-3-yl)methanol (148 mg, 85%) as a yellow oil. LCMS (ESI) calcd. for $C_{16}H_{21}BrN_2O_3$ $[M+H]^+$ m/z 369.1, found 369.5

Intermediate of Example 31:

Synthesis of

(S)-1-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)-4-(methylsulfonyl)piperazine



Step 1: Preparation of tert-butyl (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)piperazine-1-carboxylate

To a stirred solution of tert-butyl piperazine-1-carboxylate (145 mg, 0.778 mmol) in DCM (8 mL) was added (S)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl 4-methylbenzenesulfonate (300 g, 0.707 mmol) and DIEA (183 mg, 1.414 mmol). The resulting mixture was stirred at rt for 4h. The reaction was concentrated under reduced pressure. The residue was purified by FCC with MeOH/DCM = 0-5% to afford the tert-butyl (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)piperazine-1-carboxylate (200 mg, 65%) as yellow oil. LCMS (ESI) calcd. for $C_{20}H_{28}BrN_3O_3$ $[M+H]^+$ m/z 438.1, found 438.5

Step 2: Preparation of (S)-1-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)piperazine

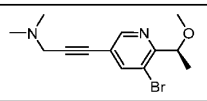
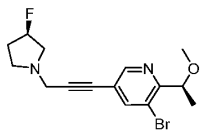
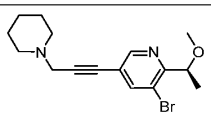
To a stirred solution of tert-butyl (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)piperazine-1-carboxylate (200 mg, 0.456 mmol) in DCM (5 mL) was added TFA (1 mL). The resulting mixture was stirred at rt for 1h. The reaction was concentrated under reduced pressure to afford the crude (S)-1-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)piperazine (220 mg) as yellow oil. LCMS (ESI) calcd. for $C_{15}H_{20}BrN_3O$ $[M+H]^+$ m/z 338.1, found 338.5

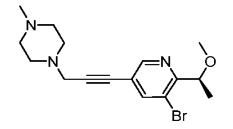
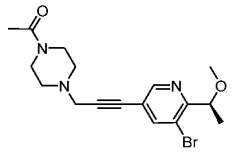
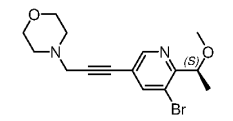
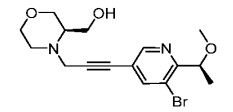
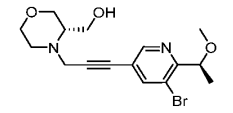
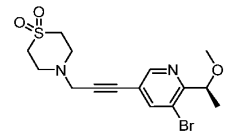
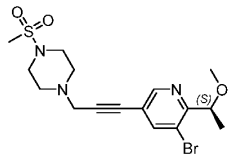
Step 3: Preparation of (S)-1-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)-4-(methylsulfonyl)piperazine

To a stirred solution of (S)-1-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)piperazine (152 mg, 0.45 mmol) in DCM (5 mL) was added TEA (136.5 mg, 1.35 mmol) and MsCl (51.5 mg, 0.45 mmol) at 0°C. The resulting mixture was stirred at 0°C for 0.5h. After completion, the reaction was quenched with H_2O (10 mL) and extracted with EtOAc (10 mL*3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was was purified by FCC with MeOH/DCM = 0-5% to afford the (S)-1-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)-4-(methylsulfonyl)piperazine (170 mg, 90%) as a light yellow oil. LCMS (ESI) calcd. for $C_{16}H_{22}BrN_3O_3S$ $[M+H]^+$ m/z 416.1, found 416.5

The following intermediates in **Table 3** were prepared using the method described above in step for the preparation of (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholine and utilizing the appropriate starting materials and modifications.

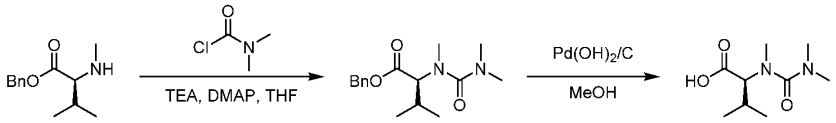
Table 3. Certain Intermediates containing alkynyl group of the Present invention

Name	Structure	LCMS
(S)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)-N,N-dimethylprop-2-yn-1-amine		$[M+H]^+$ 297.2/299.2
3-bromo-5-(3-((R)-3-fluoropyrrolidin-1-yl)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridine		$[M+H]^+$ 341.2/343.2
(S)-3-bromo-2-(1-methoxyethyl)-5-(3-(piperidin-1-yl)prop-1-yn-1-yl)pyridine		$[M+H]^+$ 337.3/339.3

(S)-1-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)-4-methylpiperazine		$[M+H]^+$ 352.1/354.1
(S)-1-(4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)piperazin-1-yl)ethan-1-one		$[M+H]^+$ 380.1/382.1
(S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)thiomorpholine 1,1-dioxide		$[M+H]^+$ 338.1/340.1
((R)-4-(3-(5-bromo-6-((S)-1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholin-3-yl)methanol		$[M+H]^+$ 369.1/371.1
((S)-4-(3-(5-bromo-6-((S)-1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholin-3-yl)methanol		$[M+H]^+$ 369.1/371.1
(S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)thiomorpholine 1,1-dioxide		$[M+H]^+$ 387.3/389.3
(S)-1-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)-4-(methylsulfonyl)piperazine		$[M+H]^+$ 416.1/418.1

Intermediate of Example 29:

Synthesis of N-(dimethylcarbamoyl)-N-methyl-L-valine



Step 1. Preparation of benzyl N-(dimethylcarbamoyl)-N-methyl-L-valinate

A mixture of benzyl (2S)-3-methy1-2-(methylamino)butanoate (500 mg, 2.26 mmol) and dimethylcarbamyl chloride (1.215 g, 11.3 mmol) in THF (5 mL), was added TEA (2.286 g, 22.59 mmol and DMAP (276.02 mg, 2.26 mmol) in portions under nitrogen atmosphere. The reaction mixture was stirred at 65°C for 12 h under nitrogen atmosphere, then quenched with water (100 ml) and was extracted with EtOAc (50 mL x 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by reverse phase chromatography to afford benzyl N-(dimethylcarbamoyl)-N-methyl-L-valinate (400 mg, 58.3% yield) as a colorless oil.

LCMS (ESI) calcd. for $C_{16}H_{25}N_2O_3$ $[M+H]^+$ m/z 293.2, found: 293.4

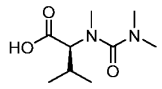
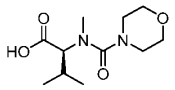
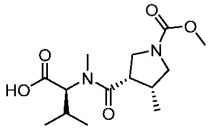
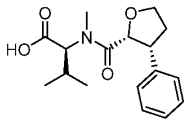
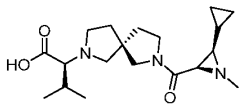
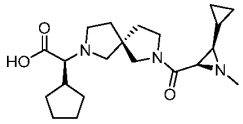
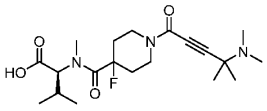
Step 2. *Preparation of N-(dimethylcarbamoyl)-N-methyl-L-valine*

A mixture of benzyl N-(dimethylcarbamoyl)-N-methyl-L-valinate (400 mg, 1.37 mmol) and palladium hydroxide on carbon (400 mg, 2.85 mmol) in MeOH (10 mL) was stirred for 4 h under hydrogen atmosphere. The reaction mixture was filtered and the filter cake was washed with MeOH (100 mL x3). The filtrate was concentrated under reduced pressure to afford N-(dimethylcarbamoyl)-N-methyl-L-valine (200 mg, crude) as a colorless oil.

LCMS (ESI) calcd. for $C_9H_{19}N_2O_3$ $[M+H]^+$ m/z 203.1, found: 203.1

The following compounds in **Table 4** were prepared according to the representative procedure described above for the synthesis of N-methyl-N-((2R,3R)-3-phenyltetrahydrofuran-2-carbonyl)-L-valine and utilizing the appropriate starting materials and modifications.

Table 4. Certain Peptides of the Present invention

Name	Structure	LCMS
N-(dimethylcarbamoyl)-N-methyl-L-valine		$[M+H]^+$ 203.3
N-methyl-N-(morpholine-4-carbonyl)-L-valine		$[M+H]^+$ 245.3
N-((3S,4R)-1-(methoxycarbonyl)-4-methylpyrrolidine-3-carbonyl)-N-methyl-L-valine		$[M+H]^+$ 301.4
N-methyl-N-((2R,3R)-3-phenyltetrahydrofuran-2-carbonyl)-L-valine		$[M+H]^+$ 306.4
(S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-3-methylbutanoic acid		$[M+H]^+$ 350.5
(S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)acetic acid		$[M+H]^+$ 376.5
N-(1-(4-(dimethylamino)-4-methylpent-2-ynoyl)-4-fluoropiperidine-4-carbonyl)-N-methyl-L-valine		$[M+H]^+$ 398.5

SPECIFIC EMBODIMENTS

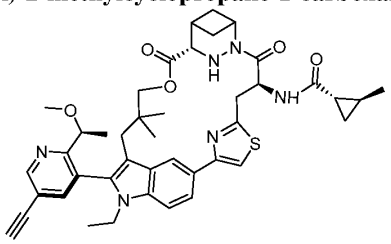
The present invention is described in detail below by embodiments, but does not imply any adverse restriction on the present invention. The compounds of the present invention can be prepared by a variety of synthesis methods well known to those skilled in the art, including the specific embodiments listed below, the embodiments formed by the combination of the invention with other chemical synthesis methods, and the equivalent substitution methods well known to those skilled in the art. Preferred embodiments include, but are not limited to, embodiments of the present invention. To those skilled in the art, various

changes and improvements to the specific embodiments of the present invention without departing from the spirit and scope of the invention will be obvious and shall also be regarded as the scope of protection of the present invention.

Each of the compounds set forth was prepared following one of the procedures set forth below. Unless otherwise specified, intermediates that do not mention the synthesis method in the following synthesis routes are obtained by purchase or customization

Example 1

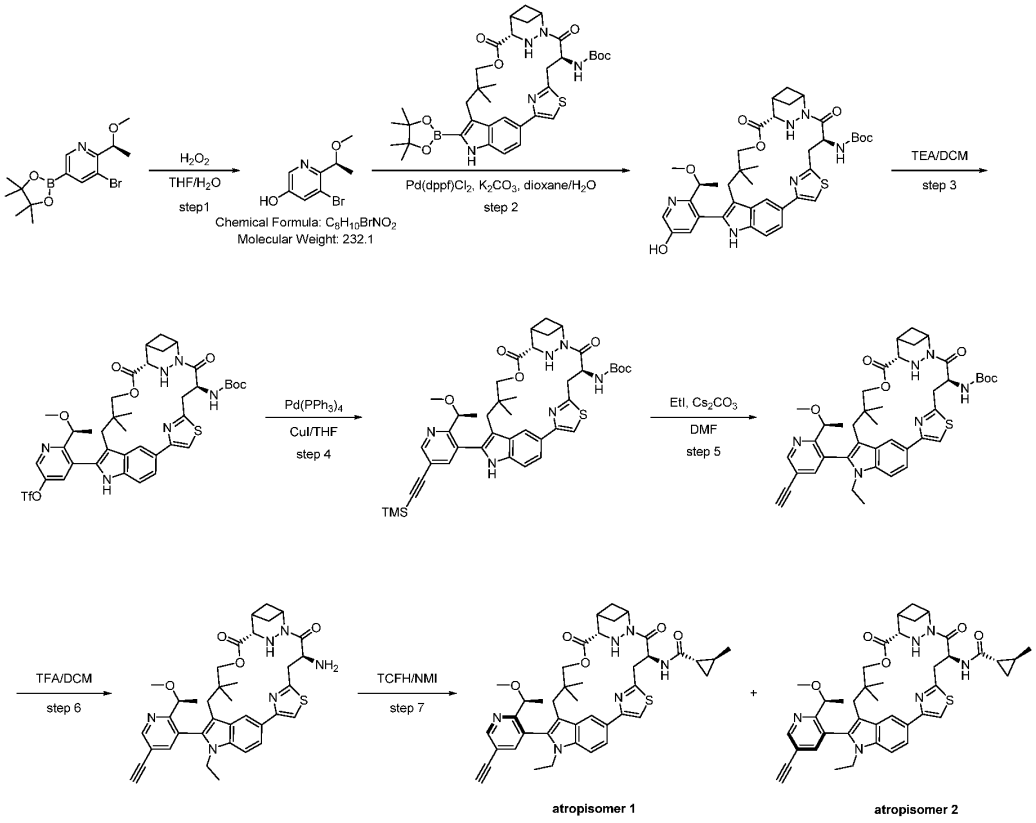
(1S,2S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-di-oxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide



Method 1:

Substituting (S)-4-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)-2-methylbut-3-yn-2-ol with (S)-3-bromo-5-ethynyl-2-(1-methoxyethyl)pyridine in the Step 1 of **Example 2** and Substituting (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid with (1S,2S)-2-methylcyclopropane-1-carboxylic acid in the Step 4 of **Example 2**, the title compound was prepared by the same procedures as described for **Example 2**.

Method 2:



Step 1: Synthesis of (S)-5-bromo-6-(1-methoxyethyl)pyridin-3-ol

To a stirred solution of crude (S)-3-bromo-2-(1-methoxyethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1.00 g, 2.93 mmol) in THF (10 mL) and H_2O (15 mL) were added NaOH (234 mg, 5.86 mmol) and H_2O_2 (195 mg, 14.6 mmol) at rt. The resulting mixture was stirred at rt for 2 h. After completion, the reaction mixture was acified by 1M HCl aquous to pH = 4. The mixture was extracted with EtOAc (2*20 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated to give the crude product which was purified by silica gel column (eluting with EtOAc/PE from 0% to 80%) to give (S)-5-bromo-6-(1-methoxyethyl)pyridin-3-ol (600 mg, 88%) as a white solid.

LCMS (ESI) calcd. for $C_8H_{10}BrNO_2$ $[M+H]^+$ m/z 231.0, found: 232.3

Step 2: Synthesis of tert-butyl ((6⁴S,4S,Z)-1²-(5-hydroxy-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

A mixture of (S)-5-bromo-6-(1-methoxyethyl)pyridin-3-ol (329 mg, 1.42 mmol), tert-butyl ((6⁴S,4S,Z)-10,10-dimethyl-5,7-dioxo-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (500 mg, 0.709 mmol), K_2CO_3 (386 mg, 2.84 mmol) and $Pd(dppf)Cl_2$ (58 mg, 0.071 mmol) in dioxane (16 mL) and H_2O (4 mL) was stirred at 85°C under N_2 for 19 h. After completion, the reaction mixture was concentrated to give the crude product which was purified by silica gel column (eluting with EtOAc 100%) to give tert-butyl

((64S,4S,Z)-12-(5-hydroxy-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-11H-8-oxa-62,63-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (500 mg, 96%) as a brown solid.

LCMS (ESI) calcd. for $C_{38}H_{46}N_6O_7S$ $[M+H]^+$ m/z 730.3, found: 731.8

Step 3: Synthesis of 5-((6^{4}S,4S,Z)-4-((tert-butoxycarbonyl)amino)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate

To a solution of tert-butyl ((6^{4}S,4S,Z)-1^2-(5-hydroxy-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (410 mg, 0.561 mmol) in DCM (6 mL) were added TEA (116 mg, 1.1 mmol) and N,N-Bis(trifluoromethanesulfonyl)aniline (228 g, 0.638 mmol) at 0°C, the mixture was stirred at 0°C for 2 h under N_2 atmosphere, the reaction was monitored by LCMS. After completion, the mixture was concentrated under reduced pressure. The residual was purified by silica gel column chromatography (eluting with EtOAc/PE, from 0% to 50% in 20 min) to obtain 5-((6^{4}S,4S,Z)-4-((tert-butoxycarbonyl)amino)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate (390 mg, yield: 80%) as a white solid.

LCMS (ESI) calcd. for $C_{39}H_{45}F_3N_6O_9S_2$ [M+H]+ m/z 862.3, found 864.2.

Step 4: Synthesis of tert-butyl ((6^{4}S,4S,Z)-1^2-(2-((S)-1-methoxyethyl)-5-((trimethylsilyl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

A mixture of 5-((6^{4}S,4S,Z)-4-((tert-butoxycarbonyl)amino)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-12-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate (340 mg, 0.394 mmol), CuI (7 mg, 0.039 mmol), TEA (199 mg, 1.97 mmol) and $Pd(PPh_3)_4$ (45 mg, 0.039 mmol) in THF (10 mL) was stirred at 75°C for 4h under N_2 atmosphere, the reaction was monitored by LCMS. After completion, the mixture was filtered and the filtrate was concentrated, the residue was purified by silica gel column chromatography (eluting with EtOAc/PE, from 0% to 50% in 10 min) to obtain tert-butyl ((6^{4}S,4S,Z)-1^2-(2-((S)-1-methoxyethyl)-5-((trimethylsilyl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (170 mg, yield: 53%) as a yellow oil.

LCMS (ESI) calcd. for $C_{43}H_{54}N_6O_6SSi$ [M+H]+ m/z 810.4, found 812.3.

Step 5: Synthesis of tert-butyl

((6^{4}S,4S,Z)-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

To a stirred solution of tert-butyl ((6^{4}S,4S,Z)-1^2-(2-((S)-1-methoxyethyl)-5-((trimethylsilyl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (120 mg, 0.148 mmol) in DMF (2 mL) were added Cs_2CO_3 (145 mg, 0.444 mmol) and Iodoethane (81 mg, 0.518 mmol) at 0°C, the resulting mixture was stirred at rt overnight. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with EtOAc (10 mL), washed with water (10 mL) and saturated NaCl (5 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column chromatography (eluting with EtOAc/PE, from 0% to 50% in 10 min) to obtain tert-butyl ((6^{4}S,4S,Z)-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (100 mg, yield: 88%) as a yellow solid.

LCMS (ESI) calcd. for $C_{42}H_{50}N_6O_6S$ $[M+H]^+$ m/z 766.4, found: 768.4

Step 6: Synthesis of (6^{4}S,4S,Z)-4-amino-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione

To a stirred solution of tert-butyl ((6^{4}S,4S,Z)-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (120 mg, 0.156 mmol) in dichloromethane (2 mL) was added TFA (1 mL) dropwisely at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was concentrated. The residue was dissolved in EtOAc (15 mL). The mixture was washed with sat.$NaHCO_3$ aquous (10 mL) and brine (10 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain (64S,4S,Z)-4-amino-11-ethyl-12-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-11H-8-oxa-62,63-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (100 mg, yield: 96%) as a white solid.

LCMS (ESI) calcd. for $C_{37}H_{42}N_6O4_S$ $[M+H]^+$ m/z 666.3, found: 667.7

Step 7: Synthesis of (1S,2S)-N-((64S,4S,Z)-11-ethyl-12-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-11H-8-oxa-62,63-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide

To a stirred solution of (6^{4}S,4S,Z)-4-amino-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (100 mg, 0.150 mmol) and (1S,2S)-2-methylcyclopropane-1-carboxylic acid (18 mg, 0.18 mmol) and 1-methyl-1H-imidazole (37 mg, 0.45 mmol) in ACN (2 mL) was added TCFH (63 mg, 0.225 mmol) at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was concentrated to give the crude

product. The crude product was purified by pre-HPLC (ACN/H_2O (0.5 % NH^4HCO^3) from 20% to 95% in 30 min) to give (1S,2S)-N-((6^4S,4S,Z)-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide as atropisomer 1 (18 mg, 15%) as a white solid and (1S,2S)-N-((6^4S,4S,Z)-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide as atropisomer 2 (i.e., compound of Example 1) (17 mg, 15%) as a white solid.

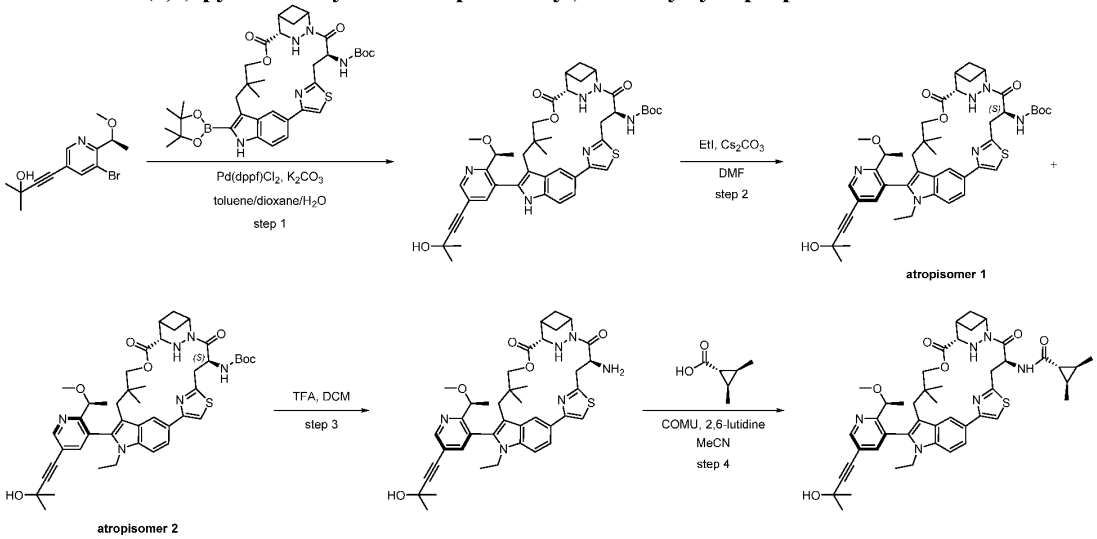
LCMS (ESI) calcd. for $C_{42}H_{48}N_6O_5S$ $[M+H]^+$ m/z 748.3, found: 749.8.

atropisomer 1: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (d, J = 1.8 Hz, 1H), 8.51 (d, J = 8.9 Hz, 1H), 8.41 (s, 1H), 8.06 (d, J = 2.0 Hz, 1H), 7.80 (s, 1H), 7.72 (d, J = 8.9 Hz, 1H), 7.52 (d, J = 8.6 Hz, 1H), 5.89 (d, J = 11.0 Hz, 1H), 5.30 (t, J = 8.3 Hz, 1H), 4.71 (d, J = 11.1 Hz, 1H), 4.50 – 4.44 (m, 2H), 3.96-3.89 (m, 2H), 3.81-3.76 (m, 1H), 3.60-3.48 (m, 2H), 3.24 (d, J = 14.8 Hz, 1H), 3.16 – 2.97 (m, 6H), 2.65-2.63 (m, 1H), 2.35 – 2.28 (m, 2H), 2.13 (t, J = 9.8 Hz, 1H), 1.60 (t, J = 9.3 Hz, 1H), 1.49 (s, 1H), 1.18 (d, J = 6.2 Hz, 3H), 1.11-1.06 (m, 7H), 0.90 (s, 4H), 0.56-0.55 (m,, 1H), 0.45 (s, 3H).

atropisomer 2 (i.e., compound of Example 1): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (d, J = 2.0 Hz, 1H), 8.50 (d, J = 8.9 Hz, 1H), 8.40 (s, 1H), 7.91 (d, J = 2.0 Hz, 1H), 7.80 (s, 1H), 7.73 (d, J = 9.9 Hz, 1H), 7.56 (d, J = 8.6 Hz, 1H), 5.92 (d, J = 11.1 Hz, 1H), 5.39-5.35 (m, 1H), 4.65 (d, J = 11.2 Hz, 1H), 4.52 (s, 1H), 4.49 – 4.44 (m, 1H), 4.34 – 4.23 (m, 2H), 4.07-4.01 (m, 1H), 3.57-3.49 (m, 2H), 3.27 – 3.08 (m, 6H), 2.91 (d, J = 14.3 Hz, 1H), 2.62-2.60 (m, 1H), 2.47-2.42 (m, 1H), 2.32-2.29 (m, 1H), 2.13 (t, J = 9.9 Hz, 1H), 1.54 (t, J = 9.5 Hz, 1H), 1.49-1.47 (m, 1H), 1.34 (d, J = 6.1 Hz, 3H), 1.05 (s, 4H), 0.91 – 0.81 (m, 7H), 0.55-0.54 (m, 2H), 0.30 (s, 3H).

Example 2

(1S,2S)-N-((6^3S,4S,Z)-1^1-ethyl-1^2-(5-(3-hydroxy-3-methylbut-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide



Step 1: Preparation of tert-butyl ((6⁴S,4S,Z)-1²-(5-(3-hydroxy-3-methylbut-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

A mixture of (S)-4-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)-2-methylbut-3-yn-2-ol (106 mg, 0.37 mmol), tert-butyl ((6⁴S,4S,Z)-10,10-dimethyl-5,7-dioxo-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (307 mg, 0.44 mmol), K_2CO_3 (127 mg, 0.92 mmol) and $Pd(dppf)Cl_2$ (27 mg, 0.037 mmol) in toluene (6 mL), dioxane (2 mL) and H_2O (2 mL) was stirred at 75°C under N_2 for 22 h. After completion, the reaction mixture was concentrated to give the crude product which was purified by silica gel column (eluting with MeOH/DCM from 0% to 100%) to give tert-butyl ((6⁴S,4S,Z)-1²-(5-(3-hydroxy-3-methylbut-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (159 mg, 54.8 %) as a brown solid.

LCMS (ESI) calcd. for $C_{42}H_{52}N_6O_7S$ $[M+H]^+$ m/z 784.36, found: 776.5

Step 2: Preparation of tert-butyl ((6⁴S,4S,Z)-1¹-ethyl-1²-(5-(3-hydroxy-3-methylbut-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

To a stirred solution of tert-butyl ((6⁴S,4S,Z)-1²-(5-(3-hydroxy-3-methylbut-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (240 mg, 0.31 mmol) in DMF (3.5 mL) was added Cs_2CO_3 (200 mg, 0.61 mmol) and Iodoethane (96 mg, 0.61 mmol) at 0°C, the resulting mixture was stirred at rt for 3 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with EtOAc (100 mL), washed with water (100 mL x 3) and saturated NaCl (100 x 2 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column (eluting with MeOH/DCM from 0% to 5%) to give tert-butyl ((6⁴S,4S,Z)-1¹-ethyl-1²-(5-(3-hydroxy-3-methylbut-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate as two atropisomers (190 mg, 75.5 %). Then the mixture was purified by prep-HPLC (Prep-HPLC method: column: Phenomenex Luna Cis75x30mmx3um; mobile phase: [water(FA)-ACN]; B%: 1%-40%, 8min) to give the atropisomer 1 (84 mg, 34%) as a brown foam.

LCMS (ESI) calcd. for $C_{44}H_{56}N_6O_7S$ $[M+H]^+$ m/z 812.39, found: 814.5

Step 3: Preparation of (6⁴S,4S,Z)-4-amino-1¹-ethyl-1²-(5-(3-hydroxy-3-methylbut-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1

0,10-dimethyl-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacyclounde caphane-5,7-dione

To a stirred solution of tert-butyl ((6^{4}S,4S,Z)-1^1-ethyl-1^2-(5-(3-hydroxy-3-methylbut-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacyclounde caphane-4-yl)carbamate (atropisomer 1) (84 mg, 0.10 mmol) in dichloromethane (4 mL) was added TFA (1 mL) dropwise at rt, the resulting mixture was stirred at rt for 1h. The reaction mixture was concentrated to give the residue. The residue was purified with reverse phase chromatography (eluting with ACN/H_2O (0.5 % NH_4HCO_3) from 0% to 60%) to give (6^{4}S,4S,Z)-4-amino-1^1-ethyl-1^2-(5-(3-hydroxy-3-methylbut-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloun decaphane-5,7-dione (62 mg, 93.6 %) as a yellow solid.

LCMS (ESI) calcd. for $C_{39}H_{48}N_6O_5S$ [M+H]+ m/z 712.34, found: 714.1

Step 4: Preparation of (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(5-(3-hydroxy-3-methylbut-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3 -yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]he ptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

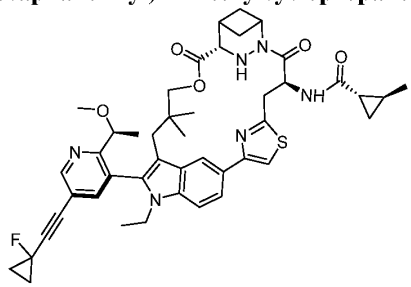
To a stirred solution of (6^{3}S,4S,Z)-4-amino-1^1-ethyl-1^2-(5-(3-hydroxy-3-methylbut-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacyc loundecaphane-5,7-dione (62 mg, 0.10 mmol) and (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid (11 mg, 0.11 mmol) and 2,6-lutidine (11 mg, 0.44 mmol) in ACN (8 mL) was added COMU (56 mg, 0.13 mmol) at rt, the resulting mixture was stirred at rt for 2h. The reaction mixture was concentrated to give the crude product. The crude product was purified by HPLC (ACN/H_2O (0.5 % NH_4HCO_3) from 20% to 95% in 30min) to give (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(5-(3-hydroxy-3-methylbut-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin -3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1] heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (40 mg, 64.5 %) as a white solid.

LCMS (ESI) calcd. for $C_{44}H_{54}N_6O_6S$ $[M+H]^+$ m/z 794.38, found: 796.3. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (d, J = 2.1 Hz, 1H), 8.55 – 8.48 (m, 2H), 7.81 (s, 1H), 7.78 – 7.73 (m, 2H), 7.58 (d, J = 8.7 Hz, 1H), 5.61 – 5.51 (m, 2H), 5.08 (d, J = 12.3 Hz, 1H), 4.37 – 4.14 (m, 4H), 4.07 (dd, J = 14.7, 7.3 Hz, 1H), 3.57 (s, 2H), 3.34 (s, 1H), 3.30 (s, 2H), 3.25 (s, 3H), 3.14 (dd, J = 14.5, 9.1 Hz, 1H), 2.98 (d, J = 14.5 Hz, 1H), 2.81 – 2.70 (m, 1H), 2.36 (d, J = 14.1 Hz, 1H), 2.08 (d, J = 10.2 Hz, 1H), 1.79 (s, 2H), 1.49 (s, 7H), 1.35 (d, J = 6.0 Hz, 3H), 1.05 (d, J = 10.9 Hz, 4H), 0.88 (dd, J = 17.3, 10.4 Hz, 6H), 0.54 (d, J = 5.4 Hz, 1H), 0.33 (s, 3H).

Example 3

(1S,2S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(5-((1-fluorocyclopropyl)ethynyl)-2-((S)-1-methoxyethyl)pyridin-3-y

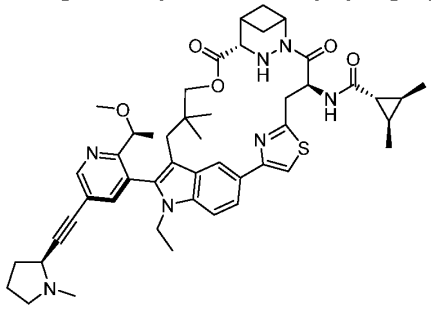
l)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide



Substituting (S)-4-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)-2-methylbut-3-yn-2-ol with (S)-3-bromo-5-((1-fluorocyclopropyl)ethynyl)-2-(1-methoxyethyl)pyridine in the Step 1 of **Example 2** and Substituting (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid with (1S,2S)-2-methylcyclopropane-1-carboxylic acid in the Step 4 of **Example 2**, the title compound was prepared by the same procedures as described for **Example 2**. LCMS (ESI): 807.4 $[M+1]^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, J = 2.0 Hz, 2H), 8.08 (d, J = 12.6 Hz, 2H), 7.92 (d, J = 2.0 Hz, 2H), 7.77 (d, J = 2.4 Hz, 2H), 7.69 (dd, J = 7.7, 2.4 Hz, 2H), 7.59 (s, 2H), 7.48 (d, J = 7.7 Hz, 2H), 5.24 (q, J = 5.4 Hz, 2H), 4.90 (d, J = 8.4 Hz, 2H), 4.64 (q, J = 12.4 Hz, 2H), 4.15 (q, J = 4.4 Hz, 4H), 4.08 – 3.99 (m, 4H), 3.99 – 3.89 (m, 4H), 3.33 (s, 6H), 3.31 – 3.23 (m, 3H), 3.22 (d, J = 3.5 Hz, 1H), 3.06 (d, J = 2.6 Hz, 4H), 2.72 (h, J = 7.9 Hz, 2H), 2.23 (q, J = 4.9 Hz, 8H), 2.13 – 1.97 (m, 8H), 1.94 (td, J = 10.2, 7.3 Hz, 2H), 1.69 – 1.60 (m, 8H), 1.55 (ddd, J = 9.9, 8.8, 4.9 Hz, 2H), 1.37 (t, J = 4.4 Hz, 6H), 1.16 – 1.04 (m, 14H), 0.90 (d, J = 5.0 Hz, 6H).

Example 4

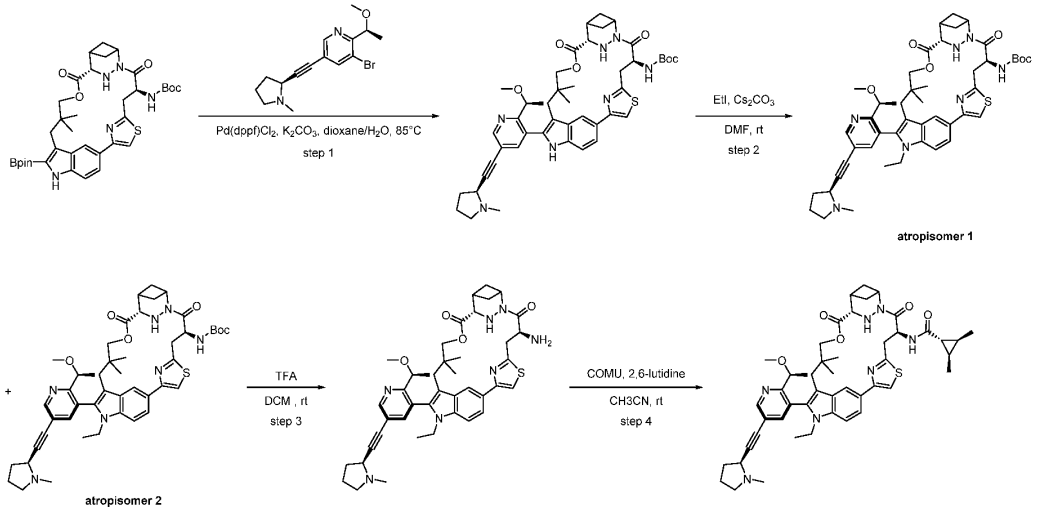
(1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(((S)-1-methylpyrrolidin-2-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide



Method 1:

Substituting 3-bromo-2-((S)-1-methoxyethyl)-5-(((S)-1-methylpyrrolidin-3-yl)ethynyl)pyridine with 3-bromo-2-((S)-1-methoxyethyl)-5-(((S)-1-methylpyrrolidin-2-yl)ethynyl)pyridine in the Step 3 of **Example 5**, the title compound was prepared by the same procedures as described for **Example 5**.

Method 2:



Step 1: Synthesis of tert-butyl ((6⁴S,4S,Z)-1²-(2-((S)-1-methoxyethyl)-5-(((S)-1-methylpyrrolidin-2-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

A mixture of 3-bromo-2-((S)-1-methoxyethyl)-5-(((S)-1-methylpyrrolidin-2-yl)ethynyl)pyridine (87 mg, 0.27 mmol), tert-butyl ((6⁴S,4S,Z)-10,10-dimethyl-5,7-dioxo-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (210 mg, 0.30 mmol), K_2CO_3 (112 mg, 0.81 mmol) and $Pd(dppf)Cl_2$ (30 mg, 0.041 mmol) in dioxane (3 mL) and H_2O (0.7 mL) was stirred at 85°C under N_2 for 16 h. After completion, the reaction mixture was concentrated to give the crude product which was purified by silica gel column (eluting with MeOH/DCM from 0% to 10%) to give tert-butyl ((6⁴S,4S,Z)-1²-(2-((S)-1-methoxyethyl)-5-(((S)-1-methylpyrrolidin-2-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (150 mg, 67.7 %) as a yellow solid.

LCMS (ESI) calcd. for $C_{45}H_{55}N_7O_6S$ $[M+H]^+$ m/z 822.4, found: 823.6.

Step 2: Synthesis of tert-butyl ((6⁴S,4S,Z)-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-(((S)-1-methylpyrrolidin-2-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

To a stirred solution of tert-butyl ((6⁴S,4S,Z)-1²-(2-((S)-1-methoxyethyl)-5-(((S)-1-methylpyrrolidin-2-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (147 mg, 0.18 mmol) in DMF (2 mL) were added Cs_2CO_3 (105 mg, 0.32 mmol) and Iodoethane (50 mg, 0.32 mmol) at 0°C, the resulting mixture was stirred at rt for 3 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with EtOAc (20 mL), washed with water (30 mL x 2) and saturated NaCl (50 mL), then dried over Na_2SO_4, following with concentration

under reduced pressure to obtain crude product which was purified by pre-TLC (eluting with DCM : MeOH = 15 : 1) to give tert-butyl ((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(((S)-1-methylpyrrolidin-2-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (26 mg, 16.9%) as atropisomer 1 and tert-butyl ((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(((S)-1-methylpyrrolidin-2-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (17 mg, 11.1%) as atropisomer 2 as pale yellow solid.

LCMS (ESI) calcd. for $C_{47}H_{59}N_7O_6S$ $[M+H]^+$ m/z 850.4, found: 851.4.

Step 3: Synthesis of (6^{4}S,4S,Z)-4-amino-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(((S)-1-methylpyrrolidin-2-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione

To a stirred solution of tert-butyl ((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(((S)-1-methylpyrrolidin-2-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate as atropisomer 2 (17 mg, 0.020 mmol) in dichloromethane (1 mL) was added TFA (0.25 mL) dropwisely at rt, the resulting mixture was stirred at rt for 2 h. The reaction mixture was concentrated to give crude (6^{4}S,4S,Z)-4-amino-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(((S)-1-methylpyrrolidin-2-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione which was used to next step without purification.

LCMS (ESI) calcd. for $C_{42}H_{51}N_7O_4S$ $[M+H]^+$ m/z 750.4, found: 750.9.

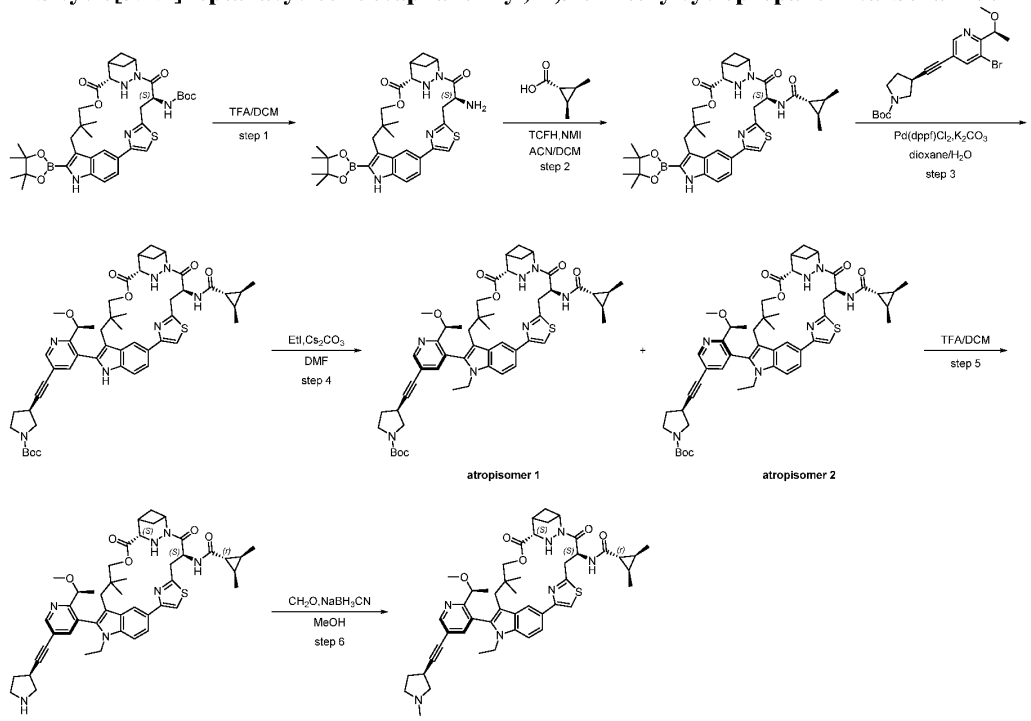
Step 4: Synthesis of (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(((S)-1-methylpyrrolidin-2-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

To a stirred solution of crude (6^{4}S,4S,Z)-4-amino-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(((S)-1-methylpyrrolidin-2-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (17 mg, 0.020 mmol) and (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid (2.2 mg, 0.020 mmol) and 2,6-lutidine (13 mg, 0.12 mmol) in ACN (1 mL) was added COMU (13 mg, 0.030 mmol) at rt, the resulting mixture was stirred at rt for 2 h. The reaction mixture was concentrated to give the crude product. The crude product was purified by pre-HPLC (ACN/H_2O (0.5 % NH_4HCO_3) from 20% to 95% in 30 min) to give (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(((S)-1-methylpyrrolidin-2-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (5.6 mg) as a white solid.

LCMS (ESI): 846.4 $[M+1]^+$. ^1H NMR (400 MHz, DMSO) δ 8.76 (d, J = 2.1 Hz, 1H), 8.42 – 8.34 (m, 2H), 7.83 – 7.77 (m, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.56 (d, J = 8.5 Hz, 1H), 5.90 (d, J = 11.0 Hz, 1H), 5.36 (s, 1H), 4.64 (d, J = 10.7 Hz, 1H), 4.46 (d, J = 4.8 Hz, 1H), 4.33 – 4.20 (m, 2H), 4.04 (dd, J = 14.4, 7.3 Hz, 1H), 3.60 – 3.46 (m, 2H), 3.40 – 3.32 (m, 1H), 3.21 (s, 3H), 3.12 (dd, J = 14.9, 7.3 Hz, 1H), 2.91 (d, J = 13.7 Hz, 1H), 2.82 – 2.72 (m, 1H), 2.61 (d, J = 5.8 Hz, 1H), 2.40 (d, J = 16.0 Hz, 2H), 2.37 – 2.27 (m, 4H), 2.19 – 2.07 (m, 2H), 1.84 (ddd, J = 46.4, 30.9, 20.3 Hz, 4H), 1.56 (d, J = 9.6 Hz, 1H), 1.33 (t, J = 6.6 Hz, 3H), 1.20 (d, J = 10.7 Hz, 4H), 1.15 (d, J = 3.2 Hz, 2H), 1.10 – 1.00 (m, 4H), 0.92 – 0.77 (m, 5H), 0.31 (s, 3H).

Example 5

(1r,2R,3S)-N-((6⁴S,4S,Z)-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-(((S)-1-methylpyrrolidin-3-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide



Step 1: Preparation of (6⁴S,4S,Z)-4-amino-10,10-dimethyl-12-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione

To a stirred solution of tert-butyl ((6⁴S,4S,Z)-10,10-dimethyl-5,7-dioxo-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (1.5 g, 2.1 mmol) in dichloromethane (30 mL) was added TFA (3 mL) dropwise at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was washed with sat. $NaHCO_3$ (30 mL), brine (30 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product (6⁴S,4S,Z)-4-amino-10,10-dimethyl-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaz

a-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (1.3 g) as a yellow solid.

LCMS (ESI) calcd. for $C_{31}H_{40}BN_5O_5S$ [M+H]+ m/z 606.3, found: 607.4

Step 2: Preparation of (1r,2R,3S)-N-((6⁴S,4S,Z)-10,10-dimethyl-5,7-dioxo-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

To a stirred solution of (6⁴S,4S,Z)-4-amino-10,10-dimethyl-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (1.3 g, 2.1 mmol) and (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid (242 mg,2.1 mmol) and NMI (436 mg, 5.3 mmol) in ACN/DCM (15 mL/15 mL) was added TCFH (896 mg, 3.2 mmol) at rt, the resulting mixture was stirred at rt for 30 min. The reaction mixture was concentrated to give the crude product. The crude product was purified by silica gel column (eluting with EtOAc/PE from 0% to 80%) to give (1r,2R,3S)-N-((6⁴S,4S,Z)-10,10-dimethyl-5,7-dioxo-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (1.5 g, 99% in 2 steps) as a yellow solid.

LCMS (ESI) calcd. for $C_{37}H_{48}BN_5O_6S$ [M+H]+ m/z 702.3, found: 703.5

Step 3: Preparation of tert-butyl (3S)-3-((5-((6⁴S,4S,Z)-4-((1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxamido)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1²-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl)ethynyl)pyrrolidine-1-carboxylate

A mixture of (1r,2R,3S)-N-((6⁴S,4S,Z)-10,10-dimethyl-5,7-dioxo-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (1 g, 1.4 mmol), tert-butyl (S)-3-((5-bromo-6-((S)-1-methoxyethyl)pyridin-3-yl)ethynyl)pyrrolidine-1-carboxylate (583 mg, 1.4 mmol), K_2CO_3 (491 mg, 3.6 mmol) and $Pd(dppf)Cl_2$ (209 mg, 0.3 mmol) in dioxane (40 mL) and H_2O (8 mL) was stirred at 90°C under N_2 for 19 h. After completion, the reaction mixture was concentrated to give the crude product which was purified by silica gel column (eluting with EA/PE from 0% to 100%) to give tert-butyl (3S)-3-((5-((6⁴S,4S,Z)-4-((1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxamido)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1²-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl)ethynyl)pyrrolidine-1-carboxylate (900 mg, 70 %) as a yellow solid.

LCMS (ESI) calcd. for $C_{50}H_{61}N_7O_7S$ $[M+H]^+$ m/z 904.4, found: 904.9

Step 4: Preparation of tert-butyl (3S)-3-((5-((6⁴S,4S,Z)-4-((1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxamido)-1¹-ethyl-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1²-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl)ethynyl)pyrrolidine-1-carboxylate

To a stirred solution of (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^4-amino-10,10-dimethyl-5,7-dioxo-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-6(2,4)-bicyclo[3.1.1]heptana-1(1,3)-benzenacyclododecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (900 mg, 1.0 mmol) in DMF (9 mL) were added Cs_2CO_3 (649 mg, 2.0 mmol) and Iodoethane (311 mg, 2.0 mmol) at 0°C, the resulting mixture was stirred at rt for 3 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with EtOAc (100 mL), washed with water (50 mL x 3) and saturated NaCl (50 x 2 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column (eluting with EA/PE from 0% to 100%) to give tert-butyl (3S)-3-((5-((6^{4}S,4S,Z)-4-((1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxamido)-11-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl)ethynyl)pyrrolidine-1-carboxylate as two atropisomers (927 mg, 99%) . Then the mixture was purified by prep-HPLC (Prep-HPLC method: column: Phenomenex Luna Cis75x30mmx3um; mobile phase: [water(FA)-ACN]; B%: 1%-40%, 8min) to give the atropisomer 1 (412 mg, 44%) as yellow solids.

LCMS (ESI) calcd. for $C_{52}H_{65}N_7O_7S$ [M+H]+ m/z 932.5, found: 933.6

Step 5: Preparation of (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(((S)-pyrrolidin-3-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

To a stirred solution of tert-butyl (3S)-3-((5-((64S,4S,Z)-4-((1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxamido)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl)ethynyl)pyrrolidine-1-carboxylate (atropisomer 1) (412 mg, 1.0 mmol) in dichloromethane (10 mL) was added TFA (2.5 mL) dropwise at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was washed with sat. $NaHCO_3$ (30 mL), brine (30 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(((S)-pyrrolidin-3-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (276 mg, 75%) as a yellow solid.

LCMS (ESI) calcd. for $C_{47}H_{57}N_7O_5S$ [M+H]+ m/z 832.4, found: 832.9

Step 6: Preparation of (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(((S)-1-methylpyrrolidin-3-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

To a stirred solution of (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(((S)-pyrrolidin-3-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (276 mg, 0.33 mmol) in MeOH (12 mL)

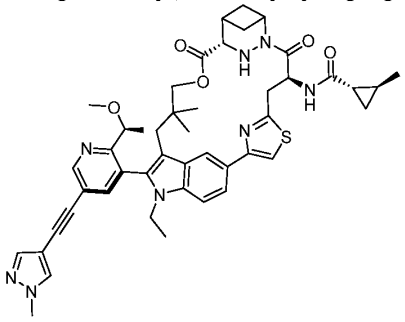
were added formaldehyde (266 mg, 3.3 mmol, 37% in water) and $NaBH_3CN$ (62 mg, 0.97 mmol) at 0°C, the resulting mixture was stirred at rt for 1 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with EtOAc (100 mL), washed with water (50 mL x 3) and saturated NaCl (50 x 2 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by pre-HPLC (eluting with CH_3CN/H_2O(0.1% NH_4HCO_3) from 20% to 80%) to give (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(((S)-1-methylpyrrolidin-3-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (156 mg, 25%) as a white solid.

LCMS (ESI) calcd. for $C_{48}H_{59}N_7O_5S$ $[M+H]^+$ m/z 846.4, found: 846.9.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (s, 1H), 8.40-8.37 (m, 2H), 7.80 (s, 1H), 7.76-7.72 (m, 2H), 7.55 (d, J = 8.4 Hz, 1H), 5.90 (d, J = 11.2 Hz, 1H), 5.35 (m, 1H), 4.64 (d, J = 11.2 Hz, 1H), 4.47-4.46 (m, 1H), 4.30 – 4.22 (m, 2H), 4.07-4.03 (m, 1H), 3.57 – 3.50 (m, 2H), 3.22-3.20 (m, 5H), 3.14-3.09 (m, 1H), 2.93-2.89 (m, 1H), 2.81 (t, J = 8.4 Hz, 1H), 2.61-2.60 (m, 1H), 2.52 – 2.48 (m, 5H), 2.45-2.37 (m, 2H), 2.32-2.30 (m, 1H), 2.23-2.11 (m, 4H), 1.89-1.81 (m, 1H), 1.57 – 1.55 (m, 1H), 1.30 (d, J = 6.0 Hz, 1H), 1.21-1.14 (m, 1H), 1.08-1.04 (m, 5H), 0.86-0.83 (m, 5H), 0.30 (s, 3H).

Example 6

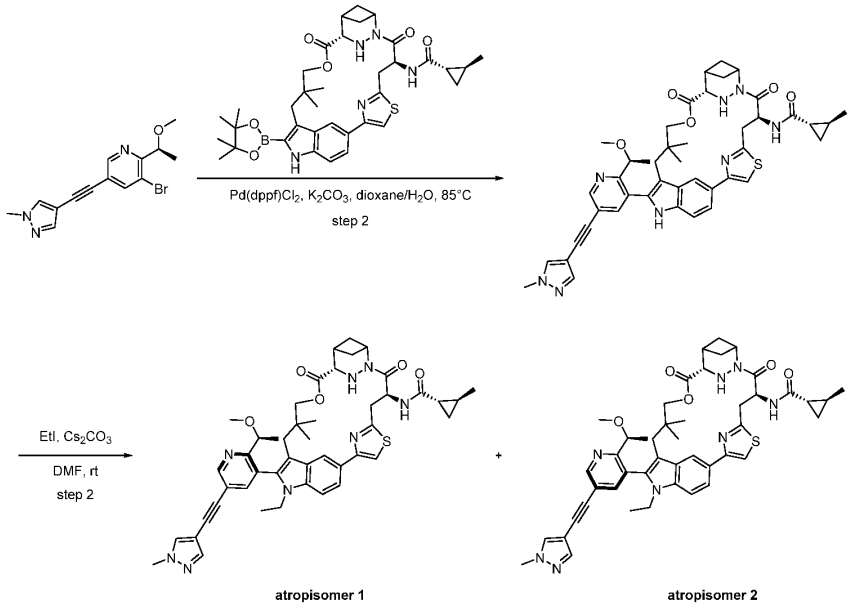
(1S,2S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((1-methyl-1H-pyrazol-4-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide



Method 1:

Substituting (S)-4-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)-2-methylbut-3-yn-2-ol with (S)-3-bromo-2-(1-methoxyethyl)-5-((1-methyl-1H-pyrazol-4-yl)ethynyl)pyridine in the Step 1 of **Example 2** and Substituting (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid with (1S,2S)-2-methylcyclopropane-1-carboxylic acid in the Step 4 of **Example 2**, the title compound was prepared by the same procedures as described for **Example 2**.

Method 2:



Step 1: Synthesis of (1S,2S)-N-((6⁴S,4S,Z)-1²-(2-((S)-1-methoxyethyl)-5-((1-methyl-1H-pyrazol-4-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide

A mixture of (S)-3-bromo-2-(1-methoxyethyl)-5-((1-methyl-1H-pyrazol-4-yl)ethynyl)pyridine (43 mg, 0.13 mmol), (6⁴S,4S,Z)-4-amino-10,10-dimethyl-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (100 mg, 0.15 mmol), K_2CO_3 (56 mg, 0.40 mmol) and $Pd(dppf)Cl_2$ (15 mg, 0.020 mmol) in dioxane (2 mL) and H_2O (0.5 mL) was stirred at 85°C under N_2 for 5 h. After completion, the reaction mixture was concentrated to give the crude product which was purified by silica gel column (eluting with MeOH/DCM from 0% to 10%) to give (1S,2S)-N-((6⁴S,4S,Z)-1²-(2-((S)-1-methoxyethyl)-5-((1-methyl-1H-pyrazol-4-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide (58 mg, 55.8 %) as a yellow solid.

LCMS (ESI) calcd. for $C_{44}H_{48}N_8O_5S$ $[M+H]^+$ m/z 801.4, found: 801.8

Step 2: Synthesis of (1S,2S)-N-((6⁴S,4S,Z)-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-((1-methyl-1H-pyrazol-4-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide

To a stirred solution of (1S,2S)-N-((6⁴S,4S,Z)-1²-(2-((S)-1-methoxyethyl)-5-((1-methyl-1H-pyrazol-4-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide (58 mg, 0.073 mmol) in DMF (1.5 mL) were added Cs_2CO_3 (47 mg, 0.15 mmol) and Iodoethane (23 mg, 0.15 mmol) at 0°C, the resulting mixture was

stirred at rt for 22 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with EtOAc (20 mL), washed with water (20 mL x 2) and saturated NaCl (20 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by pre-HPLC (eluting with CH_3CN/H_2O(0.1% NH_4HCO_3) from 20% to 80%) to give (1S,2S)-N-((6^4S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((1-methyl-1H-pyrazol-4-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide as atropisomer 1 (19 mg) and (1S,2S)-N-((6^4S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((1-methyl-1H-pyrazol-4-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide as atropisomer 2 (i.e., compound of Example 6) (16 mg) as white solids.

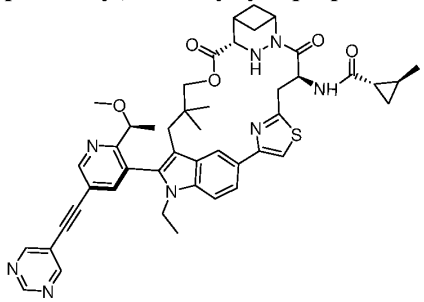
LCMS (ESI) calcd. for $C_{46}H_{52}N_8O_5S$ $[M+H]^+$ m/z 829.4, found: 829.9

atropisomer 1: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (d, J = 1.8 Hz, 1H), 8.52 (d, J = 9.0 Hz, 1H), 8.41 (s, 1H), 8.12 (s, 1H), 8.01 (d, J = 1.7 Hz, 1H), 7.80 (s, 1H), 7.72 (d, J = 4.5 Hz, 1H), 7.53 (d, J = 8.7 Hz, 1H), 5.89 (d, J = 10.8 Hz, 1H), 5.31 (t, J = 8.0 Hz, 1H), 4.72 (d, J = 11.3 Hz, 1H), 4.48 (d, J = 5.1 Hz, 1H), 3.93 (dt, J = 12.6, 6.8 Hz, 2H), 3.87 – 3.74 (m, 3H), 3.58 (d, J = 10.8 Hz, 1H), 3.50 (d, J = 10.8 Hz, 1H), 3.24 (d, J = 14.9 Hz, 1H), 3.16 – 2.98 (m, 4H), 2.64 (d, J = 5.9 Hz, 1H), 2.34 (d, J = 13.9 Hz, 2H), 2.18 – 2.08 (m, 1H), 1.60 (t, J = 9.3 Hz, 1H), 1.49 (s, 1H), 1.19 (d, J = 6.2 Hz, 3H), 1.08 (dd, J = 14.2, 6.9 Hz, 5H), 0.90 (s, 3H), 0.56 (d, J = 5.3 Hz, 1H), 0.48 (s, 2H).

atropisomer 2 (i.e., compound of Example 6): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (d, J = 1.9 Hz, 1H), 8.51 (d, J = 8.7 Hz, 1H), 8.41 (s, 1H), 8.11 (s, 1H), 7.87 (d, J = 2.0 Hz, 1H), 7.80 (s, 1H), 7.73 (d, J = 9.9 Hz, 1H), 7.57 (d, J = 8.6 Hz, 1H), 5.92 (d, J = 11.1 Hz, 1H), 5.36 (s, 1H), 4.65 (d, J = 11.0 Hz, 1H), 4.47 (d, J = 5.1 Hz, 1H), 4.36 – 4.21 (m, 2H), 4.07 (dd, J = 15.0, 7.4 Hz, 1H), 3.84 (s, 2H), 3.54 (dd, J = 20.2, 10.6 Hz, 2H), 3.28 (s, 2H), 3.22 (s, 3H), 3.11 (dd, J = 14.7, 7.3 Hz, 1H), 2.93 (d, J = 14.4 Hz, 1H), 2.61 (d, J = 5.6 Hz, 1H), 2.43 (d, J = 17.5 Hz, 2H), 2.35 – 2.25 (m, 1H), 2.14 (t, J = 9.6 Hz, 1H), 1.57 (d, J = 9.4 Hz, 1H), 1.48 (s, 1H), 1.35 (d, J = 6.0 Hz, 2H), 1.21 (s, 1H), 1.05 (s, 3H), 0.89 (q, J = 7.6 Hz, 5H), 0.55 (d, J = 5.3 Hz, 1H), 0.31 (s, 3H).

Example 7

(1S,2S)-N-((6^4S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(pyrimidin-5-ylethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide

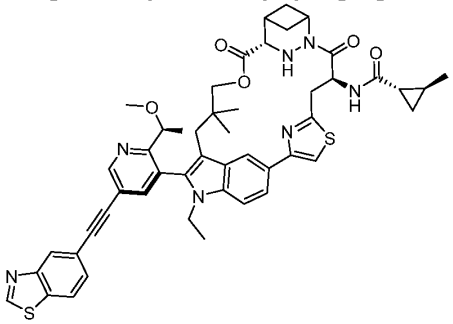


Substituting (S)-4-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)-2-methylbut-3-yn-2-ol with

(S)-5-((5-bromo-6-(1-methoxyethyl)pyridin-3-yl)ethynyl)pyrimidine in the Step 1 of **Example 2** and Substituting (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid with (1S,2S)-2-methylcyclopropane-1-carboxylic acid in the Step 4 of **Example 2**, the title compound was prepared by the same procedures as described for **Example 2**. LCMS (ESI): 827.4 $[M+1]^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 9.15 (t, J = 1.7 Hz, 2H), 8.79 (d, J = 1.8 Hz, 4H), 8.31 (d, J = 2.0 Hz, 2H), 8.08 (d, J = 12.6 Hz, 2H), 8.04 (d, J = 2.0 Hz, 2H), 7.77 (d, J = 2.4 Hz, 2H), 7.69 (dd, J = 7.7, 2.4 Hz, 2H), 7.59 (s, 2H), 7.48 (d, J = 7.7 Hz, 2H), 5.24 (q, J = 5.4 Hz, 2H), 4.90 (d, J = 8.4 Hz, 2H), 4.64 (q, J = 12.4 Hz, 2H), 4.15 (q, J = 4.4 Hz, 4H), 4.08 – 3.99 (m, 4H), 3.99 – 3.89 (m, 4H), 3.33 (s, 6H), 3.31 – 3.23 (m, 3H), 3.22 (d, J = 3.5 Hz, 1H), 3.06 (d, J = 2.6 Hz, 4H), 2.72 (h, J = 7.9 Hz, 2H), 2.13 – 2.03 (m, 6H), 2.03 – 1.97 (m, 2H), 1.94 (td, J = 10.2, 7.2 Hz, 2H), 1.67 (d, J = 5.3 Hz, 6H), 1.65 – 1.60 (m, 1H), 1.55 (ddd, J = 9.9, 8.8, 4.9 Hz, 2H), 1.37 (t, J = 4.4 Hz, 6H), 1.15 (s, 6H), 1.10 (s, 8H), 0.91 (d, J = 5.0 Hz, 6H).

Example 8

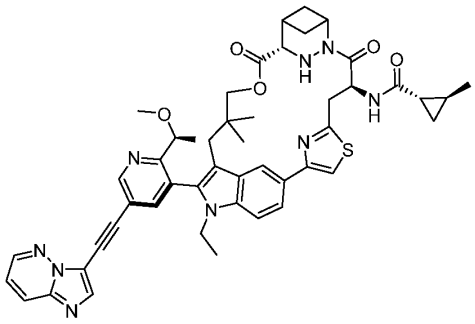
(1S,2S)-N-((6^{4}S,4S,Z)-1^2-(5-(benzo[d]thiazol-5-ylethynyl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide



Substituting (S)-4-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)-2-methylbut-3-yn-2-ol with (S)-5-((5-bromo-6-(1-methoxyethyl)pyridin-3-yl)ethynyl)benzo[d]thiazole in the Step 1 of **Example 2** and Substituting (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid with (1S,2S)-2-methylcyclopropane-1-carboxylic acid in the Step 4 of **Example 2**, the title compound was prepared by the same procedures as described for **Example 2**. LCMS (ESI): 882.3 $[M+1]^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 9.01 (s, 2H), 8.39 (d, J = 2.0 Hz, 2H), 8.11 (d, J = 12.5 Hz, 2H), 7.97 (d, J = 2.0 Hz, 2H), 7.83 (d, J = 1.7 Hz, 2H), 7.77 (d, J = 2.2 Hz, 2H), 7.72 – 7.66 (m, 4H), 7.63 – 7.57 (m, 4H), 7.48 (d, J = 7.7 Hz, 2H), 5.24 (q, J = 5.4 Hz, 2H), 4.89 (d, J = 8.6 Hz, 2H), 4.64 (q, J = 12.4 Hz, 2H), 4.15 (q, J = 4.4 Hz, 4H), 4.08 – 3.99 (m, 4H), 3.99 – 3.89 (m, 4H), 3.33 (s, 6H), 3.31 – 3.23 (m, 3H), 3.22 (d, J = 3.5 Hz, 1H), 3.06 (d, J = 2.6 Hz, 4H), 2.72 (h, J = 7.9 Hz, 2H), 2.13 – 1.89 (m, 10H), 1.69 – 1.60 (m, 8H), 1.55 (ddd, J = 9.9, 8.8, 4.9 Hz, 2H), 1.37 (t, J = 4.4 Hz, 6H), 1.12 (d, J = 24.9 Hz, 14H), 0.91 (d, J = 5.0 Hz, 6H).

Example 9

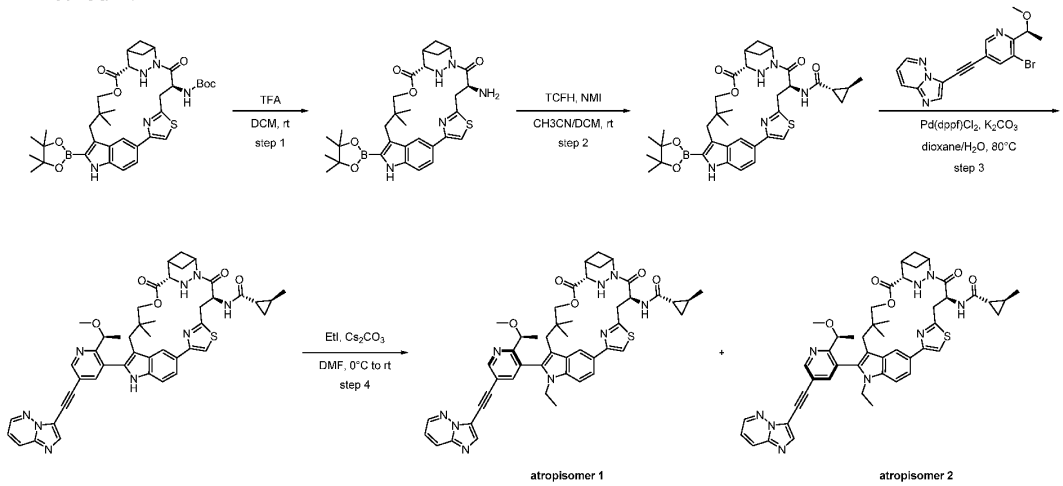
(1S,2S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(5-(imidazo[1,2-b]pyridazin-3-ylethynyl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide



Method 1:

Substituting (S)-4-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)-2-methylbut-3-yn-2-ol with (S)-3-((5-bromo-6-(1-methoxyethyl)pyridin-3-yl)ethynyl)imidazo[1,2-a]pyrimidine in the Step 1 of **Example 2** and Substituting (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid with (1S,2S)-2-methylcyclopropane-1-carboxylic acid in the Step 4 of **Example 2**, the title compound was prepared by the same procedures as described for **Example 2**.

Method 2:



Step 1: Synthesis of (6⁴S,4S,Z)-4-amino-10,10-dimethyl-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione

To a stirred solution of tert-butyl ((6⁴S,4S,Z)-10,10-dimethyl-5,7-dioxo-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (1.0 g, 0.12 mmol) in dichloromethane (10 mL) was added TFA (1 mL) dropwisely at rt, the resulting mixture was stirred at rt for 4 h. The reaction mixture was diluted with DCM and basified to pH = 7 with saturated aq. $NaHCO_3$ solution. The oaranic layer was separated, dried over anhydrous Na_2SO_4 and concentrated to give (6⁴S,4S,Z)-4-amino-10,10-dimethyl-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (777 mg) as a grey solid.

LCMS (ESI) calcd. for $C_{31}H_{40}BN_5O_5S$ $[M+H]^+$ m/z 606.3, found: 607.1.

Step 2: Synthesis of (1S,2S)-N-((6^{4}S,4S,Z)-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide

To a stirred solution of (6^{4}S,4S,Z)-4-amino-10,10-dimethyl-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione **5** (777 mg, 1.28 mmol) and (1S,2S)-2-methylcyclopropane-1-carboxylic acid (129 mg, 1.28 mmol) and NMI (316 mg, 3.85 mmol) in ACN (7 mL) and DCM (7 mL) was added TCFH (540 mg, 1.93 mmol) at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was concentrated to give the crude product. The crude product was purified by silica gel column chromatography (eluting with EtOAc/PE from 0% to 60%) to give (1S,2S)-N-((6^{4}S,4S,Z)-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide (1.15 g) as a pale yellow solid.

LCMS (ESI) calcd. for $C_{36}H_{46}BN_5O_6S$ $[M+H]^+$ m/z 688.3, found: 689.4.

Step 3: Synthesis of (1S,2S)-N-((6^{4}S,4S,Z)-1^2-(5-(imidazo[1,2-b]pyridazin-3-ylethynyl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide

A mixture of (S)-3-((5-bromo-6-(1-methoxyethyl)pyridin-3-yl)ethynyl)imidazo[1,2-b]pyridazine (57 mg, 0.16 mmol), (6^{4}S,4S,Z)-4-amino-10,10-dimethyl-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (120 mg, 0.17 mmol), K_2CO_3 (66 mg, 0.48 mmol) and Pd(dppf)Cl_2 (18 mg, 0.024 mmol) in dioxane (2 mL) and H_2O (0.5 mL) was stirred at 85°C under N_2 for 3 h. After completion, the reaction mixture was concentrated to give the crude product which was purified by silica gel column (eluting with MeOH/DCM from 0% to 10%) to give (1S,2S)-N-((6^{4}S,4S,Z)-1^2-(5-(imidazo[1,2-b]pyridazin-3-ylethynyl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide (93 mg, 79.0 %) as a brown solid.

LCMS (ESI) calcd. for $C_{46}H_{47}N_9O_5S$ $[M+H]^+$ m/z 838.3, found: 838.8.

Step 4: Synthesis of (1S,2S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(5-(imidazo[1,2-b]pyridazin-3-ylethynyl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide

To a stirred solution of (1S,2S)-N-((6^{4}S,4S,Z)-1^2-(5-(imidazo[1,2-b]pyridazin-3-ylethynyl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide (90 mg, 0.11 mmol) in DMF (2 mL) were

added Cs_2CO_3 (70 mg, 0.22 mmol) and Iodoethane (34 mg, 0.22 mmol) at 0°C, the resulting mixture was stirred at rt for 2 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with EtOAc (20 mL), washed with water (50 mL x 2) and saturated NaCl (50 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by pre-HPLC (eluting with CH_3CN/H_2O(0.1% NH_4HCO_3) from 20% to 75%) to give (1S,2S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(5-(imidazo[1,2-b]pyridazin-3-ylethynyl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide as atropisomer 1 (33.5 mg) and (1S,2S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(5-(imidazo[1,2-b]pyridazin-3-ylethynyl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide as atropisomer 2 (i.e., compound of Example 9) (23.0 mg) as white solids.

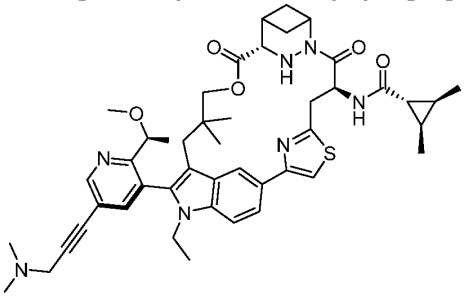
LCMS (ESI) calcd. for $C_{48}H_{51}N_9O_5S$ $[M+H]^+$ m/z 866.4, found: 866.8.

atropisomer 1: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 (d, J = 2.0 Hz, 1H), 8.73 – 8.66 (m, 1H), 8.51 (d, J = 8.9 Hz, 1H), 8.42 (s, 1H), 8.26 – 8.22 (m, 1H), 8.17 (d, J = 2.0 Hz, 1H), 7.80 (s, 1H), 7.73 (d, J = 8.6 Hz, 1H), 7.54 (d, J = 8.7 Hz, 1H), 7.38 (dd, J = 9.2, 4.5 Hz, 1H), 5.88 (d, J = 11.1 Hz, 1H), 5.31 (t, J = 8.0 Hz, 1H), 4.72 (d, J = 11.2 Hz, 1H), 4.48 (d, J = 5.0 Hz, 1H), 4.03 – 3.77 (m, 3H), 3.59 (d, J = 10.8 Hz, 1H), 3.51 (d, J = 10.9 Hz, 1H), 3.24 (d, J = 14.7 Hz, 1H), 3.19 – 2.98 (m, 4H), 2.70 – 2.61 (m, 1H), 2.34 (dd, J = 16.0, 10.2 Hz, 2H), 2.18 – 2.07 (m, 1H), 1.60 (t, J = 9.3 Hz, 1H), 1.49 (s, 1H), 1.21 (d, J = 6.2 Hz, 3H), 1.11 (t, J = 7.1 Hz, 2H), 1.06 (s, 3H), 0.91 (s, 3H), 0.58 – 0.44 (m, 3H).

atropisomer 2 (i.e., compound of Example 9): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.95 (d, J = 1.9 Hz, 1H), 8.68 (d, J = 3.8 Hz, 1H), 8.50 (d, J = 8.9 Hz, 1H), 8.42 (s, 1H), 8.24 (d, J = 6.6 Hz, 2H), 8.01 (d, J = 1.7 Hz, 1H), 7.79 (s, 1H), 7.74 (d, J = 8.3 Hz, 1H), 7.57 (d, J = 8.7 Hz, 1H), 7.37 (dd, J = 9.2, 4.4 Hz, 1H), 5.91 (d, J = 11.2 Hz, 1H), 5.37 (s, 1H), 4.65 (d, J = 11.2 Hz, 1H), 4.47 (d, J = 4.7 Hz, 1H), 4.37 – 4.21 (m, 2H), 4.08 (dd, J = 14.5, 7.2 Hz, 1H), 3.55 (dd, J = 21.5, 10.6 Hz, 2H), 3.24 (s, 3H), 3.12 (dd, J = 14.9, 7.6 Hz, 1H), 2.95 (d, J = 14.7 Hz, 1H), 2.61 (d, J = 5.3 Hz, 1H), 2.44 (d, J = 3.9 Hz, 1H), 2.35 – 2.24 (m, 1H), 2.14 (t, J = 9.6 Hz, 1H), 1.55 (t, J = 9.3 Hz, 1H), 1.48 (s, 1H), 1.37 (d, J = 6.0 Hz, 3H), 1.20 (s, 1H), 1.03 (d, J = 19.4 Hz, 4H), 0.89 (d, J = 9.7 Hz, 6H), 0.54 (d, J = 4.9 Hz, 1H), 0.34 (s, 3H).

Example 10

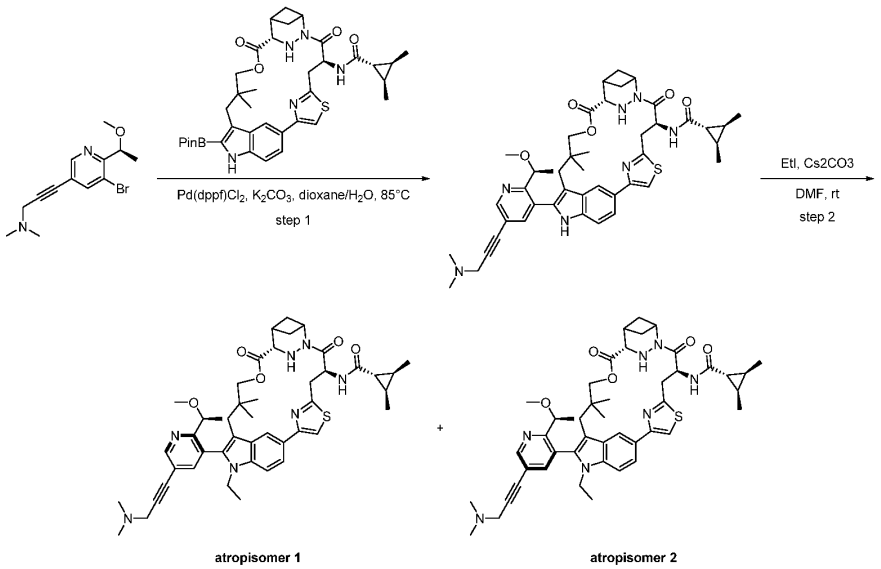
(1r,2R,3S)-N-((6^{4}S,4S,Z)-1^2-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide



Method 1:

Substituting (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholine with (S)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)-N,N-dimethylprop-2-yn-1-amine in the Step 1 of **Example 16**, the title compound was prepared by the same procedures as described for **Example 16**.

Method 2:



Step 1: Synthesis of (1r,2R,3S)-N-((6⁴S,4S,Z)-1²-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

A mixture of (S)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)-N,N-dimethylprop-2-yn-1-amine (70 mg, 0.24 mmol), (1r,2R,3S)-N-((6⁴S,4S,Z)-10,10-dimethyl-5,7-dioxo-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (191 mg, 0.27 mmol), K_2CO_3 (98 mg, 0.71 mmol) and $Pd(dppf)Cl_2$ (26 mg, 0.035 mmol) in dioxane (3 mL) and H_2O (0.7 mL) was stirred at 85°C under N_2 for 3 h. After completion, the reaction mixture was concentrated to give the crude product which was purified by silica gel column (eluting with MeOH/DCM from 0% to 10%) to give (1r,2R,3S)-N-((6⁴S,4S,Z)-1²-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (150 mg, 79.0 %) as a brown solid.

LCMS (ESI) calcd. for $C_{44}H_{53}N_7O_5S$ $[M+H]^+$ m/z 792.4, found: 792.9.

Step 2: Synthesis of (1r,2R,3S)-N-((6⁴S,4S,Z)-1²-((R)-5-(3-(dimethylamino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)-3,4-dihydropyridin-3-yl)-1¹-ethyl-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

To a stirred solution of

(1r,2R,3S)-N-((6^{4}S,4S,Z)-1^2-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (150 mg, 0.19 mmol) in DMF (4 mL) were added Cs_2CO_3 (99 mg, 0.30 mmol) and Iodoethane (48 mg, 0.30 mmol) at 0°C, the resulting mixture was stirred at rt for 4 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with EtOAc (20 mL), washed with water (100 mL x 2) and saturated NaCl (60 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by pre-HPLC (eluting with CH_3CN/H_2O(0.1% NH_4HCO_3) from 20% to 85%) to give (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^2-((R)-5-(3-(dimethylamino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)-3,4-dihydropyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide as atropisomer 1 (25.5 mg) and (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^2-((R)-5-(3-(dimethylamino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)-3,4-dihydropyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide as atropisomer 2 (i.e., compound of Example 10) (18.3 mg) as white solids.

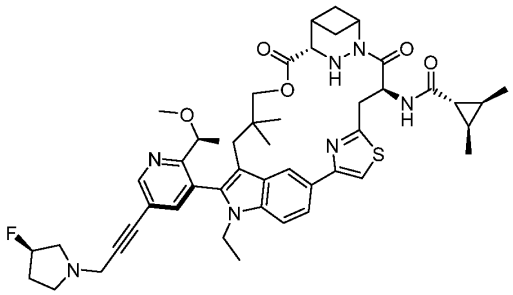
LCMS (ESI) calcd. for $C_{46}H_{59}N_7O_5S$ $[M+H]^+$ m/z 822.4, found: 822.0.

atropisomer 1: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (d, J = 2.0 Hz, 1H), 8.39 (d, J = 10.0 Hz, 2H), 7.98 (d, J = 2.0 Hz, 1H), 7.80 (s, 1H), 7.72 (d, J = 8.7 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H), 5.86 (d, J = 11.1 Hz, 1H), 5.29 (t, J = 8.5 Hz, 1H), 4.71 (d, J = 11.2 Hz, 1H), 4.47 (d, J = 5.1 Hz, 1H), 4.01 – 3.85 (m, 2H), 3.79 (dd, J = 14.6, 7.4 Hz, 1H), 3.63 – 3.45 (m, 3H), 3.23 (d, J = 14.7 Hz, 2H), 3.16 – 2.96 (m, 4H), 2.71 – 2.57 (m, 1H), 2.37 – 2.20 (m, 6H), 2.19 – 2.07 (m, 1H), 1.60 (t, J = 9.3 Hz, 1H), 1.30 – 1.11 (m, 5H), 1.14 – 0.99 (m, 6H), 0.86 (d, J = 26.9 Hz, 2H), 0.46 (s, 2H).

atropisomer 2 (i.e., compound of Example 10): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (d, J = 2.0 Hz, 1H), 8.44 – 8.34 (m, 2H), 7.85 (d, J = 1.9 Hz, 1H), 7.80 (s, 1H), 7.73 (d, J = 8.6 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 5.91 (d, J = 10.9 Hz, 1H), 5.36 (s, 1H), 4.63 (d, J = 11.3 Hz, 1H), 4.46 (d, J = 5.0 Hz, 1H), 4.27 (dt, J = 12.2, 6.8 Hz, 2H), 4.05 (dd, J = 14.6, 7.5 Hz, 1H), 3.60 – 3.47 (m, 3H), 3.27 – 3.05 (m, 5H), 2.91 (d, J = 13.6 Hz, 1H), 2.60 (d, J = 5.5 Hz, 1H), 2.45 – 2.38 (m, 1H), 2.29 (d, J = 11.6 Hz, 5H), 2.17 – 2.09 (m, 1H), 1.60 – 1.48 (m, 1H), 1.34 (d, J = 6.0 Hz, 2H), 1.28 – 1.10 (m, 4H), 1.06 (dd, J = 10.2, 5.8 Hz, 4H), 0.93 – 0.77 (m, 4H), 0.31 (s, 2H).

Example 11

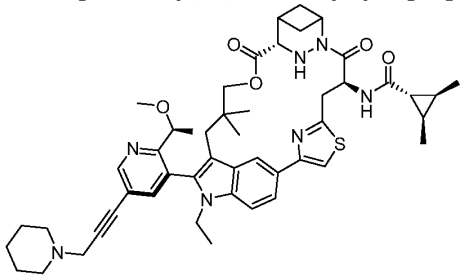
(1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(5-(3-((R)-3-fluoropyrrolidin-1-yl)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide



Substituting (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholine with 3-bromo-5-(3-((R)-3-fluoropyrrolidin-1-yl)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridine in the Step 1 of **Example 16**, the title compound was prepared by the same procedures as described for **Example 16**. LCMS (ESI): 864.4 $[M+1]^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J = 2.0 Hz, 1H), 8.20 (d, J = 13.0 Hz, 1H), 8.02 (d, J = 2.0 Hz, 1H), 7.77 (d, J = 2.4 Hz, 1H), 7.69 (dd, J = 7.7, 2.4 Hz, 1H), 7.59 (s, 1H), 7.48 (d, J = 7.7 Hz, 1H), 5.24 (q, J = 5.4 Hz, 1H), 4.89 (d, J = 8.6 Hz, 1H), 4.87 – 4.80 (m, 1H), 4.63 (dt, J = 13.0, 12.3 Hz, 1H), 4.15 (q, J = 4.4 Hz, 2H), 4.08 – 3.99 (m, 2H), 3.99 – 3.89 (m, 2H), 3.63 – 3.57 (m, 1H), 3.55 (s, 1H), 3.52 – 3.45 (m, 1H), 3.33 (s, 3H), 3.31 – 3.18 (m, 3H), 3.06 (d, J = 2.6 Hz, 2H), 2.94 (t, J = 5.6 Hz, 2H), 2.72 (h, J = 7.9 Hz, 1H), 2.47 (t, J = 8.6 Hz, 1H), 2.29 (q, J = 5.6 Hz, 1H), 2.14 – 1.97 (m, 5H), 1.74 (dq, J = 8.6, 5.2 Hz, 2H), 1.67 (d, J = 5.3 Hz, 3H), 1.37 (t, J = 4.4 Hz, 3H), 1.15 (s, 3H), 1.10 (s, 3H), 0.95 (d, J = 5.1 Hz, 6H).

Example 12

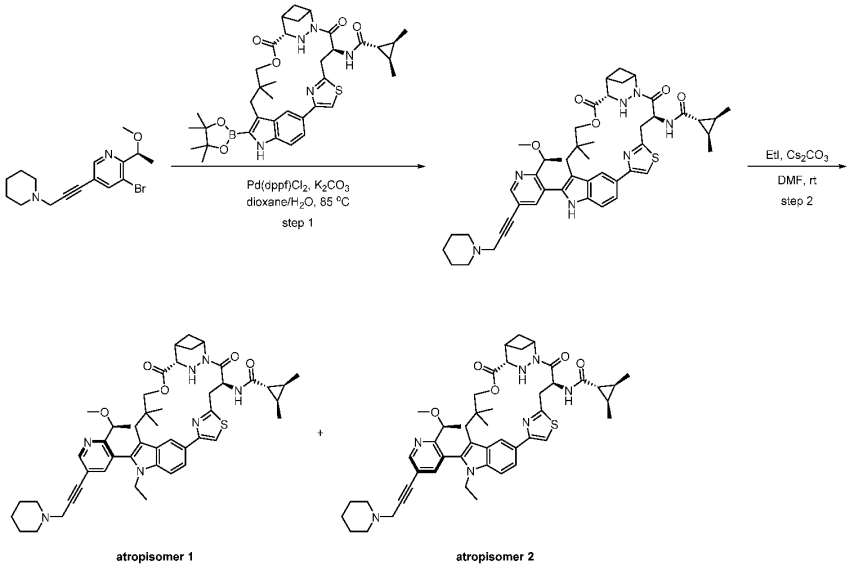
(1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-(piperidin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide



Method 1:

Substituting (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholine with (S)-3-bromo-2-(1-methoxyethyl)-5-(3-(piperidin-1-yl)prop-1-yn-1-yl)pyridine in the Step 1 of **Example 16**, the title compound was prepared by the same procedures as described for **Example 16**.

Method 2:



Step 1: Preparation of (1r,2R,3S)-N-((6⁴S,4S,Z)-1²-(2-((S)-1-methoxyethyl)-5-(3-(piperidin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

A mixture of (S)-3-bromo-2-(1-methoxyethyl)-5-(3-(piperidin-1-yl)prop-1-yn-1-yl)pyridine (48 mg, 0.14 mmol), (1r,2R,3S)-N-((6⁴S,4S,Z)-10,10-dimethyl-5,7-dioxo-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (100 mg, 0.14 mmol), K_2CO_3 (58 mg, 0.42 mmol) and $Pd(dppf)Cl_2$ (22 mg, 0.03 mmol) in dioxane (5 mL) and H_2O (1 mL) was stirred at 85°C under N_2 for 16h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by FCC with MeOH/DCM = 0-6% to afford the (1r,2R,3S)-N-((6⁴S,4S,Z)-1²-(2-((S)-1-methoxyethyl)-5-(3-(piperidin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (98 mg, 84%) as a yellow solid. LCMS (ESI) calcd. for $C_{47}H_{57}N_7O_5S$ $[M+H]^+$ m/z 832.4, found: 832.9

Step 2: Preparation of (1r,2R,3S)-N-((6⁴S,4S,Z)-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-(3-(piperidin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

To a stirred solution of (1r,2R,3S)-N-((6⁴S,4S,Z)-1²-(2-((S)-1-methoxyethyl)-5-(3-(piperidin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (98 mg, 0.117 mmol) in DMF (5 mL) were added Cs_2CO_3 (115.1 mg, 0.353 mmol) and Iodoethane (55.2 mg, 0.353 mmol). The resulting mixture was stirred at rt for 0.5h. After completion, the reaction mixture was diluted with EtOAc (20 mL) and H_2O

(20 mL). The mixture was extracted with EtOAc (10 mL*3). The combined organic layer was washed with brine (20 mL*2), dried over anhydrous Na_2SO_4 and concentration under reduced pressure. The residue was purified by pre-HPLC to give the (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-(piperidin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide as atropisomer 1 (38 mg) and (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-(piperidin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide as atropisomer 2 (i.e., compound of Example 12) (28 mg) as white solids.

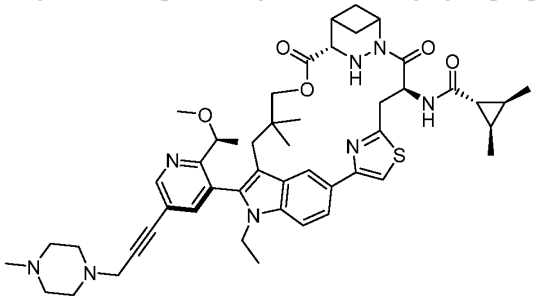
LCMS (ESI) calcd. for $C_{49}H_{61}N_7O_5S$ $[M+H]^+$ m/z 860.4, found: 860.5.

atropisomer 1: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (d, J = 1.8 Hz, 1H), 8.42 (d, J = 8.8 Hz, 2H), 7.99 (d, J = 1.9 Hz, 1H), 7.82 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 8.7 Hz, 1H), 5.89 (d, J = 10.9 Hz, 1H), 5.31 (t, J = 8.3 Hz, 1H), 4.73 (d, J = 11.1 Hz, 1H), 4.49 (d, J = 5.0 Hz, 1H), 3.99 – 3.89 (m, 2H), 3.81 (dd, J = 14.8, 7.4 Hz, 1H), 3.60 (d, J = 10.8 Hz, 1H), 3.52 (d, J = 7.2 Hz, 3H), 3.30 – 2.98 (m, 7H), 2.66 (dd, J = 11.4, 5.6 Hz, 1H), 2.44 (s, 3H), 2.39 – 2.29 (m, 2H), 2.15 (t, J = 9.8 Hz, 1H), 1.67 – 1.46 (m, 5H), 1.43 – 1.01 (m, 18H), 0.92 (s, 3H), 0.48 (s, 3H).

atropisomer 2 (i.e., compound of Example 12): ^{1}H NMR (400 MHz, DMSO) δ 8.78 (d, J = 1.8 Hz, 1H), 8.40 (d, J = 8.8 Hz, 2H), 7.97 (d, J = 1.9 Hz, 1H), 7.80 (s, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H), 5.87 (d, J = 10.9 Hz, 1H), 5.29 (t, J = 8.3 Hz, 1H), 4.71 (d, J = 11.1 Hz, 1H), 4.47 (d, J = 5.0 Hz, 1H), 3.99 – 3.86 (m, 2H), 3.79 (dd, J = 14.8, 7.4 Hz, 1H), 3.63 – 3.42 (m, 4H), 3.26 – 2.98 (m, 6H), 2.64 (d, J = 5.7 Hz, 1H), 2.36 – 2.27 (m, 2H), 2.13 (t, J = 9.8 Hz, 1H), 1.60 (t, J = 9.4 Hz, 1H), 1.54 – 1.47 (m, 3H), 1.35 (s, 2H), 1.29 – 1.00 (m, 14H), 0.90 (s, 3H), 0.46 (s, 3H).

Example 13

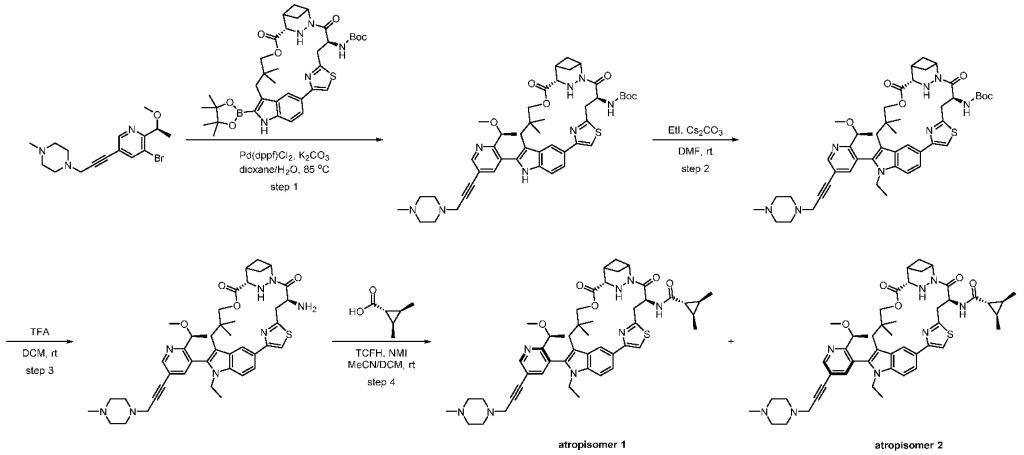
(1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide



Method 1:

Substituting (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholine with (S)-1-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)-4-methylpiperazine in the Step 1 of **Example 16**, the title compound was prepared by the same procedures as described for **Example 16**.

Method 2:



Step 1: Preparation of tert-butyl ((6⁴S,4S,Z)-1²-(2-((S)-1-methoxyethyl)-5-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

A mixture of (S)-1-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)-4-methylpiperazine (100 mg, 0.28 mmol), tert-butyl ((6⁴S,4S,Z)-10,10-dimethyl-5,7-dioxo-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (200 mg, 0.28 mmol), K_2CO_3 (117.5 mg, 0.85 mmol) and $Pd(dppf)Cl_2$ (41.5 mg, 0.06 mmol) in dioxane (6 mL) and H_2O (1.5 mL) was stirred at 85°C under N_2 for 16h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by FCC with MeOH/DCM = 0-10% to afford the tert-butyl ((6⁴S,4S,Z)-1²-(2-((S)-1-methoxyethyl)-5-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (180 mg, 76%) as a yellow solid. LCMS (ESI) calcd. for $C_{46}H_{58}N_8O_6S$ $[M+H]^+$ m/z 851.4, found: 852.1

Step 2: Preparation of tert-butyl ((6⁴S,4S,Z)-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

To a stirred solution of tert-butyl ((6⁴S,4S,Z)-1²-(2-((S)-1-methoxyethyl)-5-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (180 mg, 0.21 mmol) in DMF (6 mL) were added Cs_2CO_3 (206.4 mg, 0.64 mmol) and Iodoethane (99 mg, 0.64 mmol). The resulting mixture was stirred at rt for 0.5h. After completion, the reaction mixture was diluted with EtOAc (20 mL) and H_2O (20 mL). The mixture was extracted with

EtOAc (10 mL*3). The combined organic layer was washed with brine (20 mL*2), dried over anhydrous Na_2SO_4 and concentration under reduced pressure. The residue was purified by FCC with MeOH/DCM = 0-7% to afford the tert-butyl ((6⁴S,4S,Z)-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (115 mg, 62%) as yellow solid.

LCMS (ESI) calcd. for $C_{48}H_{62}N_8O_6S$ $[M+H]^+$ m/z 879.5, found: 880.0

Step 3: Preparation of (6⁴S,4S,Z)-4-amino-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione

To a stirred solution of tert-butyl ((6⁴S,4S,Z)-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (115 mg, 0.13 mmol) in DCM (5 mL) was added TFA (1 mL). The resulting mixture was stirred at rt for 1 h. The reaction mixture was concentrated under reduced pressure to give (6⁴S,4S,Z)-4-amino-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione 7 (186 mg) of its TFA salt as a yellow solid. LCMS (ESI) calcd. for $C_{43}H_{54}N_8O_4S$ $[M+H]^+$ m/z 779.4, found: 779.9

Step 4: Preparation of (1r,2R,3S)-N-((6⁴S,4S,Z)-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

To a stirred solution of (6⁴S,4S,Z)-4-amino-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (101.3 mg, 0.13 mmol) in MeCN (2.5 mL) and DCM (2.5 mL) was added (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid (16.3 mg, 0.14 mmol), TCFH (109.3 mg, 0.39 mmol) and NMI (106.7 mg, 1.3 mmol). The resulting mixture was stirred at rt for 0.5h. The reaction mixture was concentrated under reduced pressure. The residue was purified by pre-HPLC to give the (1r,2R,3S)-N-((6⁴S,4S,Z)-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide as atropisomer 1 (38 mg) and (1r,2R,3S)-N-((6⁴S,4S,Z)-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicycl

o[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide as atropisomer 2 (i.e., compound of Example 13) (22 mg) as white solids.

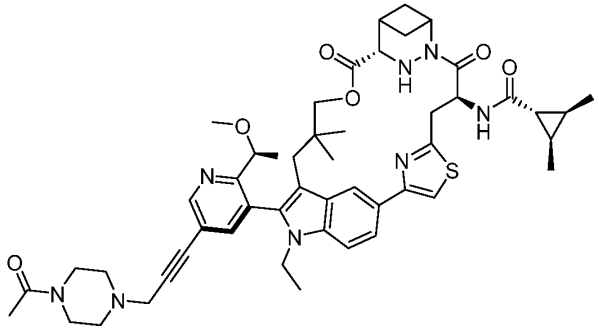
LCMS (ESI) calcd. for $C_{49}H_{62}N_8O_5S$ $[M+H]^+$ m/z 875.5, found: 875.6

atropisomer 1: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (d, J = 1.9 Hz, 1H), 8.39 (d, J = 11.7 Hz, 2H), 7.97 (d, J = 2.0 Hz, 1H), 7.79 (s, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.52 (d, J = 8.6 Hz, 1H), 5.86 (d, J = 11.1 Hz, 1H), 5.29 (t, J = 7.9 Hz, 1H), 4.71 (d, J = 11.1 Hz, 1H), 4.47 (d, J = 5.1 Hz, 1H), 3.99 – 3.72 (m, 4H), 3.60 – 3.47 (m, 4H), 3.27 – 2.98 (m, 8H), 2.64 (dd, J = 11.6, 5.9 Hz, 1H), 2.52 (s, 2H), 2.41 – 2.22 (m, 6H), 2.17 – 2.09 (m, 4H), 1.59 (t, J = 9.2 Hz, 1H), 1.27 – 1.13 (m, 7H), 1.11 – 1.03 (m, 8H), 0.89 (s, 3H), 0.45 (s, 3H).

atropisomer 2 (i.e., compound of Example 13): ^{1}H NMR (400 MHz, DMSO) δ 8.78 (d, J = 1.9 Hz, 1H), 8.39 (d, J = 11.7 Hz, 2H), 7.97 (d, J = 2.0 Hz, 1H), 7.79 (s, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.52 (d, J = 8.6 Hz, 1H), 5.86 (d, J = 11.1 Hz, 1H), 5.29 (t, J = 7.9 Hz, 1H), 4.71 (d, J = 11.1 Hz, 1H), 4.47 (d, J = 5.1 Hz, 1H), 3.99 – 3.72 (m, 4H), 3.60 – 3.47 (m, 4H), 3.27 – 2.98 (m, 8H), 2.60 (dd, J = 27.9, 22.1 Hz, 5H), 2.41 – 2.22 (m, 6H), 2.17 – 2.09 (m, 4H), 1.59 (t, J = 9.2 Hz, 1H), 1.29 – 1.02 (m, 16H), 0.89 (s, 3H), 0.45 (s, 3H).

Example 14

(1r,2R,3S)-N-((6^{4}S,4S,Z)-1^2-(5-(3-(4-acetylpiperazin-1-yl)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

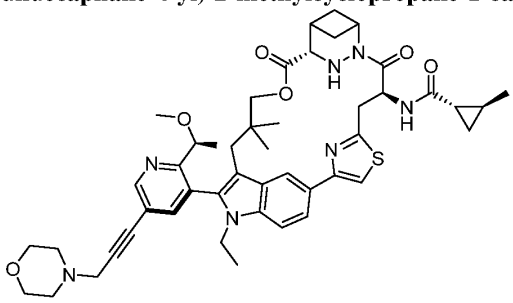


Substituting (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholine with (S)-1-(4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)piperazin-1-yl)ethan-1-one in the Step 1 of **Example 16**, the title compound was prepared by the same procedures as described for **Example 16**. LCMS (ESI): 903.5 $[M+1]^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J = 2.0 Hz, 1H), 8.20 (d, J = 13.0 Hz, 1H), 8.02 (d, J = 2.0 Hz, 1H), 7.77 (d, J = 2.3 Hz, 1H), 7.69 (dd, J = 7.7, 2.4 Hz, 1H), 7.59 (s, 1H), 7.48 (d, J = 7.7 Hz, 1H), 5.24 (q, J = 5.4 Hz, 1H), 4.89 (d, J = 8.6 Hz, 1H), 4.63 (dt, J = 13.0, 12.3 Hz, 1H), 4.15 (q, J = 4.4 Hz, 2H), 4.08 – 3.99 (m, 2H), 3.99 – 3.89 (m, 2H), 3.60 – 3.52 (m, 3H), 3.52 – 3.45 (m, 4H), 3.33 (s, 3H), 3.31 – 3.23 (m, 2H), 3.22 (d, J = 3.5 Hz, 1H), 3.06 (d, J = 2.6 Hz, 2H), 2.72 (h, J = 7.9 Hz, 1H), 2.55 – 2.50 (m, 4H), 2.50 – 2.43 (m, 2H), 2.13 – 1.97 (m, 7H), 1.74 (dq, J = 8.6, 5.2 Hz, 2H), 1.67 (d, J = 5.3 Hz, 3H), 1.37 (t, J = 4.4 Hz, 3H), 1.15 (s, 3H), 1.10 (s, 3H), 0.95 (d, J = 5.1 Hz, 6H).

Example 15

(1S,2S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]he

ptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide

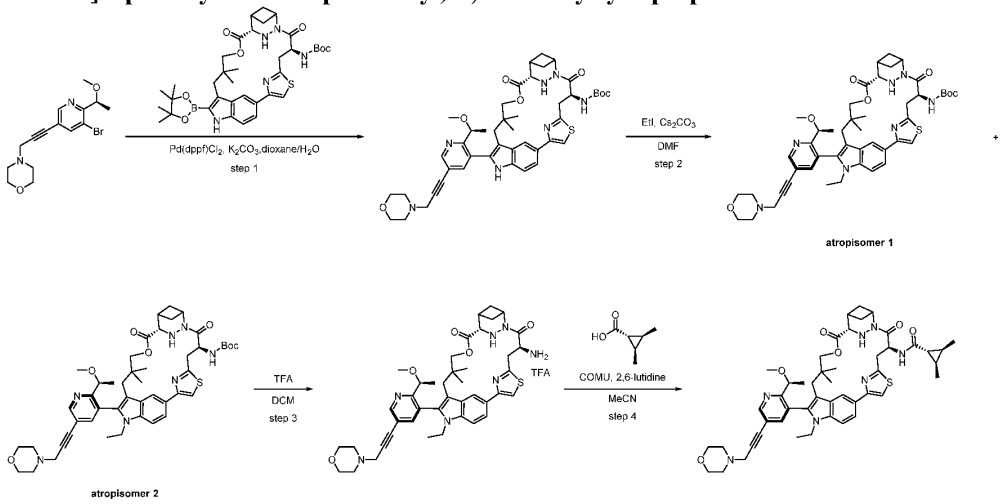


Substituting (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid with (1S,2S)-2-methylcyclopropane-1-carboxylic acid in the Step 4 of **Example 16**, the title compound was prepared by the same procedures as described for **Example 16**. LCMS (ESI): 848.4 $[M+1]^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J = 2.0 Hz, 1H), 8.11 (d, J = 12.5 Hz, 1H), 8.00 (d, J = 2.0 Hz, 1H), 7.77 (d, J = 2.3 Hz, 1H), 7.69 (dd, J = 7.7, 2.4 Hz, 1H), 7.59 (s, 1H), 7.48 (d, J = 7.7 Hz, 1H), 5.24 (q, J = 5.4 Hz, 1H), 4.89 (d, J = 8.6 Hz, 1H), 4.64 (q, J = 12.4 Hz, 1H), 4.15 (q, J = 4.4 Hz, 2H), 4.08 – 3.99 (m, 2H), 3.99 – 3.89 (m, 2H), 3.73 (dd, J = 6.5, 3.8 Hz, 2H), 3.66 (dd, J = 6.5, 3.8 Hz, 2H), 3.58 (d, J = 2.6 Hz, 2H), 3.33 (s, 3H), 3.31 – 3.23 (m, 2H), 3.22 (d, J = 3.5 Hz, 1H), 3.06 (d, J = 2.6 Hz, 2H), 2.78 – 2.66 (m, 5H), 2.13 – 2.03 (m, 3H), 2.03 – 1.97 (m, 1H), 1.94 (td, J = 10.2, 7.2 Hz, 1H), 1.67 (d, J = 5.3 Hz, 3H), 1.65 – 1.60 (m, 1H), 1.55 (ddd, J = 9.9, 8.8, 4.9 Hz, 1H), 1.37 (t, J = 4.4 Hz, 3H), 1.15 (s, 3H), 1.10 (s, 4H), 0.91 (d, J = 5.0 Hz, 3H).

Example 16

Synthesis of

(1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide



Step 1: Preparation of tert-butyl ((6^{4}S,4S,Z)-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

A mixture of (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholine (253 mg, 0.74 mmol), tert-butyl ((6^{4}S,4S,Z)-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (525 mg, 0.74 mmol), K_2CO_3 (309 mg, 2.24 mmol) and $Pd(dppf)Cl_2$ (55 mg, 0.075 mmol) in dioxane (8 mL) and H_2O (2 mL) was stirred at 85°C under N_2 for 19 h. After completion, the reaction mixture was concentrated to give the crude product which was purified by silica gel column (eluting with MeOH/DCM from 0% to 100%) to give tert-butyl ((6^{4}S,4S,Z)-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (323 mg, 52.1 %) as a yellow solid.

LCMS (ESI) calcd. for $C_{45}H_{55}N_7O_7S$ $[M+H]^+$ m/z 838.4, found: 839.5

Step 2: Preparation of tert-butyl ((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

To a stirred solution of tert-butyl ((6^{4}S,4S,Z)-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (323 mg, 0.39 mmol) in DMF (4.5 mL) were added Cs_2CO_3 (251 mg, 0.77 mmol) and Iodoethane (120 mg, 0.77 mmol) at 0°C, the resulting mixture was stirred at rt for 3 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with EtOAc (100 mL), washed with water (50 mL x 3) and saturated NaCl (50 x 2 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by pre-HPLC (eluting with CH_3CN/H_2O(0.1% NH_4HCO_3) from 20% to 80%) to give tert-butyl ((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate as atropisomer 1 (100 mg) and atropisomer 2 (140 mg) as white solids.

LCMS (ESI) calcd. for $C_{47}H_{59}N_7O_7S$ $[M+H]^+$ m/z 866.4, found: 866.8. *Step 3: Preparation of (6^{4}S,4S,Z)-4-amino-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione*

To a stirred solution of tert-butyl ((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate as atropisomer 1 (100 mg, 0.12 mmol) in dichloromethane (4 mL) was added TFA (1 mL) dropwisely at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was concen-

trated and lyophilized to give (6^4S,4S,Z)-4-amino-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (110 mg) of its TFA salt as a yellow solid.

LCMS (ESI) calcd. for $C_{42}H_{51}N_7O_5S$ $[M+H]^+$ m/z 766.4, found: 766.9

Step 4: Preparation of (1r,2R,3S)-N-((6^4S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

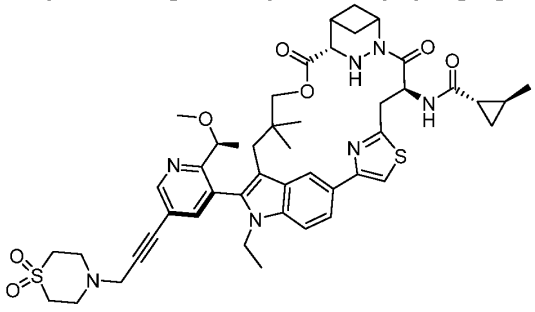
To a stirred solution of (6^4S,4S,Z)-4-amino-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (125 mg, 0.16 mmol) and (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid (19 mg, 0.16 mmol) and 2,6-lutidine (88 mg, 0.82 mmol) in ACN (5 mL) was added COMU (105 mg, 0.24 mmol) at rt, the resulting mixture was stirred at rt for 2 h. The reaction mixture was concentrated to give the crude product. The crude product was purified by pre-HPLC (ACN/H_2O (0.5 % NH_4HCO_3) from 20% to 95% in 30 min) to give (1r,2R,3S)-N-((6^4S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (85 mg, 61.7%) as a white solid.

LCMS (ESI) calcd. for $C_{48}H_{59}N_7O_6S$ $[M+H]^+$ m/z 862.4, found: 862.9.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (s, 1H), 8.40 (d, J = 13.3 Hz, 2H), 7.90 (s, 1H), 7.81 (s, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 5.92 (d, J = 10.8 Hz, 1H), 5.34 (d, J = 22.7 Hz, 2H), 4.64 (d, J = 11.2 Hz, 1H), 4.48 (d, J = 4.9 Hz, 1H), 4.37 – 4.21 (m, 2H), 4.06 (d, J = 7.6 Hz, 5H), 3.75 – 3.48 (m, 6H), 3.22 (s, 3H), 3.16 (s, 10H), 3.00 – 2.85 (m, 2H), 2.62 (d, J = 5.7 Hz, 3H), 2.41 (d, J = 15.0 Hz, 1H), 2.32 (s, 1H), 2.21 – 2.09 (m, 1H), 1.99 (d, J = 8.0 Hz, 1H), 1.55 (s, 1H), 1.35 (d, J = 6.1 Hz, 2H), 1.22 (s, 4H), 1.16 (s, 2H), 1.07 (dd, J = 10.3, 5.8 Hz, 4H), 0.87 (t, J = 9.6 Hz, 4H), 0.32 (s, 3H).

Example 17

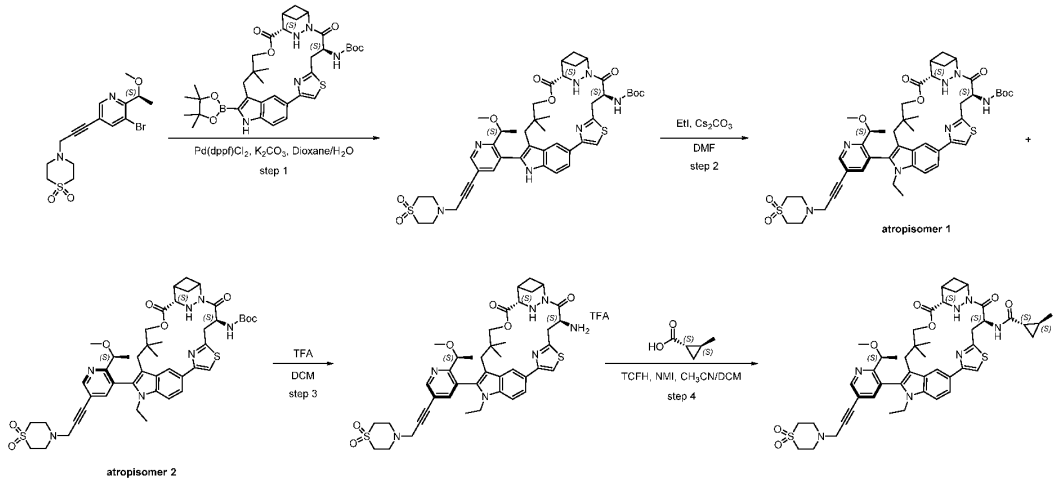
(1S,2S)-N-((6^4S,4S,Z)-1^2-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide



Method 1:

Substituting (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholine with (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)thiomorpholine 1,1-dioxide in the Step 1 of **Example 16** and Substituting (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid with (1S,2S)-2-methylcyclopropane-1-carboxylic acid in the Step 4 of **Example 16**, the title compound was prepared by the same procedures as described for **Example 16**.

Method 2:



Step 1: Preparation of tert-butyl ((6⁴S,4S,Z)-1²-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

A mixture of (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)thiomorpholine 1,1-dioxide (209 mg, 0.54 mmol), tert-butyl ((64S,4S,Z)-10,10-dimethyl-5,7-dioxo-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (383 mg, 0.54 mmol), K_2CO_3 (225 mg, 1.62 mmol) and $Pd(dppf)Cl_2$ (78 mg, 0.11 mmol) in dioxane (10 mL) and H_2O (2.5 mL) was stirred at 85°C under N_2 for 5 h. After completion, the reaction mixture was concentrated to give the crude product which was purified by silica gel column (eluting with MeOH/DCM from 0% to 10%) to give tert-butyl ((6⁴S,4S,Z)-1²-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (312 mg, 65.1%) as a yellow solid.

LCMS (ESI) calcd. for $C_{45}H_{55}N_7O_8S_2$ $[M+H]^+$ m/z 886.3, found: 886.9

Step 2: tert-butyl ((6⁴S,4S,Z)-1²-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1¹-ethyl-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

To a stirred solution of tert-butyl ((6^{4}S,4S,Z)-1^2-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (310 mg, 0.35 mmol) in DMF (5 mL) were added Cs_2CO_3 (183 mg, 0.56 mmol) and Iodoethane (88 mg, 0.56 mmol) at 0°C, the resulting mixture was stirred at rt for 3 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with EtOAc (20 mL), washed with water (50 mL x 3) and saturated NaCl (50 x 2 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by column chromatography (eluting with EtOAc/PE from 0% to 100%) to give tert-butyl ((6^{4}S,4S,Z)-1^2-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate as atropisomer 1 (160 mg) and atropisomer 2 (156 mg) (Yield: 98.8%) as a yellow foam.

LCMS (ESI) calcd. for $C_{47}H_{59}N_7O_8S_2$ $[M+H]^+$ m/z 914.4, found: 914.9

Step 3: (6^{4}S,4S,Z)-4-amino-1^2-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione

To a stirred solution of tert-butyl ((6^{4}S,4S,Z)-1^2-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate as atropisomer 1 (160 mg, 0.18 mmol) in dichloromethane (3 mL) was added TFA (1 mL) dropwise at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was concentrated and lyophilized to give (6^{4}S,4S,Z)-4-amino-1^2-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (190 mg) of its TFA salt as a yellow solid.

LCMS (ESI) calcd. for $C_{42}H_{51}N_7O_6S_2$ $[M+H]^+$ m/z 814.3, found: 814.8

Step 4: (1S,2S)-N-((6^{4}S,4S,Z)-1^2-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide

To a stirred solution of (6^{4}S,4S,Z)-4-amino-1^2-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (190 mg, 0.16 mmol) and (1S,2S)-2-methylcyclopropane-1-carboxylic acid (18 mg, 0.16 mmol) and NMI (128 mg, 1.56 mmol) in ACN (2 mL) and DCM (2 mL) was added TCFH (131 mg, 0.47 mmol) at rt, the resulting mixture was stirred at rt for 2 h. The reaction mixture was concentrated to give the crude product. The crude product was purified by pre-TLC (with EA) to give

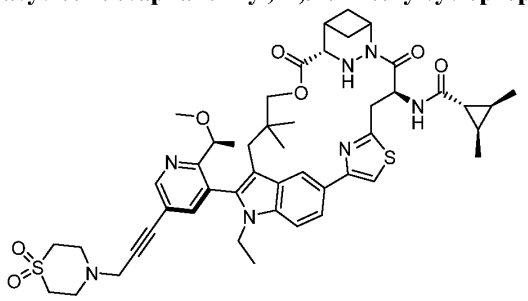
(1S,2S)-N-((6^{4}S,4S,Z)-1^2-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide (23 mg, 16.1%) as a white solid.

LCMS (ESI) calcd. for $C_{47}H_{57}N_7O_7S_2$ $[M+H]^+$ m/z 896.3, found: 896.4.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (d, J = 2.0 Hz, 1H), 8.49 (d, J = 8.8 Hz, 1H), 8.40 (s, 1H), 7.85 (d, J = 2.1 Hz, 1H), 7.79 (s, 1H), 7.73 (d, J = 7.4 Hz, 1H), 7.56 (d, J = 8.6 Hz, 1H), 5.91 (d, J = 11.1 Hz, 1H), 5.37 (s, 1H), 4.64 (d, J = 10.8 Hz, 1H), 4.47 (d, J = 5.1 Hz, 1H), 4.37 – 4.20 (m, 2H), 4.04 (dd, J = 15.2, 7.3 Hz, 1H), 3.73 (s, 2H), 3.54 (dd, J = 20.9, 11.1 Hz, 2H), 3.21 (s, 4H), 3.11 (t, J = 10.5 Hz, 4H), 3.03 (s, 3H), 2.91 (d, J = 14.3 Hz, 1H), 2.61 (d, J = 5.7 Hz, 1H), 2.40 (d, J = 14.1 Hz, 1H), 2.31 (s, 1H), 2.18 – 2.08 (m, 1H), 1.55 (s, 1H), 1.47 (s, 1H), 1.34 (d, J = 6.0 Hz, 2H), 1.21 (s, 1H), 1.05 (s, 3H), 0.86 (t, J = 6.9 Hz, 5H), 0.54 (d, J = 5.4 Hz, 1H), 0.31 (s, 3H).

Example 18

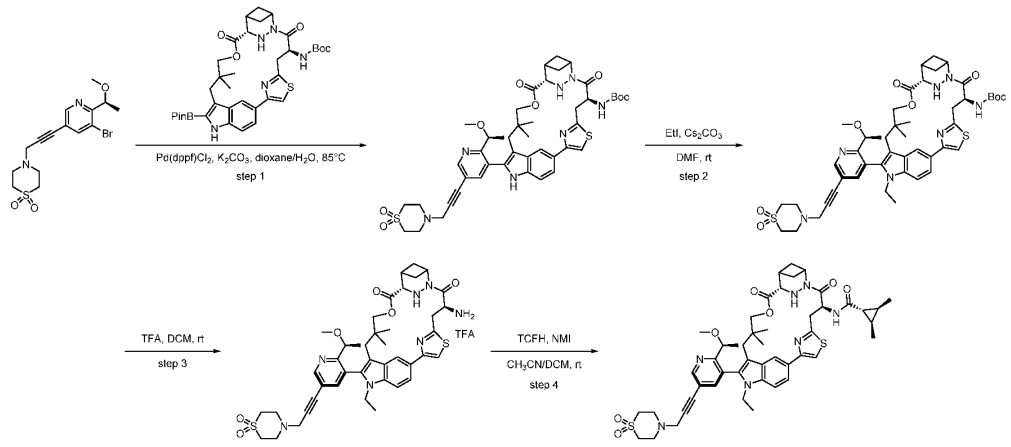
(1r,2R,3S)-N-((6^{4}S,4S,Z)-1^2-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide



Method 1:

Substituting (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholine with (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)thiomorpholine 1,1-dioxide in the Step 1 of **Example 16**, the title compound was prepared by the same procedures as described for **Example 16**.

Method 2:



Step 1: Synthesis of tert-butyl ((6⁴S,4S,Z)-1²-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

A mixture of (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)thiomorpholine 1,1-dioxide (186 mg, 0.48 mmol), tert-butyl ((6⁴S,4S,Z)-10,10-dimethyl-5,7-dioxo-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (341 mg, 0.48 mmol), K_2CO_3 (200 mg, 1.45 mmol) and $Pd(dppf)Cl_2$ (71 mg, 0.097 mmol) in dioxane (7.6 mL) and H_2O (1.9 mL) was stirred at 85°C under N_2 for 15 h. After completion, the reaction mixture was concentrated to give the crude product which was purified by silica gel column (eluting with MeOH/DCM from 0% to 10%) to give tert-butyl ((6⁴S,4S,Z)-1²-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (312 mg, 73.5 %) as a brown solid.

LCMS (ESI) calcd. for $C_{45}H_{55}N_7O_8S_2$ $[M+H]^+$ m/z 886.4, found: 886.9

Step 2: Synthesis of tert-butyl ((6⁴S,4S,Z)-1²-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1¹-ethyl-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

To a stirred solution of tert-butyl ((6⁴S,4S,Z)-1²-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (310 mg, 0.35 mmol) in DMF (5 mL) were added Cs_2CO_3 (183 mg, 0.56 mmol) and Iodoethane (88 mg, 0.56 mmol) at 0°C, the resulting mixture was stirred at rt for 3 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with EtOAc (20 mL), washed with water (50 mL x 2) and saturated NaCl (50 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column (eluting with EtOAc/PE from 0% to 100%) to give tert-butyl ((6⁴S,4S,Z)-1²-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1¹-ethyl-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (316 mg, 97.8%) as brown solid.

LCMS (ESI) calcd. for $C_{47}H_{59}N_7O_8S_2$ $[M+H]^+$ m/z 914.4, found: 914.9.

Step 3: Synthesis of (6⁴S,4S,Z)-4-amino-1²-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1¹-ethyl-10,10-dimethyl-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione

To a stirred solution of tert-butyl ((6⁴S,4S,Z)-1²-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-11-

ethyl-10,10-dimethyl-5,7-dioxo-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (316mg, 0.35mmol) in dichloromethane (3 mL) was added TFA (1 mL) dropwisely at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was concentrated to give crude (6^4S,4S,Z)-4-amino-1^2-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione which was used to next step without purification.

LCMS (ESI) calcd. for $C_{42}H_{51}N_7O_6S_2$ $[M+H]^+$ m/z 814.3, found: 814.8

Step 4: Synthesis of (1r,2R,3S)-N-((6^4S,4S,Z)-1^2-((R)-5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)-3,4-dihydropyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

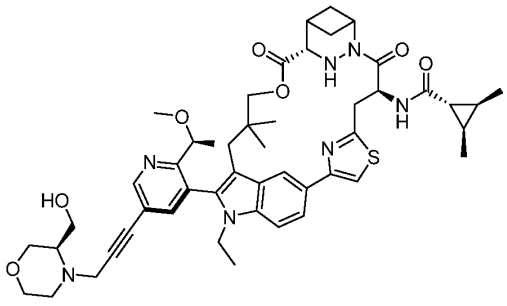
To a stirred solution of crude (6^4S,4S,Z)-4-amino-1^1-ethyl-1^2-(5-(3-((R)-3-(hydroxymethyl)morpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (220 mg, 0.27 mmol) and (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid (24 mg, 0.21 mmol) and NMI (132 mg, 1.61 mmol) in ACN (3 mL) and DCM (3 mL) was added TCFH (136 mg, 0.49 mmol) at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was concentrated to give the crude product. The crude product was purified by pre-TLC (eluting with 100% EtOAc) to give (1r,2R,3S)-N-((6^4S,4S,Z)-1^2-((R)-5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)-3,4-dihydropyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (34.3 mg) as a white solid.

LCMS (ESI) calcd. for $C_{48}H_{61}N_7O_7S_2$ $[M+H]^+$ m/z 912.4, found: 911.2.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.39 (d, J = 11.6 Hz, 2H), 7.86 (s, 1H), 7.80 (s, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 5.91 (d, J = 11.0 Hz, 1H), 5.36 (s, 1H), 4.64 (d, J = 11.0 Hz, 1H), 4.46 (d, J = 4.6 Hz, 1H), 4.35 – 4.21 (m, 2H), 4.05 (dd, J = 14.8, 6.9 Hz, 2H), 3.73 (s, 2H), 3.53 (dd, J = 20.6, 10.7 Hz, 2H), 3.21 (s, 3H), 3.13 (d, J = 4.9 Hz, 4H), 3.03 (s, 3H), 2.61 (d, J = 6.0 Hz, 1H), 2.42 (s, 1H), 2.30 (s, 1H), 2.17 – 2.09 (m, 1H), 1.56 (d, J = 8.9 Hz, 1H), 1.40 – 1.28 (m, 3H), 1.25 – 1.10 (m, 5H), 1.11 – 0.99 (m, 5H), 0.94 – 0.80 (m, 5H), 0.31 (s, 3H).

Example 19

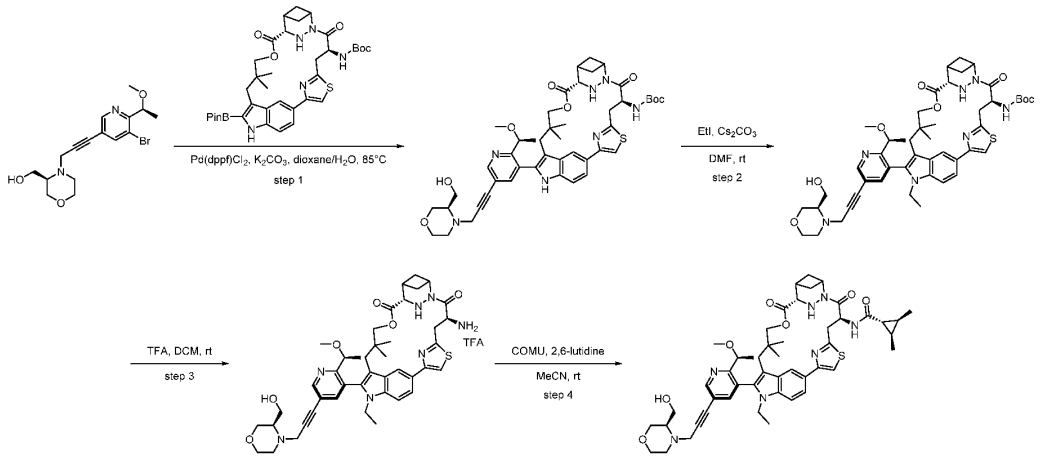
(1r,2R,3S)-N-((6^4S,4S,Z)-1^1-ethyl-1^2-(5-(3-((R)-3-(hydroxymethyl)morpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide



Method 1:

Substituting (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholine with ((R)-4-(3-(5-bromo-6-((S)-1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholin-3-yl)methanol in the Step 1 of **Example 16**, the title compound was prepared by the same procedures as described for **Example 16**.

Method 2:



Step 1: Synthesis of tert-butyl ((6⁴S,4S,Z)-1²-(5-(3-((R)-3-(hydroxymethyl)morpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

A mixture of ((R)-4-(3-(5-bromo-6-((S)-1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholin-3-yl)methanol (71 mg, 0.19 mmol), tert-butyl ((6⁴S,4S,Z)-10,10-dimethyl-5,7-dioxo-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (150 mg, 0.21 mmol), K_2CO_3 (80 mg, 0.58 mmol) and $Pd(dppf)Cl_2$ (21 mg, 0.029 mmol) in dioxane (3 mL) and H_2O (0.7 mL) was stirred at 85°C under N_2 for 16 h. After completion, the reaction mixture was concentrated to give the crude product which was purified by silica gel column (eluting with MeOH/DCM from 0% to 10%) to give tert-butyl ((6⁴S,4S,Z)-1²-(5-(3-((R)-3-(hydroxymethyl)morpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (146 mg, 88.5 %) as a pale yellow solid.

LCMS (ESI) calcd. for $C_{46}H_{57}N_7O_8S$ $[M+H]^+$ m/z 868.4, found: 868.9

Step 2: Synthesis of tert-butyl ((6⁴S,4S,Z)-1¹-ethyl-1²-(5-(3-((R)-3-(hydroxymethyl)morpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

To a stirred solution of tert-butyl ((6⁴S,4S,Z)-1²-(5-(3-((R)-3-(hydroxymethyl)morpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (915 mg, 1.05 mmol) in DMF (10 mL) were added Cs_2CO_3 (628 mg, 1.93 mmol) and Iodoethane (301 mg, 1.93 mmol) at 0°C, the resulting mixture was stirred at rt for 2 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with EtOAc (20 mL), washed with water (100 mL x 2) and saturated NaCl (60 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by pre-HPLC (eluting with CH_3CN/H_2O(0.1% NH_4HCO_3) from 20% to 85%) to give tert-butyl ((6⁴S,4S,Z)-1¹-ethyl-1²-(5-(3-((R)-3-(hydroxymethyl)morpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (190 mg, 20.0%) as white solid.

LCMS (ESI) calcd. for $C_{47}H_{59}N_7O_6S$ $[M+H]^+$ m/z 896.4, found: 896.9

Step 3: Synthesis of (6⁴S,4S,Z)-4-amino-1¹-ethyl-1²-(5-(3-((R)-3-(hydroxymethyl)morpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione

To a stirred solution of tert-butyl ((6⁴S,4S,Z)-1¹-ethyl-1²-(5-(3-((R)-3-(hydroxymethyl)morpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (190 mg, 0.21 mmol) in dichloromethane (3 mL) was added TFA (0.75 mL) dropwisely at rt, the resulting mixture was stirred at rt for 2 h. The reaction mixture was concentrated to give crude (6⁴S,4S,Z)-4-amino-1¹-ethyl-1²-(5-(3-((R)-3-(hydroxymethyl)morpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione which was used to next step without purification.

LCMS (ESI) calcd. for $C_{43}H_{53}N_7O_6S$ $[M+H]^+$ m/z 796.4, found: 796.9.

Step 4: Synthesis of (1r,2R,3S)-N-((6⁴S,4S,Z)-1¹-ethyl-1²-(5-(3-((R)-3-(hydroxymethyl)morpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

To a stirred solution of crude (6^4S,4S,Z)-4-amino-1^1-ethyl-1^2-(5-(3-((R)-3-(hydroxymethyl)morpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyeth-yl)pyridin-3-yl)-10,10-dimethyl-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (256 mg, 0.29 mmol) and (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid (32 mg, 0.29 mmol) and 2,6-lutidine (181 mg, 1.68 mmol) in ACN (10 mL) was added COMU (181 mg, 0.42 mmol) at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was concentrated to give the crude product. The crude product was purified by pre-HPLC (eluting with ACN/H_2O (0.5 % NH_4HCO_3) from 20% to 95% in 30 min) to give (1r,2R,3S)-N-((6^4S,4S,Z)-1^1-ethyl-1^2-(5-(3-((R)-3-(hydroxymethyl)morpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyeth-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (98 mg) as a white solid.

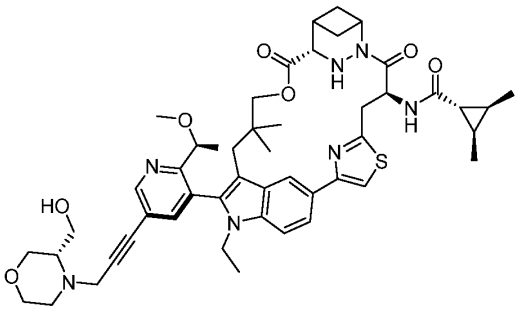
LCMS (ESI) calcd. for $C_{49}H_{61}N_7O_7S$ $[M+H]^+$ m/z 892.4, found: 892.9.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (d, J = 1.8 Hz, 1H), 8.43 – 8.35 (m, 2H), 7.87 – 7.76 (m, 2H), 7.73 (d, J = 8.6 Hz, 1H), 7.56 (d, J = 8.7 Hz, 1H), 5.91 (d, J = 11.2 Hz, 1H), 5.36 (s, 1H), 4.68 – 4.41 (m, 3H), 4.35 – 4.18 (m, 2H), 4.05 (dd, J = 14.8, 7.2 Hz, 1H), 3.86 – 3.61 (m, 4H), 3.62 – 3.39 (m, 4H), 3.33 (s, 1H), 3.27 – 3.16 (m, 4H), 3.17 – 3.03 (m, 2H), 2.92 (d, J = 14.1 Hz, 1H), 2.68 (d, J = 11.4 Hz, 1H), 2.63 – 2.56 (m, 2H), 2.53 (d, J = 10.6 Hz, 1H), 2.45 – 2.35 (m, 2H), 2.34 – 2.25 (m, 1H), 2.13 (t, J = 9.9 Hz, 1H), 1.60 – 1.49 (m, 1H), 1.34 (d, J = 6.0 Hz, 3H), 1.18 (d, J = 24.3 Hz, 4H), 1.06 (dd, J = 10.2, 5.7 Hz, 5H), 0.87 (d, J = 10.1 Hz, 5H), 0.32 (s, 3H).

LCMS (ESI): 892.4 $[M+1]^+$. ^{1}H NMR (400 MHz, DMSO) δ 8.78 (d, J = 1.8 Hz, 1H), 8.43 – 8.35 (m, 2H), 7.87 – 7.76 (m, 2H), 7.73 (d, J = 8.6 Hz, 1H), 7.56 (d, J = 8.7 Hz, 1H), 5.91 (d, J = 11.2 Hz, 1H), 5.36 (s, 1H), 4.68 – 4.41 (m, 3H), 4.35 – 4.18 (m, 2H), 4.05 (dd, J = 14.8, 7.2 Hz, 1H), 3.86 – 3.61 (m, 4H), 3.62 – 3.39 (m, 4H), 3.33 (s, 1H), 3.27 – 3.16 (m, 4H), 3.17 – 3.03 (m, 2H), 2.92 (d, J = 14.1 Hz, 1H), 2.68 (d, J = 11.4 Hz, 1H), 2.63 – 2.56 (m, 2H), 2.53 (d, J = 10.6 Hz, 1H), 2.45 – 2.35 (m, 2H), 2.34 – 2.25 (m, 1H), 2.13 (t, J = 9.9 Hz, 1H), 1.60 – 1.49 (m, 1H), 1.34 (d, J = 6.0 Hz, 3H), 1.18 (d, J = 24.3 Hz, 4H), 1.06 (dd, J = 10.2, 5.7 Hz, 5H), 0.87 (d, J = 10.1 Hz, 5H), 0.32 (s, 3H).

Example 20

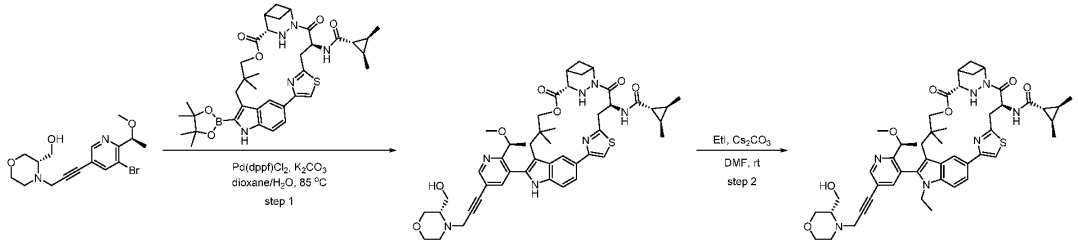
(1r,2R,3S)-N-((6^4S,4S,Z)-1^1-ethyl-1^2-(5-(3-((S)-3-(hydroxymethyl)morpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide



Method 1:

Substituting (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholine with ((S)-4-(3-(5-bromo-6-((S)-1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholin-3-yl)methanol in the Step 1 of **Example 16**, the title compound was prepared by the same procedures as described for **Example 16**.

Method 2:



Step 1: Preparation of (1r,2R,3S)-N-((6⁴S,4S,Z)-1²-(5-(3-((S)-3-(hydroxymethyl)morpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

A mixture of ((S)-4-(3-(5-bromo-6-((S)-1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholin-3-yl)methanol (70.2 mg, 0.19 mmol), (1r,2R,3S)-N-((6⁴S,4S,Z)-10,10-dimethyl-5,7-dioxo-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (160 mg, 0.23 mmol), K_2CO_3 (79 mg, 0.57 mmol) and $Pd(dppf)Cl_2$ (27.8 mg, 0.04 mmol) in dioxane (8 mL) and H_2O (1.6 mL) was stirred at 85°C under N_2 for 16h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by FCC with MeOH/DCM = 0-7% to afford the (1r,2R,3S)-N-((6⁴S,4S,Z)-1²-(5-(3-((S)-3-(hydroxymethyl)morpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (145 mg, 88%) as a yellow solid.

LCMS (ESI) calcd. for C47H57N7O7S [M+H]+ m/z 864.4, found: 865.1

Step 2: Preparation of (1r,2R,3S)-N-((6⁴S,4S,Z)-1¹-ethyl-1²-(5-(3-((S)-3-(hydroxymethyl)morpholino)prop-1-yn-1-yl)-2-((S)-1-met

hoxyeth-

yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

To a stirred solution of (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^2-(5-(3-((S)-3-(hydroxymethyl)morpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (115 mg, 0.133 mmol) in DMF (5 mL) were added Cs_2CO_3 (129.8 mg, 0.4 mmol) and Iodoethane (62.3 mg, 0.4 mmol). The resulting mixture was stirred at rt for 0.5h. After completion, the reaction mixture was diluted with EtOAc (20 mL) and H2O (20 mL). The mixture was extracted with EtOAc (10 mL*3). The combined organic layer was washed with brine (20 mL*2), dried over anhydrous Na_2SO_4 and concentration under reduced pressure. The residue was purified by pre-HPLC to give the (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(5-(3-((S)-3-(hydroxymethyl)morpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyeth-

yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (38 mg) as white solid.

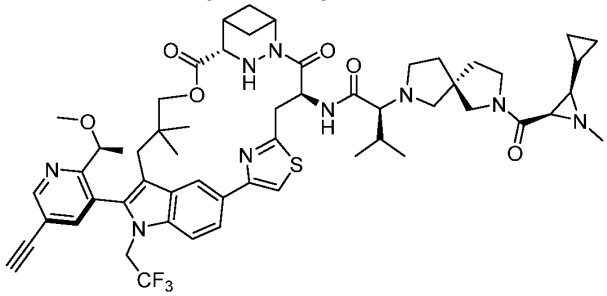
LCMS (ESI) calcd. for $C_{49}H_{61}N_7O_7S$ $[M+H]^+$ m/z 892.4, found: 892.9.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J = 2.0 Hz, 1H), 8.20 (d, J = 13.0 Hz, 1H), 7.95 (d, J = 2.0 Hz, 1H), 7.77 (d, J = 2.4 Hz, 1H), 7.69 (dd, J = 7.7, 2.4 Hz, 1H), 7.59 (s, 1H), 7.48 (d, J = 7.7 Hz, 1H), 5.24 (q, J = 5.4 Hz, 1H), 4.89 (d, J = 8.6 Hz, 1H), 4.63 (dt, J = 13.0, 12.3 Hz, 1H), 4.15 (q, J = 4.4 Hz, 2H), 4.08 – 3.99 (m, 2H), 3.99 – 3.89 (m, 2H), 3.84 – 3.78 (m, 1H), 3.78 – 3.73 (m, 3H), 3.73 – 3.64 (m, 4H), 3.59 (d, J = 8.2 Hz, 1H), 3.33 (s, 3H), 3.31 – 3.23 (m, 1H), 3.22 (d, J = 3.5 Hz, 1H), 3.11 – 3.01 (m, 3H), 3.01 – 2.93 (m, 2H), 2.72 (h, J = 7.9 Hz, 1H), 2.47 (t, J = 8.6 Hz, 1H), 2.13 – 2.03 (m, 3H), 2.03 – 1.97 (m, 1H), 1.74 (dq, J = 8.6, 5.2 Hz, 2H), 1.67 (d, J = 5.3 Hz, 3H), 1.37 (t, J = 4.4 Hz, 3H), 1.15 (s, 3H), 1.10 (s, 3H), 0.95 (d, J = 5.1 Hz, 6H).

Example 21

(2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((6^{4}S,4S,Z)-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1-(2,2,2-trifluoro-

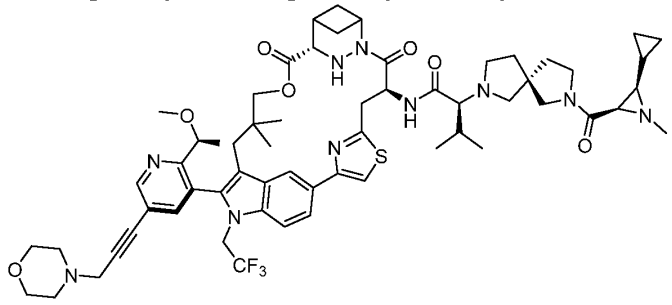
ethyl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide



Substituting (S)-4-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)-2-methylbut-3-yn-2-ol with (S)-3-bromo-5-ethynyl-2-(1-methoxyethyl)pyridine in the Step 1 of **Example 2**, Substituting iodoethane with 1,1,1-trifluoro-2-iodoethane in the Step 2 of **Example 2** and Substituting (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid with (S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-3-methylbutanoic acid in the Step 4 of **Example 2**, the title compound was prepared by the same procedures as described for **Example 2**. LCMS (ESI): 1052.5 $[M+1]^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 8.49 (d, J = 2.0 Hz, 1H), 8.25 (d, J = 12.5 Hz, 1H), 8.03 (d, J = 2.0 Hz, 1H), 7.86 (d, J = 2.4 Hz, 1H), 7.64 (dd, J = 7.7, 2.4 Hz, 1H), 7.59 (s, 1H), 7.46 (d, J = 7.9 Hz, 1H), 5.24 (q, J = 5.4 Hz, 1H), 4.90 (d, J = 8.4 Hz, 1H), 4.72 (d, J = 2.7 Hz, 2H), 4.57 (q, J = 12.4 Hz, 1H), 4.08 – 3.99 (m, 2H), 3.99 – 3.89 (m, 2H), 3.85 (d, J = 6.2 Hz, 1H), 3.64 – 3.54 (m, 3H), 3.46 (s, 1H), 3.37 (d, J = 1.3 Hz, 2H), 3.33 (s, 3H), 3.31 – 3.18 (m, 2H), 3.01 (d, J = 2.0 Hz, 2H), 2.99 – 2.92 (m, 1H), 2.88 – 2.80 (m, 3H), 2.79 – 2.72 (m, 1H), 2.70 (d, J = 8.0 Hz, 1H), 2.41 (t, J = 1.5 Hz, 3H), 2.21 (dp, J = 6.5, 5.7 Hz, 1H), 2.13 – 2.08 (m, 1H), 2.08 – 2.04 (m, 2H), 2.04 – 1.98 (m, 2H), 1.94 (t, J = 6.7 Hz, 1H), 1.89 – 1.81 (m, 3H), 1.67 (d, J = 5.3 Hz, 3H), 1.21 (dd, J = 7.9, 4.9 Hz, 2H), 1.15 (s, 3H), 1.10 (s, 3H), 1.05 (dd, J = 7.6, 5.0 Hz, 2H), 0.95 (d, J = 5.7 Hz, 3H), 0.90 (d, J = 5.5 Hz, 3H).

Example 22

(2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((6^{4}S,4S,Z)-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1-(2,2,2-trifluoroethyl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide

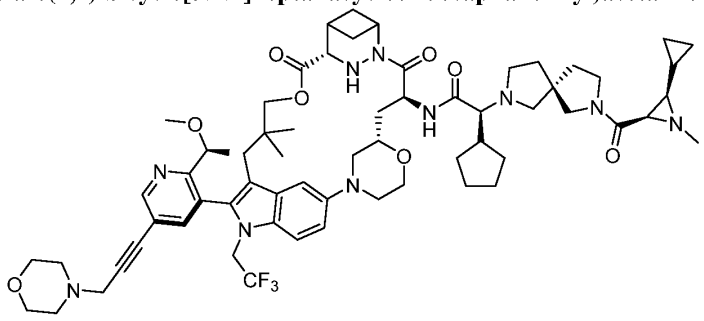


Substituting iodoethane with 1,1,1-trifluoro-2-iodoethane in the Step 2 of **Example 16** and Substituting (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid with (S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-3-methylbutanoic acid in the Step 4 of **Example 16**, the title compound was prepared by the same procedures as described for **Example 16**. LCMS (ESI): 1151.6 $[M+1]^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J = 2.0 Hz, 1H), 8.25 (d, J = 12.5 Hz, 1H), 8.01 (d, J = 1.8 Hz, 1H), 7.86 (d, J = 2.4 Hz, 1H), 7.64 (dd, J = 7.7, 2.4 Hz, 1H), 7.59 (s, 1H), 7.46 (d, J = 7.9 Hz, 1H), 5.24 (q, J = 5.4 Hz, 1H), 4.90 (d, J = 8.4 Hz, 1H), 4.72 (d, J = 2.7 Hz, 2H), 4.57 (q, J = 12.4 Hz, 1H), 4.08 – 3.99 (m, 2H), 3.99 – 3.89 (m, 2H), 3.85 (d, J = 6.2 Hz, 1H), 3.73 (dd, J = 6.5, 3.8 Hz, 2H), 3.66 (dd, J = 6.5, 3.8 Hz, 2H), 3.63 – 3.54 (m, 5H), 3.37 (d, J = 1.3 Hz, 2H), 3.33 (s, 3H), 3.31 – 3.18 (m, 2H), 3.01 (d, J = 2.0 Hz, 2H), 3.00 – 2.92 (m, 1H), 2.88 – 2.80 (m, 3H), 2.79 – 2.66 (m, 6H), 2.41 (t, J = 1.5 Hz, 3H), 2.21 (dp, J = 6.5, 5.7 Hz, 1H), 2.13 – 2.08 (m, 1H), 2.08 – 2.04 (m, 2H), 2.04 – 1.97 (m, 2H), 1.94 (t, J = 6.7 Hz, 1H), 1.89 – 1.81 (m, 3H), 1.67 (d, J = 5.3 Hz, 3H), 1.21 (dd, J

= 7.9, 4.9 Hz, 2H), 1.15 (s, 3H), 1.10 (s, 3H), 1.05 (dd, J = 7.6, 5.0 Hz, 2H), 0.95 (d, J = 5.7 Hz, 3H), 0.90 (d, J = 5.5 Hz, 3H).

Example 23

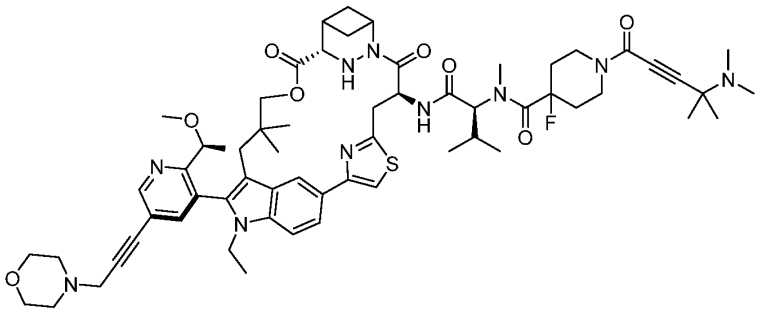
(2S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{4}S,4S)-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1-(2,2,2-trifluoroethyl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)acetamide



Substituting tert-butyl ((6^{4}S,4S,Z)-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate with tert-butyl ((2^{2}S,6^{4}S,4S)-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate in the Step 1 of **Example 16**, Substituting iodoethane with 1,1,1-trifluoro-2-iodoethane in the Step 2 of **Example 16** and Substituting (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid with (S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)acetic acid in the Step 4 of **Example 16**, the title compound was prepared by the same procedures as described for **Example 16**. LCMS (ESI): 1179.7 $[M+1]^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.38 (d, J = 1.3 Hz, 1H), 8.14 (s, 1H), 8.06 (d, J = 1.3 Hz, 1H), 7.56 (s, 1H), 7.33 (s, 1H), 7.13 (s, 1H), 4.76 (s, 1H), 4.57 – 4.51 (m, 2H), 4.46 (d, J = 12.5 Hz, 1H), 4.32 (s, 1H), 4.24 (s, 1H), 4.15 (s, 1H), 4.01 (d, J = 13.7 Hz, 2H), 3.89 (d, J = 12.8 Hz, 2H), 3.84 – 3.78 (m, 3H), 3.77 (s, 1H), 3.73 (d, J = 17.2 Hz, 3H), 3.68 (s, 2H), 3.63 (s, 2H), 3.50 (d, J = 16.8 Hz, 2H), 3.38 – 3.24 (m, 7H), 2.85 – 2.75 (m, 3H), 2.67 (s, 1H), 2.62 – 2.55 (m, 6H), 2.52 (s, 1H), 2.47 (d, J = 10.1 Hz, 4H), 2.25 (s, 1H), 2.20 (d, J = 10.3 Hz, 2H), 1.98 (s, 1H), 1.92 (d, J = 11.5 Hz, 2H), 1.88 (s, 1H), 1.85 – 1.77 (m, 4H), 1.75 (d, J = 12.3 Hz, 1H), 1.72 – 1.65 (m, 7H), 1.59 (d, J = 13.0 Hz, 2H), 1.44 (d, J = 13.0 Hz, 2H), 1.37 (d, J = 4.9 Hz, 2H), 1.23 (d, J = 4.9 Hz, 2H), 1.16 (s, 3H), 1.11 (s, 3H).

Example 24

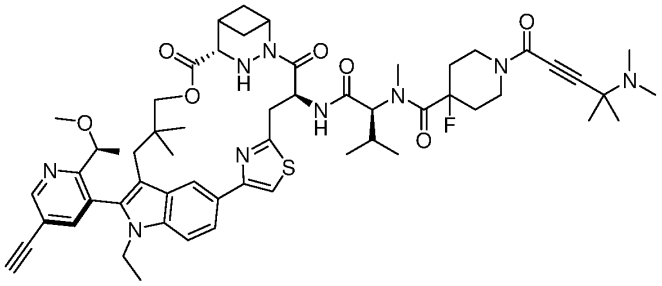
1-(4-(dimethylamino)-4-methylpent-2-ynoyl)-N-((2S)-1-(((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide



Substituting (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid with N-(1-(4-(dimethylamino)-4-methylpent-2-ynoyl)-4-fluoropiperidine-4-carbonyl)-N-methyl-L-valine in the Step 4 of **Example 16**, the title compound was prepared by the same procedures as described for **Example 16**. LCMS (ESI): 1145.6 $[M+1]^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J = 2.0 Hz, 1H), 8.25 (d, J = 12.6 Hz, 1H), 8.00 (d, J = 2.0 Hz, 1H), 7.77 (d, J = 2.4 Hz, 1H), 7.69 (dd, J = 7.7, 2.4 Hz, 1H), 7.59 (s, 1H), 7.48 (d, J = 7.7 Hz, 1H), 5.24 (q, J = 5.4 Hz, 1H), 4.90 (d, J = 8.4 Hz, 1H), 4.75 (d, J = 7.3 Hz, 1H), 4.65 (q, J = 12.4 Hz, 1H), 4.15 (q, J = 4.4 Hz, 2H), 4.08 – 3.99 (m, 2H), 3.99 – 3.89 (m, 2H), 3.76 – 3.68 (m, 4H), 3.68 – 3.54 (m, 6H), 3.33 (s, 3H), 3.32 – 3.18 (m, 2H), 3.06 (d, J = 2.6 Hz, 2H), 2.96 (s, 3H), 2.78 – 2.66 (m, 5H), 2.47 (dt, J = 9.3, 6.5 Hz, 4H), 2.35 (s, 6H), 2.21 (dhept, J = 7.3, 5.1 Hz, 1H), 2.13 – 1.97 (m, 4H), 1.67 (d, J = 5.3 Hz, 3H), 1.43 – 1.35 (m, 9H), 1.15 (s, 3H), 1.10 (s, 3H), 0.79 (d, J = 5.1 Hz, 3H), 0.75 (d, J = 5.0 Hz, 3H).

Example 25

1-(4-(dimethylamino)-4-methylpent-2-ynoyl)-N-((2S)-1-(((6^{4}S,4S,Z)-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide

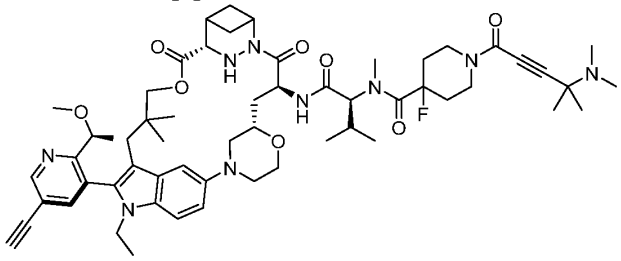


Substituting (S)-4-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)-2-methylbut-3-yn-2-ol with (S)-3-bromo-5-ethynyl-2-(1-methoxyethyl)pyridine in the Step 1 of **Example 2** and Substituting (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid with N-(1-(4-(dimethylamino)-4-methylpent-2-ynoyl)-4-fluoropiperidine-4-carbonyl)-N-methyl-L-valine in the Step 4 of **Example 2**, the title compound was prepared by the same procedures as described for **Example 2**. LCMS (ESI): 1046.5 $[M+1]^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 8.49 (d, J = 2.0 Hz, 1H), 8.25 (d, J = 12.6 Hz, 1H), 8.08 (d, J = 2.0 Hz, 1H), 7.77 (d, J = 2.4 Hz, 1H), 7.69 (dd, J = 7.7, 2.4 Hz, 1H), 7.59 (s, 1H), 7.48 (d,

J = 7.7 Hz, 1H), 5.24 (q, J = 5.4 Hz, 1H), 4.90 (d, J = 8.4 Hz, 1H), 4.75 (d, J = 7.3 Hz, 1H), 4.65 (q, J = 12.4 Hz, 1H), 4.15 (q, J = 4.4 Hz, 2H), 4.08 – 3.99 (m, 2H), 3.99 – 3.89 (m, 2H), 3.71 (dd, J = 9.3, 6.8 Hz, 2H), 3.62 (dd, J = 9.4, 6.7 Hz, 2H), 3.46 (s, 1H), 3.33 (s, 3H), 3.32 – 3.18 (m, 2H), 3.06 (d, J = 2.6 Hz, 2H), 2.96 (s, 3H), 2.72 (h, J = 7.9 Hz, 1H), 2.47 (dt, J = 9.3, 6.5 Hz, 4H), 2.35 (s, 6H), 2.21 (dhept, J = 7.3, 5.1 Hz, 1H), 2.13 – 1.97 (m, 4H), 1.67 (d, J = 5.3 Hz, 3H), 1.43 – 1.35 (m, 9H), 1.15 (s, 3H), 1.10 (s, 3H), 0.79 (d, J = 5.1 Hz, 3H), 0.75 (d, J = 5.0 Hz, 3H).

Example 26

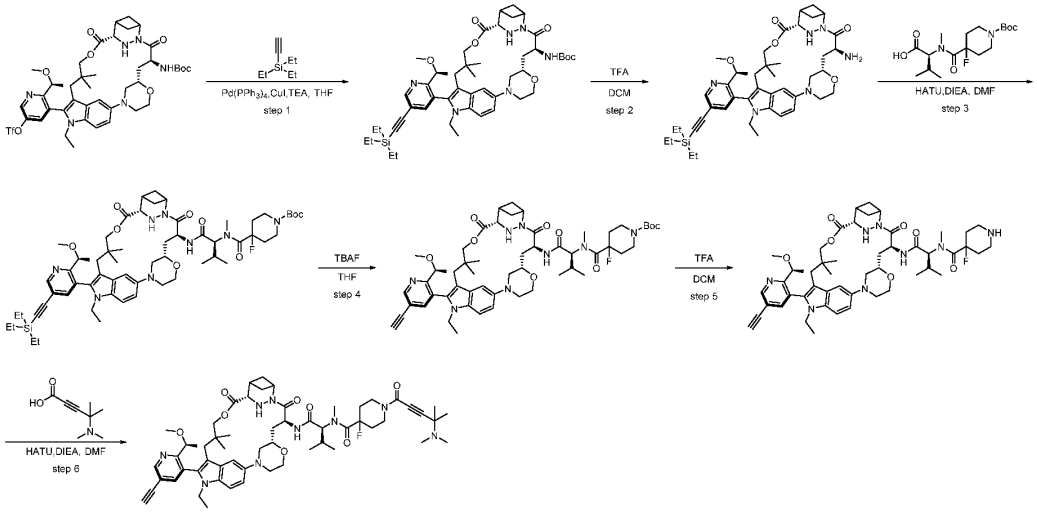
1-(4-(dimethylamino)-4-methylpent-2-ynoyl)-N-((2S)-1-(((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyeth-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide



Method 1:

Substituting (S)-4-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)morpholine with (S)-3-bromo-5-ethynyl-2-(1-methoxyethyl)pyridine in the Step 1 of **Example 23** and Substituting (S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)acetic acid with N-(1-(4-(dimethylamino)-4-methylpent-2-ynoyl)-4-fluoropiperidine-4-carbonyl)-N-methyl-L-valine in the Step 4 of **Example 23**, the title compound was prepared by the same procedures as described for **Example 23**.

Method 2:



Step 1: Synthesis of methyl tert-butyl ((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((triethylsilyl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

A mixture of 5-((2^{2}S,6^{4}S,4S)-4-((tert-butoxycarbonyl)amino)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate (190 mg, 0.21 mmol), (triethylsilyl)acetylene (149 mg, 1.06 mmol), CuI (8 mg, 0.04 mmol) and $Pd(PPh_3)_4$ (49 mg, 0.04 mmol) in TEA/DMF (2 mL/10 mL) was stirred at 100°C for 1 h under N_2 atmosphere, the reaction was monitored by LCMS. After completion, the mixture was filtered and the filtrate was concentrated, the residue was purified by silica gel column eluting with EtOAc/PE from 0% to 100% to afford tert-butyl ((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((triethylsilyl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (170 mg, 90 %) as a light yellow solid.

LCMS (ESI) calcd. for $C_{49}H_{70}N_6O_7Si$ $[M+H]^+$ m/z 883.5, found: 884.4.

Step 2: Synthesis of (2^{2}S,6^{4}S,4S)-4-amino-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((triethylsilyl)ethynyl)pyridin-3-yl)-10,10-dimethyl-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione

To a stirred solution of tert-butyl ((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((triethylsilyl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (170 mg, 0.2 mmol) in dichloromethane (3 mL) was added TFA (1 mL) dropwise at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was washed with sat. $NaHCO_3$ (3 mL), brine (3 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product (2^{2}S,6^{4}S,4S)-4-amino-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((triethylsilyl)ethynyl)pyridin-3-yl)-10,10-dimethyl-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (150 mg, crude) as a yellow solid.

LCMS (ESI) calcd. for $C_{44}H_{62}N_6O_5Si$ [M+H]+ m/z 783.5, found: 784.5.

Step 3: Synthesis of tert-butyl 4-(((2S)-1-(((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((triethylsilyl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)-4-fluoropiperidine-1-carboxylate

To a solution of N-(1-(tert-butoxycarbonyl)-4-fluoropiperidine-4-carbonyl)-N-methyl-L-valine (83 mg,

0.23 mmol) in DMF (3 mL) were added HATU (109 mg, 0.29 mmol) and DIEA (123 mg, 0.96 mmol) at 0-10°C. The resulting mixture was stirred at 0-10°C for 10 min. Then (2^2S,6^4S,4S)-4-amino-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((triethylsilyl)ethynyl)pyridin-3-yl)-10,10-dimethyl-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (150 mg, 0.20 mmol) was added into the reaction mixture, the resulting mixture was stirred at rt for 2 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with brine and extracted with EtOAc (2 x 30 mL), the combined organic phase was washed with saturated NaCl (100 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column eluting with EtOAc/PE from 0% to 100% to afford tert-butyl 4-(((2S)-1-((((2^2S,6^4S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((triethylsilyl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)-4-fluoropiperidine-1-carboxylate (40 mg, 19 %) as a light yellow solid.

LCMS (ESI) calcd. for $C_{61}H_{89}FN_8O_9Si$ $[M+H]^+$ m/z 1125.7, found: 1126.7.

Step 4: Synthesis of tert-butyl 4-(((2S)-1-((((2^2S,6^4S,4S)-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)-4-fluoropiperidine-1-carboxylate

To a solution of tert-butyl 4-(((2S)-1-((((2^2S,6^4S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((triethylsilyl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)-4-fluoropiperidine-1-carboxylate (40 mg, 0.036 mmol) in THF (3 mL) was added TBAF (0.07 mL, 1M in THF, 0.07 mmol) at 0-10°C. The resulting mixture was stirred at rt for 2 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with brine and extracted with EtOAc (2 x 30 mL), the combined organic phase was washed with saturated NaCl (100 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude tert-butyl 4-(((2S)-1-((((2^2S,6^4S,4S)-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)-4-fluoropiperidine-1-carboxylate (36 mg, crude) as a light yellow solid.

LCMS (ESI) calcd. for $C_{55}H_{75}FN_8O_9$ $[M+H]^+$ m/z 1011.6, found: 1012.7.

Step 5: Synthesis of N-((2S)-1-((((2^2S,6^4S,4S)-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane

-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide

To a stirred solution of tert-butyl 4-(((2S)-1-(((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)-4-fluoropiperidine-1-carboxylate (36 mg, 0.036 mmol) in dichloromethane (3 mL) was added TFA (1 mL) dropwise at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was washed with sat. $NaHCO_3$ (3 mL), brine (3 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product N-((2S)-1-(((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide (32 mg, crude) as a yellow solid.

LCMS (ESI) calcd. for $C_{37}H_{47}F_3N_6O_8S$ [M+H]+ m/z 911.5, found: 912.1.

Step 6: Synthesis of 1-(4-(dimethylamino)-4-methylpent-2-ynoyl)-N-((2S)-1-(((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide

To a solution of 4-(dimethylamino)-4-methylpent-2-ynoic acid (9.2 mg, 0.06 mmol) in DMF (2 mL) were added HATU (23 mg, 0.06 mmol) and DIEA (25 mg, 0.20 mmol) at 0-10°C. The resulting mixture was stirred at 0-10°C for 10 min. Then N-((2S)-1-(((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide (36 mg, 0.04 mmol) was added into the reaction mixture, the resulting mixture was stirred at rt for 2 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with brine and extracted with EtOAc (2 x 30 mL), the combined organic phase was washed with saturated NaCl (100 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by pre-HPLC (ACN/H_2O (0.5 % NH_4HCO_3) from 20% to 95% in 30 min) to give 1-(4-(dimethylamino)-4-methylpent-2-ynoyl)-N-((2S)-1-(((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide (5 mg, 12%) as a white solid.

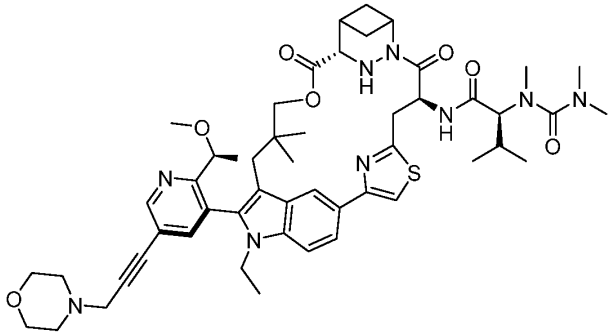
LCMS (ESI) calcd. for $C_{61}H_{79}N_{11}O_7$ $[M+H]^+$ m/z 1048.6, found: 1049.5.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (d, J = 2.0 Hz, 1H), 8.24 (d, J = 12.1 Hz, 1H), 8.06 (d, J = 2.0 Hz,

1H), 7.36 (d, J = 7.9 Hz, 1H), 7.21 (d, J = 2.2 Hz, 1H), 7.01 (dd, J = 7.9, 2.2 Hz, 1H), 5.24 (q, J = 5.4 Hz, 1H), 4.90 (d, J = 8.6 Hz, 1H), 4.75 (d, J = 7.3 Hz, 1H), 4.47 (q, J = 11.9 Hz, 1H), 4.15 (q, J = 4.4 Hz, 2H), 4.12 – 4.06 (m, 1H), 4.06 – 3.99 (m, 2H), 3.99 – 3.89 (m, 2H), 3.86 (dd, J = 7.5, 4.8 Hz, 1H), 3.81 (dd, J = 7.5, 4.8 Hz, 1H), 3.74 – 3.65 (m, 3H), 3.65 – 3.58 (m, 3H), 3.55 (d, J = 8.6 Hz, 1H), 3.48 – 3.42 (m, 2H), 3.33 (s, 3H), 3.09 (s, 2H), 2.96 (s, 3H), 2.72 (h, J = 7.9 Hz, 1H), 2.47 (dt, J = 9.3, 6.5 Hz, 4H), 2.35 (s, 6H), 2.25 – 1.97 (m, 7H), 1.67 (d, J = 5.3 Hz, 3H), 1.43 – 1.35 (m, 9H), 1.15 (s, 3H), 1.10 (s, 3H), 0.79 (d, J = 5.1 Hz, 3H), 0.75 (d, J = 5.0 Hz, 3H).

Example 27

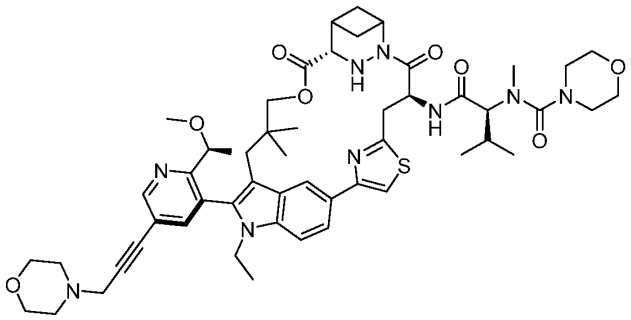
(2S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methyl-2-(1,3,3-trimethylureido)butanamide



Substituting (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid with N-(dimethylcarbamoyl)-N-methyl-L-valine in the Step 4 of **Example 16**, the title compound was prepared by the same procedures as described for **Example 16**. LCMS (ESI): 950.5 $[M+1]^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J = 2.0 Hz, 1H), 8.25 (d, J = 12.6 Hz, 1H), 8.00 (d, J = 2.0 Hz, 1H), 7.77 (d, J = 2.3 Hz, 1H), 7.69 (dd, J = 7.7, 2.4 Hz, 1H), 7.59 (s, 1H), 7.48 (d, J = 7.7 Hz, 1H), 5.24 (q, J = 5.4 Hz, 1H), 4.89 (d, J = 8.6 Hz, 1H), 4.70 – 4.59 (m, 2H), 4.15 (q, J = 4.4 Hz, 2H), 4.08 – 3.99 (m, 2H), 3.99 – 3.89 (m, 2H), 3.73 (dd, J = 6.5, 3.8 Hz, 2H), 3.66 (dd, J = 6.5, 3.8 Hz, 2H), 3.58 (d, J = 2.6 Hz, 2H), 3.33 (s, 3H), 3.32 – 3.18 (m, 2H), 3.06 (d, J = 2.6 Hz, 2H), 2.93 (d, J = 1.6 Hz, 9H), 2.78 – 2.66 (m, 5H), 2.21 (dhept, J = 8.1, 5.1 Hz, 1H), 2.13 – 1.97 (m, 4H), 1.67 (d, J = 5.3 Hz, 3H), 1.37 (t, J = 4.4 Hz, 3H), 1.15 (s, 3H), 1.10 (s, 3H), 0.79 (d, J = 5.1 Hz, 3H), 0.75 (d, J = 5.1 Hz, 3H).

Example 28

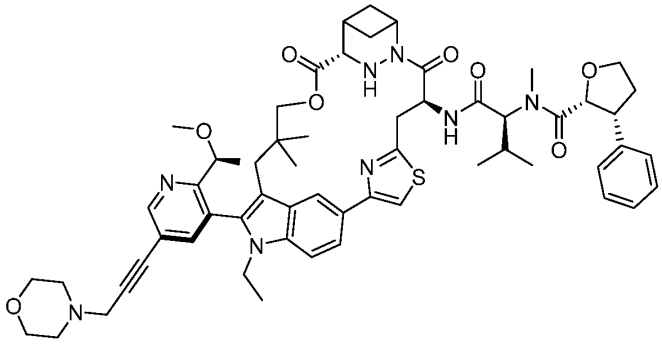
N-((2S)-1-(((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-N-methylmorpholine-4-carboxamide



Substituting (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid with N-methyl-N-(morpholine-4-carbonyl)-L-valine in the Step 4 of **Example 16**, the title compound was prepared by the same procedures as described for **Example 16**. LCMS (ESI): 992.5 $[M+1]^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J = 2.0 Hz, 1H), 8.25 (d, J = 12.6 Hz, 1H), 8.00 (d, J = 2.0 Hz, 1H), 7.77 (d, J = 2.3 Hz, 1H), 7.69 (dd, J = 7.7, 2.4 Hz, 1H), 7.59 (s, 1H), 7.48 (d, J = 7.7 Hz, 1H), 5.24 (q, J = 5.4 Hz, 1H), 4.89 (d, J = 8.6 Hz, 1H), 4.70 – 4.59 (m, 2H), 4.15 (q, J = 4.4 Hz, 2H), 4.08 – 3.99 (m, 2H), 3.99 – 3.89 (m, 2H), 3.73 (dd, J = 6.5, 3.8 Hz, 2H), 3.66 (dd, J = 6.5, 3.8 Hz, 2H), 3.64 – 3.58 (m, 2H), 3.58 – 3.51 (m, 8H), 3.33 (s, 3H), 3.31 – 3.18 (m, 2H), 3.06 (d, J = 2.6 Hz, 2H), 2.93 (s, 3H), 2.78 – 2.66 (m, 5H), 2.22 (dhept, J = 8.1, 5.1 Hz, 1H), 2.13 – 1.97 (m, 4H), 1.67 (d, J = 5.3 Hz, 3H), 1.37 (t, J = 4.4 Hz, 3H), 1.15 (s, 3H), 1.10 (s, 3H), 0.79 (d, J = 5.1 Hz, 3H), 0.75 (d, J = 5.0 Hz, 3H).

Example 29

(2R,3R)-N-((2S)-1-(((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-N-methyl-3-phenyltetrahydrofuran-2-carboxamide



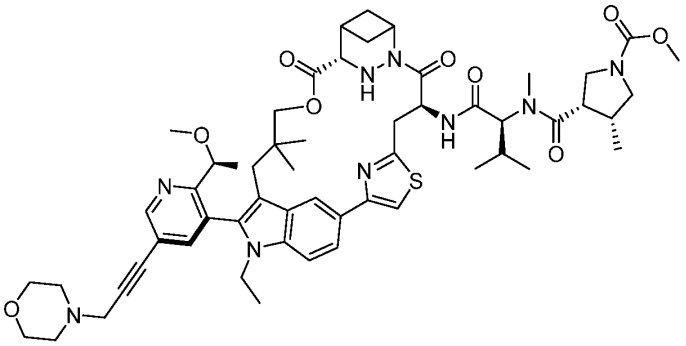
Substituting (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid with N-methyl-N-((2R,3R)-3-phenyltetrahydrofuran-2-carbonyl)-L-valine in the Step 4 of **Example 16**, the title compound was prepared by the same procedures as described for **Example 16**. LCMS (ESI): 1053.5 $[M+1]^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J = 2.0 Hz, 1H), 8.25 (d, J = 12.6 Hz, 1H), 8.00 (d, J = 2.0 Hz, 1H), 7.77 (d, J = 2.4 Hz, 1H), 7.69 (dd, J = 7.7, 2.4 Hz, 1H), 7.59 (s, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.33 – 7.22 (m, 5H), 5.24 (q, J = 5.4 Hz, 1H), 4.90 (d, J = 8.4 Hz, 1H), 4.79 (d, J = 8.1 Hz, 1H), 4.75 (d, J = 7.3 Hz, 1H), 4.65 (q, J = 12.4 Hz, 1H), 4.15 (q, J = 4.4 Hz, 2H), 4.08 – 3.99 (m, 2H), 3.99 – 3.94 (m, 2H), 3.94 – 3.89 (m, 1H), 3.89 – 3.84 (m, 1H), 3.79 – 3.70 (m, 3H), 3.66 (dd, J = 6.5, 3.8 Hz, 2H), 3.58 (d, J = 2.6 Hz, 2H), 3.33 (s, 3H), 3.31 – 3.18 (m, 2H), 3.06 (d, J = 2.6 Hz, 2H), 2.97 (s, 3H), 2.78 – 2.66 (m, 5H), 2.30

(ddd, J = 7.5, 5.5, 4.8 Hz, 1H), 2.26 – 2.15 (m, 2H), 2.13 – 1.97 (m, 4H), 1.67 (d, J = 5.3 Hz, 3H), 1.37 (t, J = 4.4 Hz, 3H), 1.15 (s, 3H), 1.10 (s, 3H), 0.79 (d, J = 5.1 Hz, 3H), 0.74 (d, J = 5.0 Hz, 3H).

Example 30

methyl

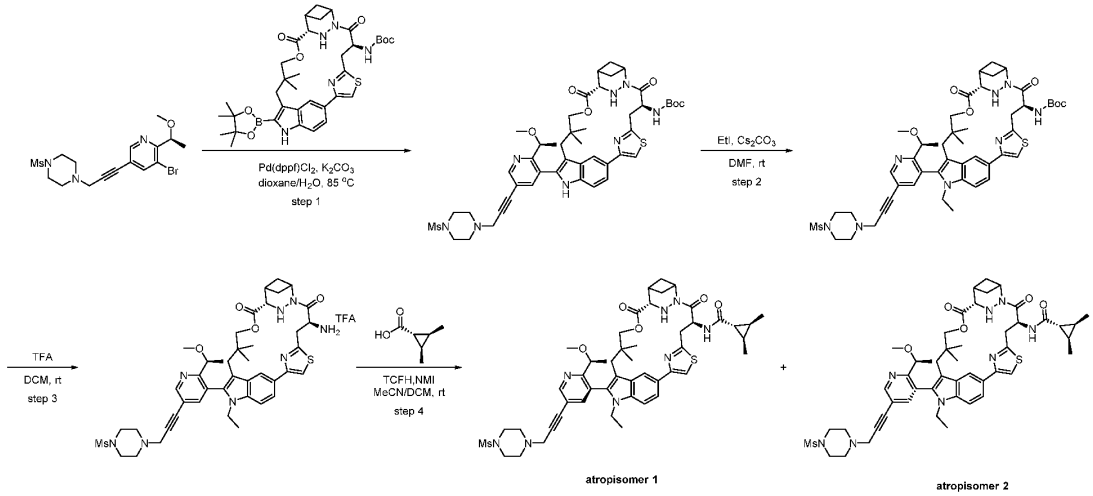
(3S,4R)-3-(((2S)-1-(((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)-4-methylpyrrolidine-1-carboxylate



Substituting (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid with N-((3S,4R)-1-(methoxycarbonyl)-4-methylpyrrolidine-3-carbonyl)-N-methyl-L-valine in the Step 4 of **Example 16**, the title compound was prepared by the same procedures as described for **Example 16**. LCMS (ESI): 1048.5 $[M+1]^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J = 2.0 Hz, 1H), 8.30 (d, J = 12.6 Hz, 1H), 8.00 (d, J = 2.0 Hz, 1H), 7.77 (d, J = 2.3 Hz, 1H), 7.69 (dd, J = 7.7, 2.4 Hz, 1H), 7.59 (s, 1H), 7.48 (d, J = 7.7 Hz, 1H), 5.24 (q, J = 5.4 Hz, 1H), 4.90 (d, J = 8.4 Hz, 1H), 4.77 (d, J = 8.1 Hz, 1H), 4.65 (q, J = 12.4 Hz, 1H), 4.15 (q, J = 4.4 Hz, 2H), 4.08 – 3.99 (m, 2H), 3.99 – 3.89 (m, 2H), 3.79 – 3.70 (m, 3H), 3.69 – 3.61 (m, 6H), 3.61 – 3.54 (m, 2H), 3.54 – 3.48 (m, 1H), 3.40 (dd, J = 9.5, 6.4 Hz, 1H), 3.33 (s, 3H), 3.31 – 3.21 (m, 2H), 3.21 – 3.12 (m, 1H), 3.06 (d, J = 2.6 Hz, 2H), 2.99 (s, 3H), 2.78 – 2.66 (m, 5H), 2.54 (dt, J = 12.4, 6.3 Hz, 1H), 2.20 (dhept, J = 8.1, 5.1 Hz, 1H), 2.13 – 1.97 (m, 4H), 1.67 (d, J = 5.3 Hz, 3H), 1.37 (t, J = 4.4 Hz, 3H), 1.15 (s, 3H), 1.10 (s, 3H), 1.01 (d, J = 6.2 Hz, 3H), 0.79 (d, J = 5.1 Hz, 3H), 0.74 (d, J = 5.0 Hz, 3H).

Example 31

(1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide



Step 1: Preparation of tert-butyl ((6⁴S,4S,Z)-1²-(2-((S)-1-methoxyethyl)-5-(3-(4-(methylsulfonyl)piperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

A mixture of (S)-1-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)-4-(methylsulfonyl)piperazine (118.1 mg, 0.28 mmol), tert-butyl ((6⁴S,4S,Z)-10,10-dimethyl-5,7-dioxo-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (200 mg, 0.28 mmol), K_2CO_3 (117.5 mg, 0.85 mmol) and $Pd(dppf)Cl_2$ (41.5 mg, 0.06 mmol) in dioxane (6 mL) and H_2O (1.5 mL) was stirred at 85°C under N_2 for 4h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by FCC with MeOH/DCM = 0-5% to afford the tert-butyl ((6⁴S,4S,Z)-1²-(2-((S)-1-methoxyethyl)-5-(3-(4-(methylsulfonyl)piperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate 7 (176 mg, 69%) as a yellow solid.

LCMS (ESI) calcd. for $C_{46}H_{58}N_8O_8S_2$ $[M+H]^+$ m/z 915.4, found: 915.9

Step 2: Preparation of tert-butyl ((6⁴S,4S,Z)-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-(3-(4-(methylsulfonyl)piperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

To a stirred solution of tert-butyl ((6⁴S,4S,Z)-1²-(2-((S)-1-methoxyethyl)-5-(3-(4-(methylsulfonyl)piperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (176 mg, 0.192 mmol) in DMF (5 mL) were added Cs_2CO_3 (187.7 mg, 0.577 mmol) and Iodoethane (90 mg, 0.577 mmol). The resulting mixture was stirred at rt for 2h. After completion, the reaction mixture was diluted with EtOAc (5 mL) and H_2O (10 mL). The mixture was extracted with EtOAc (10 mL*3). The combined organic layer was washed with brine (10 mL*2), dried over

anhydrous Na_2SO_4 and concentration under reduced pressure. The residue was purified by FCC with MeOH/DCM = 0-5% to afford the tert-butyl ((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-(4-(methylsulfonyl)piperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (131 mg, 72%) as white solid.

LCMS (ESI) calcd. for $C_{48}H_{62}N_8O_8S_2$ $[M+H]^+$ m/z 943.4, found: 943.9

Step 3: Preparation of (6^{4}S,4S,Z)-4-amino-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-(4-(methylsulfonyl)piperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione

To a stirred solution of tert-butyl ((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-(4-(methylsulfonyl)piperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (131 mg, 0.138 mmol) in DCM (5 mL) was added TFA (1 mL). The resulting mixture was stirred at rt for 1 h. The reaction mixture was concentrated under reduced pressure to give (6^{4}S,4S,Z)-4-amino-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-(4-(methylsulfonyl)piperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (162 mg) of its TFA salt as a yellow oil.

LCMS (ESI) calcd. for $C_{43}H_{54}N_8O_6S_2$ $[M+H]^+$ m/z 843.4, found: 843.8

Step 4: Preparation of (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-(4-(methylsulfonyl)piperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

To a stirred solution of (6^{4}S,4S,Z)-4-amino-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-(4-(methylsulfonyl)piperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (116 mg, 0.138 mmol) in ACN (3 mL) and DCM (3 mL) was added (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid (17.4 mg, 0.152 mmol), TCFH (116 mg, 0.414 mmol) and NMI (113 mg, 1.38 mmol). The resulting mixture was stirred at rt for 0.5h. The reaction mixture was concentrated under reduced pressure. The residue was purified by pre-TLC with EtOAc to give the (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-(4-(methylsulfonyl)piperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide as atropisomer 1 (11 mg) and (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-(4-(methylsulfonyl)piperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2

,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide as atropisomer 2 (i.e., compound of Example 31) (15 mg) as white solids.

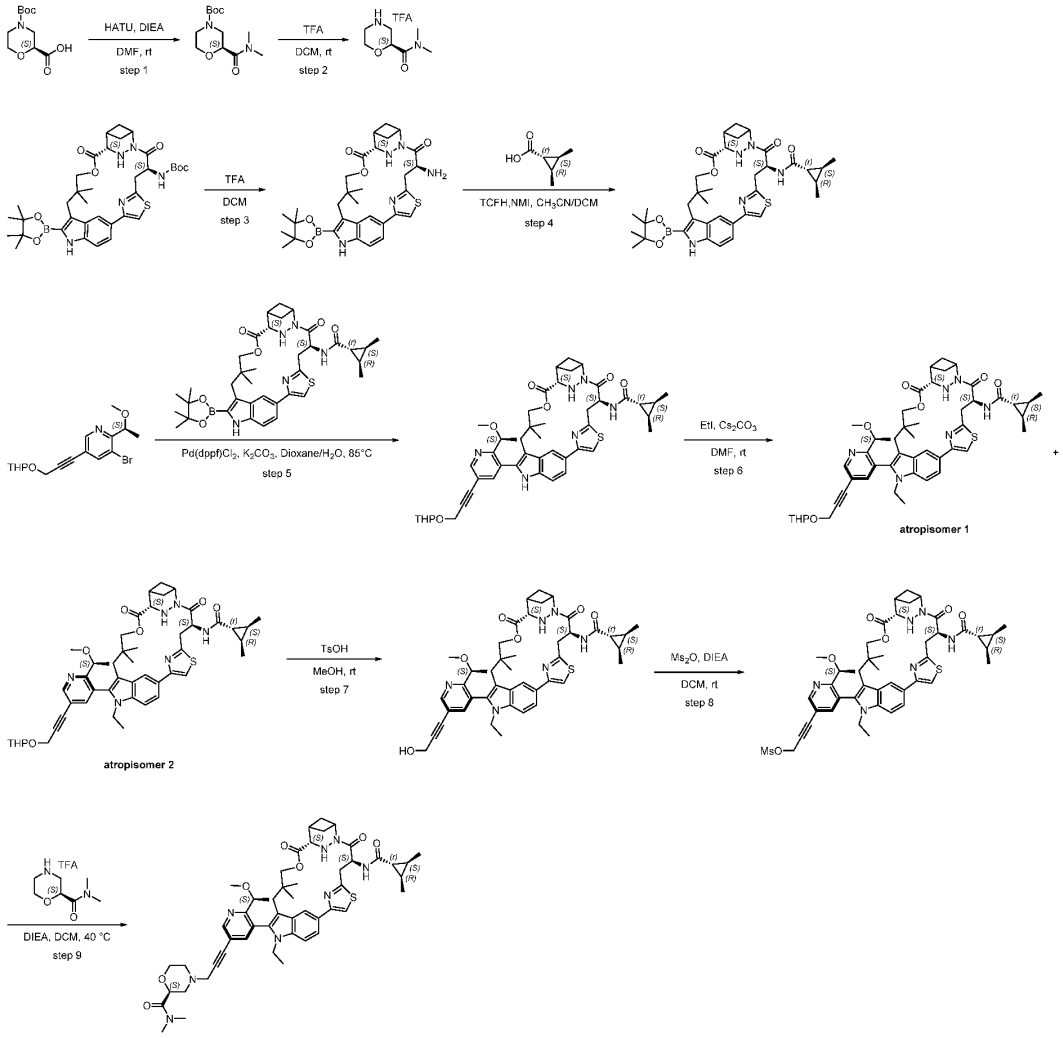
LCMS (ESI) calcd. for $C_{49}H_{62}N_8O_7S_2$ $[M+H]^+$ m/z 939.4, found: 939.9

atropisomer 1: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 – 8.76 (m, 1H), 8.40 (t, J = 10.7 Hz, 2H), 7.87 (d, J = 2.1 Hz, 1H), 7.80 (s, 1H), 7.73 (d, J = 7.3 Hz, 1H), 7.56 (d, J = 8.6 Hz, 1H), 5.91 (d, J = 11.3 Hz, 1H), 5.35 (s, 1H), 4.64 (d, J = 10.9 Hz, 1H), 4.46 (dd, J = 9.6, 4.2 Hz, 1H), 4.37 – 4.21 (m, 2H), 4.05 (dd, J = 15.4, 7.9 Hz, 1H), 3.67 – 3.48 (m, 4H), 3.27 – 3.19 (m, 3H), 3.17 – 3.08 (m, 4H), 2.86 (s, 2H), 2.70 – 2.56 (m, 4H), 2.32 (ddd, J = 15.5, 12.2, 10.3 Hz, 2H), 2.17 – 2.10 (m, 1H), 1.55 (s, 1H), 1.37 – 0.99 (m, 18H), 0.94 – 0.73 (m, 7H), 0.31 (s, 2H).

atropisomer 2: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (d, J = 1.8 Hz, 1H), 8.42 (d, J = 8.6 Hz, 2H), 8.03 (d, J = 1.9 Hz, 1H), 7.82 (s, 1H), 7.74 (d, J = 7.9 Hz, 1H), 7.54 (d, J = 8.7 Hz, 1H), 5.89 (d, J = 11.1 Hz, 1H), 5.31 (t, J = 8.1 Hz, 1H), 4.73 (d, J = 11.0 Hz, 1H), 4.49 (d, J = 5.0 Hz, 1H), 3.99 – 3.90 (m, 2H), 3.82 (dd, J = 14.6, 7.2 Hz, 1H), 3.70 – 3.57 (m, 3H), 3.51 (d, J = 10.6 Hz, 1H), 3.25 (d, J = 14.6 Hz, 1H), 3.19 – 2.99 (m, 8H), 2.88 (s, 2H), 2.64 (s, 4H), 2.40 – 2.28 (m, 2H), 2.15 (t, J = 9.6 Hz, 1H), 1.62 (t, J = 9.4 Hz, 1H), 1.31 – 1.04 (m, 18H), 0.94 – 0.77 (m, 4H), 0.48 (s, 3H).

Example 32

(2S)-4-(3-(5-((6^{4}S,4S,Z)-4-((1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxamido)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundeca-phane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)-N,N-dimethylmorpholine-2-carboxamide



Step 1: tert-butyl (S)-2-(dimethylcarbamoyl)morpholine-4-carboxylate

To a stirred solution of (S)-4-(tert-butoxycarbonyl)morpholine-2-carboxylic acid (833 mg, 3.60 mmol), dimethylamine hydrochloride (352 mg, 4.32 mmol) in DMF (10 mL) were added DIEA (1.4 g, 10.81 mmol) and HATU (2.1 g, 5.40 mmol) at rt , the resulting mixture was stirred at rt for 22 h. The reaction was monitored by LCMS. After completion, The reaction was diluted with H_2O (100 mL) and extracted with EtOAc (20 mL x 2), the combined organic phase was washed with saturated NaCl (500 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column (eluting with CH_3OH/DCM from 0% to 10%) to afford tert-butyl (S)-2-(dimethylcarbamoyl)morpholine-4-carboxylate (405 mg, 43.6 %) as a brown oil.

LCMS (ESI) calcd. for $C_{12}H_{22}N_2O_4$ $[M+H]^+$ m/z 259.2, found: 259.5.

Step 2: (S)-N,N-dimethylmorpholine-2-carboxamide

To a stirred solution of tert-butyl (S)-2-(dimethylcarbamoyl)morpholine-4-carboxylate (405 mg, 1.57 mmol) in DCM (6 mL) was TFA (2 mL) at rt , the resulting mixture was stirred at rt for 2 h. The reaction was monitored by LCMS. After completion, the reaction mixture was concentrated to give the crude (S)-N,N-dimethylmorpholine-2-carboxamide (880 mg) as a brown oil of its TFA salt.

LCMS (ESI) calcd. for $C_7H_{14}N_2O_2$ $[M+H]^+$ m/z 159.1, found: 159.3.

Step 3: (6⁴S,4S,Z)-4-amino-10,10-dimethyl-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4) bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione

To a stirred solution of tert-butyl ((6⁴S,4S,Z)-10,10-dimethyl-5,7-dioxo-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (4.3 g, 6.10 mmol) in DCM (40 mL) was added TFA (5 mL) at rt, the resulting mixture was stirred at rt for 1 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with DCM (50 mL), washed with saturated $NaHCO_3$ (100 x 2 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain (6⁴S,4S,Z)-4-amino-10,10-dimethyl-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4) bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (3.4 g, 91.9 %) as a brown foam.

LCMS (ESI) calcd. for $C_{31}H_{40}BN_5O_5S$ $[M+H]^+$ m/z 606.3, found: 607.0.

Step 4: (1r,2R,3S)-N-((6⁴S,4S,Z)-10,10-dimethyl-5,7-dioxo-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

To a stirred solution of (6⁴S,4S,Z)-4-amino-10,10-dimethyl-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4) bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (2.1 g, 3.42 mmol) and (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid (390 mg, 3.42 mmol) and NMI (702 mg, 8.55 mmol) in ACN (20 mL) and DCM (20 mL) was added TCFH (1.4 g, 5.13 mmol) at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was concentrated to give the crude product. The crude product was purified by column chromatography (eluting with EtOAc/PE from 0% to 65%) to give (1r,2R,3S)-N-((6⁴S,4S,Z)-10,10-dimethyl-5,7-dioxo-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (2.2 g, 93.4%) as a pale yellow foam.

LCMS (ESI) calcd. for $C_{37}H_{48}BN_5O_6S$[M+H]$^+$ m/z 702.3, found: 701.7.

Step 5: (1r,2R,3S)-N-((6⁴S,4S,Z)-1²-(2-((S)-1-methoxyethyl)-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

A mixture of 3-bromo-2-((S)-1-methoxyethyl)-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridine (1.0 g, 2.83 mmol), (1r,2R,3S)-N-((6⁴S,4S,Z)-10,10-dimethyl-5,7-dioxo-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-di

methylcyclopropane-1-carboxamide (2.1 g, 2.97 mmol), K_2CO_3 (1.2 g, 8.50 mmol) and Pd(dppf)Cl_2 (311 mg, 0.42 mmol) in dioxane (30 mL) and H_2O (7.5 mL) was stirred at 85°C under N_2 for 6 h. After completion, the reaction mixture was concentrated to give the crude product which was purified by silica gel column (eluting with MeOH/DCM from 0% to 10%) to give (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^2-(2-((S)-1-methoxyethyl)-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (1.1 g, 46.7 %) as a yellow foam.

LCMS (ESI) calcd. for $C_{47}H_{56}N_6O_7S[M+H]^+$ m/z 849.4, found: 849.9.

Step 6: (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

To a stirred solution of (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^2-(2-((S)-1-methoxyethyl)-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (1.1 g, 1.30 mmol) in DMF (11 mL) were added Cs_2CO_3 (844 mg, 2.59 mmol) and Iodoethane (405 mg, 2.59 mmol) at 0°C, the resulting mixture was stirred at rt for 2 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with EtOAc (25 mL), washed with water (50 mL x 3) and saturated NaCl (50 x 2 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by pre-HPLC (eluting with CH_3CN/H_2O(0.1% NH_4HCO_3) from 10% to 95%) to give (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide as atropisomer 1 (171 mg) and atropisomer 2 (168 mg) (Yield: 29.8%) as a white solid.

LCMS (ESI) calcd. for $C_{49}H_{60}N_6O_7S$ $[M+H]^+$ m/z 877.4, found: 877.9

Step 7: (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(5-(3-hydroxyprop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

To a stirred solution of (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide as atropisomer 1 (171 mg, 0.20 mmol) in MeOH (9 mL) was added TsOH (329 mg)at rt, the resulting mixture was stirred at rt for 16 h. The reaction mixture was concentrated and purified by silica gel column (eluting with

EtOAc/PE from 0% to 100%) to give crude (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(5-(3-hydroxyprop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (183 mg) as a yellow foam.

LCMS (ESI) calcd. for $C_{44}H_{52}N_6O_6S$ [M+H]+ m/z 793.4, found: 793.9

Step 8: 3-(5-((6^{4}S,4S,Z)-4-((1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxamido)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-12-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl methanesulfonate

To a stirred solution of crude (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(5-(3-hydroxyprop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (183 mg, 0.23 mmol) in DCM (7.5 mL) were added DIEA (298 mg, 2.30 mmol) and Ms_2O (241 mg, 1.38 mmol) at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was diluted with DCM (15 mL) and washed with H_2O (20 mL) and brine (20 mL). The organic layer was separated and concentrated to give crude 3-(5-((6^{4}S,4S,Z)-4-((1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxamido)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl methanesulfonate (132 mg, Yield: 65.7%) as a pale yellow foam.

LCMS (ESI) calcd. for $C_{45}H_{54}N_6O_8S_2$ $[M+H]^+$ m/z 871.3, found: 871.9

Step 9: (2S)-4-(3-(5-((64S,4S,Z)-4-((1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxamido)-11-ethyl-10,10-dimethyl-5,7-dioxo-11H-8-oxa-62,63-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-12-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)-N,N-dimethylmorpholine-2-carboxamide

To a stirred solution of (S)-N,N-dimethylmorpholine-2-carboxamide (132 mg, 0.23 mmol) in DCM (10 mL) were added DIEA (391 mg, 3.02 mmol) and the crude 3-(5-((6^{4}S,4S,Z)-4-((1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxamido)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl methanesulfonate (263 mg, 0.30 mmol) at rt, the resulting mixture was stirred at 40°C for 16 h. The reaction mixture was concentrated to give the crude product. The crude product was purified by pre-HPLC (eluting with CH_3CN/H_2O (0.1% NH_4HCO_3) from 10% to 80%) to give (2S)-4-(3-(5-((6^{4}S,4S,Z)-4-((1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxamido)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)-N,N-dimethylmorpholine-2-carboxamide (18 mg, Yield: 64.3%) as a white solid.

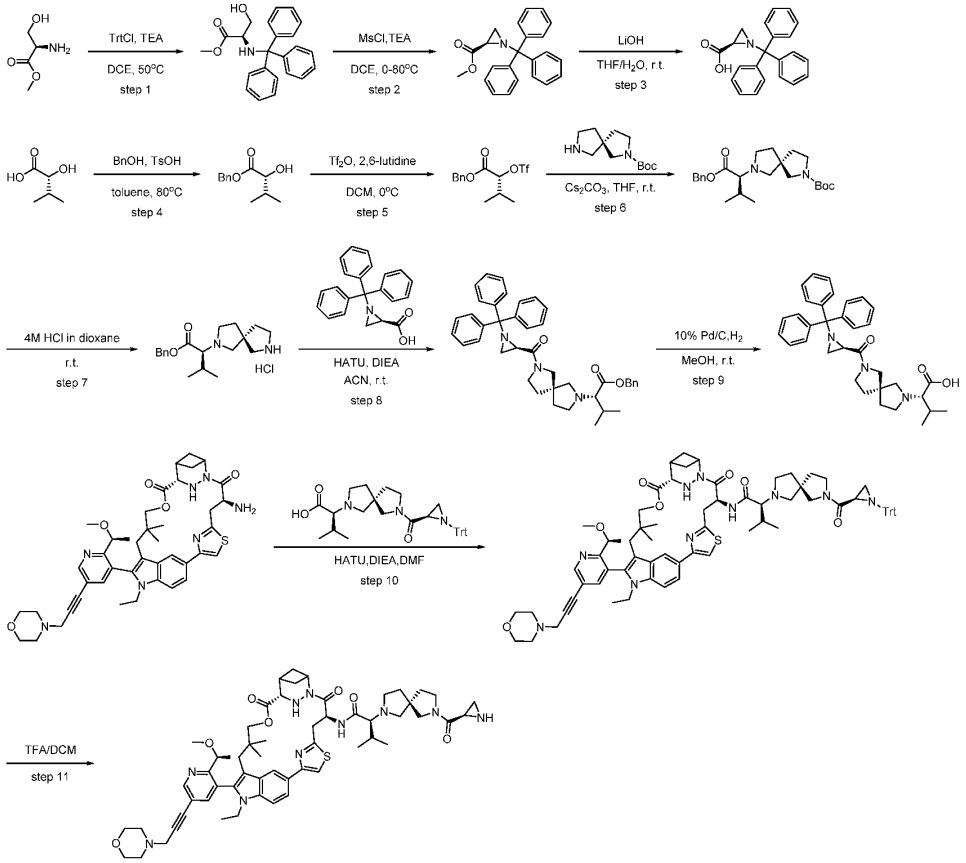
LCMS (ESI) calcd. for $C_{51}H_{64}N_8O_7S$ $[M+H]^+$ m/z 933.5, found: 934.0.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (d, J = 1.9 Hz, 1H), 8.41 (d, J = 9.0 Hz, 2H), 7.90 – 7.80 (m,

2H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 1H), 5.94 (d, *J* = 11.1 Hz, 1H), 5.38 (s, 1H), 4.66 (d, *J* = 10.9 Hz, 1H), 4.48 (d, *J* = 5.0 Hz, 1H), 4.36 – 4.22 (m, 3H), 4.07 (dd, *J* = 15.0, 7.5 Hz, 1H), 3.87 (d, *J* = 10.1 Hz, 1H), 3.67 – 3.49 (m, 4H), 3.23 (s, 3H), 3.19 – 3.07 (m, 1H), 3.01 (s, 3H), 2.94 (d, *J* = 14.3 Hz, 1H), 2.86 – 2.71 (m, 4H), 2.63 (d, *J* = 5.8 Hz, 1H), 2.43 (dd, *J* = 20.4, 9.5 Hz, 3H), 2.34 (dd, *J* = 11.2, 8.0 Hz, 2H), 2.20 – 2.10 (m, 1H), 1.57 (s, 1H), 1.36 (d, *J* = 6.0 Hz, 3H), 1.28 – 1.20 (m, 1H), 1.17 (d, *J* = 4.1 Hz, 2H), 1.08 (dd, *J* = 10.4, 5.7 Hz, 5H), 0.87 (d, *J* = 7.1 Hz, 5H), 0.33 (s, 3H).

Example 33

(2S)-2-(7-((R)-aziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide



Step 1: Synthesis of methyl trityl-D-serinate

To a mixture of methyl D-serinate hydrochloride (5.00 g, 32.14 mmol) and TEA (8.13 g, 80.34 mmol) in DCE (70 mL) was added TrtCl (8.96 g, 32.14 mmol) at room temperature, the mixture was stirred at 50℃ under N_2 atmosphere overnight. The reaction was monitored by LCMS, after completion, the mixture was concentrated and the residue was purified by silica gel column chromatography (eluting with EtOAc/PE, from 0% to 6% in 20 min) to obtain methyl trityl-D-serinate (11.20 g, 30.99 mmol, yield: 96.4 %) as a light yellow solid.

LCMS (ESI) calcd. for $C_{23}H_{23}NO_3$ $[M+Na]^+$ m/z 384.2, found 384.5.

Step 2: Synthesis of methyl (R)-1-tritylaziridine-2-carboxylate

To a mixture of (1.00 g, 2.77 mmol) and TEA (0.84 g, 8.30 mmol) in DCE (10 mL) was added MsCl (0.38 g, 3.32 mmol) at 0℃, the mixture was stirred at r.t. for 4h and at 80℃ for 16 h under N_2 atmosphere, the reaction was monitored by LCMS. After completion, the mixture was diluted with water (40 mL) and extracted with DCM (20 mL x 3), the combined organic layer was washed with brine (40 mL), dried over Na_2SO_4, concentrated and purified by flash chromatography column (eluting with EtOAc/ PE from 0% to 2% in 10 min) to obtain methyl (R)-1-tritylaziridine-2-carboxylate (760 mg, 2.21 mmol, yield: 79.8 %) as a white solid.

LCMS (ESI) calcd. for $C_{23}H_{21}NO_2$ $[M+H]^+$ m/z 344.2, found 344.6.

Step 3: Synthesis of (R)-1-tritylaziridine-2-carboxylic acid

Methyl (R)-1-tritylaziridine-2-carboxylate (500 mg, 1.46 mmol) was dissolved in a mixture of THF (15 mL) and H_2O (2 mL) at 0℃, 1M NaOH (20 mL) was added, followed by 1M LiOH (10 mL), the mixture was stirred for 2h at 0℃. The reaction was monitored by LCMS, after completion, the mixture was diluted with DCM (50 mL) and 15% aqueous citric acid (40 mL), the organic phase was further washed with 15% citric acid solution (3 x 20 mL) and the combined aqueous phases were extracted with DCM (3 x 20 mL), the combined organic phase was concentrated and the residue was purified by reverse phase column (eluting with MeCN/H_2O, from 5% to 34% in 35 min) to give (R)-1-tritylaziridine-2-carboxylic acid (380 mg, 1.15 mmol, yield: 78.8%) as a white solid.

LCMS (ESI) calcd. for $C_{22}H_{19}NO_2$ $[M-H]^-$ m/z 328.1, found: 328.5.

Step 4: Synthesis of benzyl (R)-2-hydroxy-3-methylbutanoate

To a mixture of BnOH (3.84 g, 35.55 mmol) in toluene (50 mL) was added TsOH (0.58g, 3.39 mmol) at r.t., the mixture was stirred at 80℃ for 1h and then (R)-2-hydroxy-3-methylbutanoic acid (4.00 g, 33.86 mmol) was added, the reaction was stirred at 80℃ for 1 h under N_2 atmosphere, the mixture was monitored by LCMS. After completion, the mixture was diluted with water (100 mL) and extracted with EA (50 mL x 3). The combined organic phase was concentrated under reduced pressure and the the residue was purified by silica gel column chromatography (eluting with EtOAc/PE, from 0% to 5% in 20 min) to afford benzyl (R)-2-hydroxy-3-methylbutanoate (5.21 g, 25.02 mmol, yield: 73.9%) as a colorless oil.

LCMS (ESI) calcd. for $C_{12}H_{16}O_3$ $[M+H]^+$ m/z 209.1, found: 209.3.

Step 5: Synthesis of benzyl (R)-3-methyl-2-(((trifluoromethyl)sulfonyl)oxy)butanoate

To a mixture of benzyl (R)-2-hydroxy-3-methylbutanoate (5.21 g, 25.02 mmol) and 2,6-lutidine (2.95g, 27.52 mmol) in DCM (100 mL) was added Tf_2O (7.41 g, 26.27 mmol) slowly at 0℃, the mixture was stirred at 0℃ for 2 h under N_2 atmosphere, the reaction was monitored by LCMS. After completion, the mixture was diluted with water (100 mL) and extracted with DCM (50 mL x 3), the combined organic layer was washed with brine (100 mL), dried over Na_2SO_4 and concentrated, the residue was purified by flash chromatography column (eluting with EtOAc/PE, from 0% to 2% in 10 min) to obtain benzyl (R)-3-methyl-2-(((trifluoromethyl)sulfonyl)oxy)butanoate (6.70 g, 19.69 mmol, yield: 78.7 %) as a colorless oil.

LCMS (ESI) calcd. for $C_{13}H_{15}F_3O_5S$ $[M+NH_4]^+$ m/z 358.1, found: 358.4.

Step 6: Synthesis of tert-butyl 7-((S)-1-(benzyloxy)-3-methyl-1-oxobutan-2-yl)-2,7-diazaspiro[4.4]nonane-2-carboxylate

A mixture of benzyl (R)-3-methyl-2-(((trifluoromethyl)sulfonyl)oxy)butanoate (376 mg, 1.10 mmol) and tert-butyl 2,7-diazaspiro[4.4]nonane-2-carboxylate (250 mg, 1.10 mmol) in THF (10 mL) was stirred at r.t. for 2h, the reaction was monitored by LCMS. After completion, the mixture was diluted with EtOAc (20) and water (40 mL), then extracted with EtOAc (20 mL x 3), the combined organic layer was washed with brine (40 mL), dried over Na_2SO_4 and concentrated , the residual was purified by silica gel column chromatography (eluting with EtOAc/ PE, from 0% to 10% in 15 min) to obtain tert-butyl 7-((S)-1-(benzyloxy)-3-methyl-1-oxobutan-2-yl)-2,7-diazaspiro[4.4]nonane-2-carboxylate (200 mg, 0.48 mmol, yield: 43.6%) as a colorless oil.

LCMS (ESI) calcd. for $C_{24}H_{36}N_2O_4$ $[M+H]^+$ m/z 417.3, found: 418.2.

Step 7: Synthesis of benzyl (2S)-3-methyl-2-(2,7-diazaspiro[4.4]nonan-2-yl)butanoate hydrochloride

A mixture of tert-butyl 7-((S)-1-(benzyloxy)-3-methyl-1-oxobutan-2-yl)-2,7-diazaspiro[4.4]nonane-2-carboxylate (200 mg, 0.48 mmol) in 4M HCl in dioxane (3 mL) was stirred at r.t. for 1h under N_2 atmosphere, the reaction was monitored by LCMS. After completion, the mixture was concentrated to afford benzyl (2S)-3-methyl-2-(2,7-diazaspiro[4.4]nonan-2-yl)butanoate hydrochloride (169 mg, 0.48 mmol, yield: 100.0%) as a white solid.

LCMS (ESI) calcd. for $C_{19}H_{28}N_2O_2$ $[M+H]^+$ m/z 317.2, found: 317.6.

Step 8: Synthesis of benzyl (2S)-3-methyl-2-(7-((R)-1-tritylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)butanoate

To a mixture of benzyl (2S)-3-methyl-2-(2,7-diazaspiro[4.4]nonan-2-yl)butanoate hydrochloride (169 mg, 0.48 mmol), DIEA (619 mg, 4.79 mmol) and (R)-1-tritylaziridine-2-carboxylic acid (175 mg, 0.48 mmol) in ACN (5 mL) was added HATU (273 mg, 0.72mmol), the mixture was stirred at r.t. for 3 h under N_2 atmosphere, the reaction was monitored by LCMS. After completion, the mixture was purified by reverse phase column (eluting with MeCN/H_2O, from 5% to 88% in 35 min) to afford benzyl (2S)-3-methyl-2-(7-((R)-1-tritylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)butanoate (210 mg, 0.33 mmol, yield: 69.6%) as a light yellow solid.

LCMS (ESI) calcd. for $C_{41}H_{45}N_3O_3$ $[M+H]^+$ m/z 628.4, found: 629.6.

Step 9: Synthesis of (2S)-3-methyl-2-(7-((R)-1-tritylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)butanoic acid

A mixture of benzyl (2S)-3-methyl-2-(7-((R)-1-tritylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)butanoate (210 mg, 0.33 mmol) and 10% Pd/C (40 mg) in MeOH (5 mL) was stirred at room temperature for 16 h under H_2 atmosphere, the reaction was monitored by LCMS. After completion, the mixture was filtered and the filtrate was concentrated to afford (2S)-3-methyl-2-(7-((R)-1-tritylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)butanoic acid (120 mg, 0.22 mmol, yield: 66.7 %) as a white solid.

LCMS (ESI) calcd. for $C_{34}H_{39}N_3O_3$ $[M+H]^+$ m/z 538.3, found: 538.7.

Step 10: Synthesis of (2S)-N-((6⁴S,4S,Z)-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methyl-2-(7-((R)-1-tritylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)butanamide

To a solution of (2S)-3-methyl-2-(7-((R)-1-tritylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)butanoic acid (16 mg, 0.03 mmol) in DMF (1 mL) were added HATU (16 mg, 0.04 mmol) and DIEA (19 mg, 0.14 mmol) at 0-10°C. The resulting mixture was stirred at RT for 10 min. Then (6⁴S,4S,Z)-4-amino-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (22 mg, 0.03 mmol) was added into the reaction mixture, the resulting mixture was stirred at rt for 2 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with brine and extracted with EtOAc (2 x 30 mL), the combined organic phase was washed with saturated NaCl (50 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column eluting with EtOAc/PE from 0% to 100% to afford (2S)-N-((6⁴S,4S,Z)-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methyl-2-(7-((R)-1-tritylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)butanamide (27 mg, 73 %) as a yellow solid.

LCMS (ESI) calcd. for $C_{76}H_{88}N_{10}O_7S$ $[M+H]^+$ m/z 1285.7.

Step 11: Synthesis of (2S)-2-(7-((R)-aziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((6⁴S,4S,Z)-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide

To a stirred solution of (2S)-N-((6⁴S,4S,Z)-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methyl-2-(7-((R)-1-tritylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)butanamide (27 mg, 0.02 mmol) in dichloromethane (2 mL) was added TFA (0.5 mL) dropwisely at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was washed with sat. $NaHCO_3$ (10 mL), brine (10 mL), then dried over Na_2SO_4, following with concentration under reduced pressure, the residue was purified by pre-HPLC (eluting with CH_3CN/H_2O(0.1% NH_4HCO_3) from 20% to 70%) to give (2S)-2-(7-((R)-aziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((6⁴S,4S,Z)-1¹-ethyl-1²-(2-((S)-1-methoxyeth-

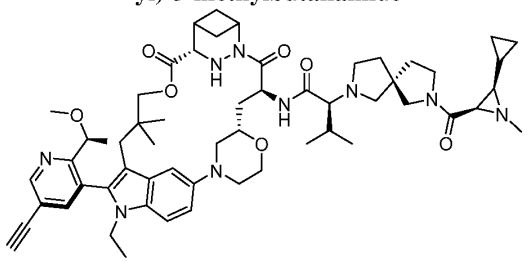
yl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide (1.4 mg, 6.4 %) as a white solid.

LCMS (ESI) calcd. for $C_{57}H_{74}N_{10}O_7S$ $[M+H]^+$ m/z 1043.6, found: 1045.2.

^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.78 (d, *J* = 1.9 Hz, 1H), 8.40 (s, 1H), 8.22 (m, 1H), 7.83 (d, *J* = 9.8 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 5.98 – 5.88 (m, 1H), 5.33 (s, 1H), 4.73 (d, *J* = 10.4 Hz, 1H), 4.49 (s, 1H), 4.37 – 4.21 (m, 2H), 4.07 (m, 1H), 3.75 (m, 1H), 3.67 – 3.45 (m, 7H), 3.42 – 3.30 (m, 8H), 3.27 – 3.15 (m, 4H), 2.96 (d, *J* = 14.2 Hz, 1H), 2.78 (m, 3H), 2.61 (m, 3H), 2.54 – 2.50 (m, 3H), 2.47 – 2.43 (m, 2H), 2.34 (dd, *J* = 20.4, 9.5 Hz, 2H), 2.18 – 2.09 (m, 1H), 2.03 – 1.54 (m, 7H), 1.34 (d, *J* = 6.0 Hz, 3H), 1.24 – 1.12 (m, 2H), 1.04 – 0.74 (m, 9H), 0.28 (s, 3H).

Example 34

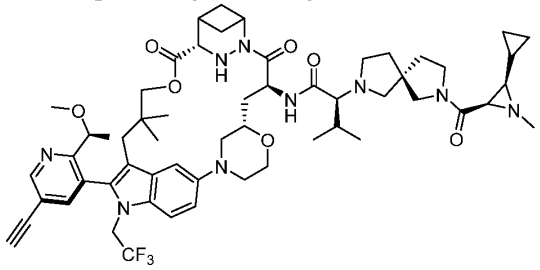
(2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide



Substituting N-(1-(tert-butoxycarbonyl)-4-fluoropiperidine-4-carbonyl)-N-methyl-L-valine with (S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-3-methylbutanoic acid in the Step 3 of **Example 26**, the title compound was prepared by the same procedures as described for **Example 26**.

Example 35

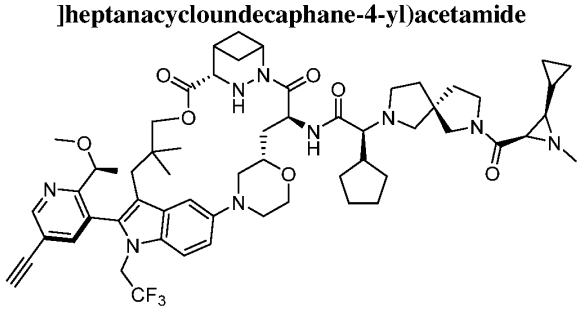
(2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{4}S,4S)-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1-(2,2,2-trifluoro-ethyl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide



Substituting bromoethane with 2-bromo-1,1,1-trifluoroethane in the Step of **Example 34**, the title compound was prepared by the same procedures as described for **Example 34**.

Example 36

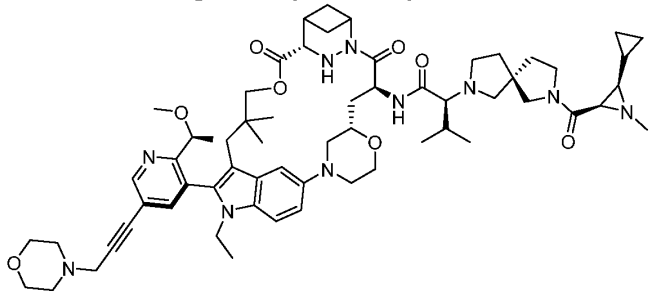
(2S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{4}S,4S)-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1-(2,2,2-trifluoroethyl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)acetamide



Substituting (S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-3-methylbutanoic acid with (S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)acetic acid in the Step 3 of **Example 34**, the title compound was prepared by the same procedures as described for **Example 34**.

Example 37

(2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide

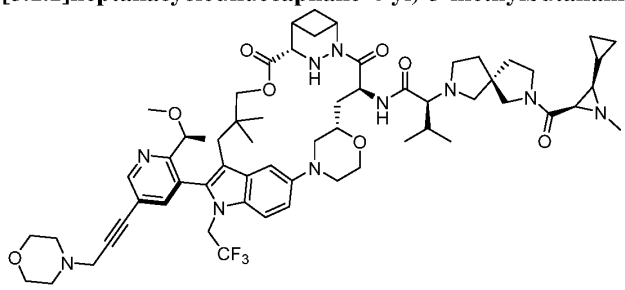


Substituting triethyl(ethynyl)silane with 4-(prop-2-yn-1-yl)morpholine in the Step 1 and substituting N-(1-(tert-butoxycarbonyl)-4-fluoropiperidine-4-carbonyl)-N-methyl-L-valine with (S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-3-methylbutanoic acid in the Step 3 of **Example 26**, the title compound was prepared by the same procedures as described for **Example 26**.

Example 38

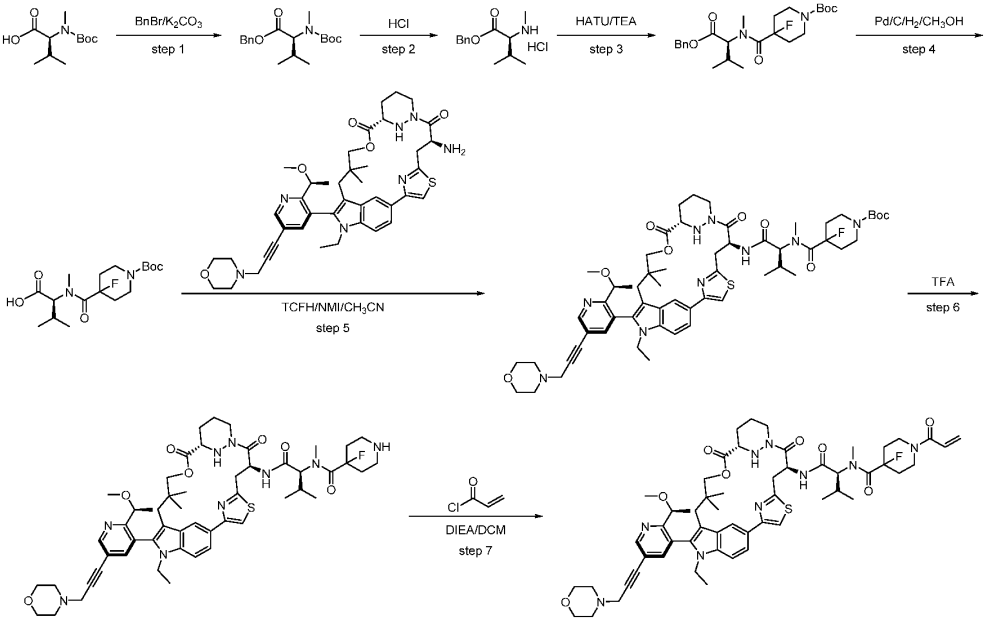
(2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{4}S,4S)-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1-(2,2,2-trifluoroethyl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicy

clo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide



Substituting bromoethane with 2-bromo-1,1,1-trifluoroethane in the Step of **Example 37**, the title compound was prepared by the same procedures as described for **Example 37**.**Example 39**

1-acryloyl-N-((2S)-1-(((6^{3}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide



Step 1: Synthesis of benzyl N-(tert-butoxycarbonyl)-N-methyl-L-valinate

To a stirred solution of (S)-2,3-bis(tert-butoxycarbonyl)-2,3-diazabicyclo[3.1.1]heptane-4-carboxylic acid (2.31 g, 10.0 mmol) in DMF (20 mL) was added K_2CO_3 (2.72 g, 20.0 mmol) and (bromomethyl)benzene (2.05 g, 12.0 mmol) at r.t.. The reaction mixture was stirred at r.t. for 3 h. After completion, the reaction mixture was diluted with brine and extracted with EtOAc (2 x 50 mL). The organic layers were combined, washed with saturated NaCl (2 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated to give the crude product which was purified by silica gel column (eluting with EA/PE from 0% to 10%) to give benzyl N-(tert-butoxycarbonyl)-N-methyl-L-valinate (2) (2.9 g, 90%) as a colorless oil.

LCMS (ESI) calcd. for $C_{18}H_{27}NO_4$ [M-H]$^+$ m/z 321.2, found: 322.6.

Step 2: Synthesis of benzyl methyl-L-valinate HCl salt

To a stirred solution of benzyl N-(tert-butoxycarbonyl)-N-methyl-L-valinate (2.90 g, 9.03 mmol) in DCM (10 mL) was added HCl/dioxane (15 mL, 4M), the resulting mixture was stirred at rt for 2 h. The reaction mixture was concentrated to give the crude product benzyl methyl-L-valinate HCl salt (2.3 g, 99%) as a white solid.

LCMS (ESI) calcd. for $C_{13}H_{19}NO_2$ $[M+H]^+$ m/z 221.1, found:222.9.

Step 3: Synthesis of tert-butyl (S)-4-((1-(benzyloxy)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)-4-fluoropiperidine-1-carboxylate

To a solution of benzyl methyl-L-valinate HCl salt (362 mg, 1.41 mmol) in DMF (3 mL) was added 1-(tert-butoxycarbonyl)-4-fluoropiperidine-4-carboxylic acid (347 mg, 1.41 mmol), HATU (770 mg, 2.03 mmol) and DIEA (404 mg, 4.00 mmol) at rt. The resulting mixture was stirred atrt overnight. After completion, the reaction mixture was diluted with brine and extracted with EtOAc (2 x 10 mL), the combined organic phase was washed with saturated NaCl (10 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column eluting with EtOAc/PE from 0% to 35% to afford tert-butyl (S)-4-((1-(benzyloxy)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)-4-fluoropiperidine-1-carboxylate (300 mg, 47 %) as a colorless oil.

LCMS (ESI) calcd. for $C_{24}H_{35}FN_2O_5$ $[M+H]^+$ m/z 450.3, found: 396.1.

Step 4: Synthesis of N-(1-(tert-butoxycarbonyl)-4-fluoropiperidine-4-carbonyl)-N-methyl-L-valine

To a solution of tert-butyl (S)-4-((1-(benzyloxy)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)-4-fluoropiperidine-1-carboxylate (300 mg, 0.667 mmol) in CH_3OH (10 mL) was added Pd/C (60 mg, 10%), the resulting mixture was stirred at rt for 3 hours under H_2 atmosphere (1 atm). The reaction was monitored by LCMS. After completion, the mixture was filtered and concentrated to give the N-(1-(tert-butoxycarbonyl)-4-fluoropiperidine-4-carbonyl)-N-methyl-L-valine (230 mg, 96%) as a colorless oil.

LCMS (ESI) calcd. for $C_{17}H_{29}FN_2O_5$ $[M+H]^+$ m/z 360.2, found: 361.6.

Step 5: Synthesis of tert-butyl 4-(((2S)-1-(((6^{3}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)-4-fluoropiperidine-1-carboxylate

To a stirred solution of (6^{3}S,4S,Z)-4-amino-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (45 mg, 0.06 mmol) and N-(1-(tert-butoxycarbonyl)-4-fluoropiperidine-4-carbonyl)-N-methyl-L-valine (18 mg, 0.072 mmol) and 1-methyl-1H-imidazole (9 mg, 0.12 mmol) in ACN (2 mL) was added TCFH (21 mg, 0.078 mmol) at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was concentrated to give the crude product. The crude product was purified by pre-HPLC (ACN/H_2O (0.5 % NH_4HCO_3) from 20% to 95% in

30 min) to give tert-butyl 4-(((2S)-1-(((6^{3}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)-4-fluoropiperidine-1-carboxylate (20 mg, 30%) as a white solid.

LCMS (ESI) calcd. for $C_{58}H_{78}FN_9O_9S$ $[M+H]^+$ m/z 1095.6, found: 1097.1.

Step 6: Synthesis of N-((2S)-1-(((6^{3}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide TFA salt

To a stirred solution of tert-butyl 4-(((2S)-1-(((6^{3}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)-4-fluoropiperidine-1-carboxylate (20 mg, 0.018 mmol) in dichloromethane (2 mL) was added TFA (1 mL) dropwisely at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was concentrated and lyophilized to give N-((2S)-1-(((63S,4S,Z)-11-ethyl-12-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-61,62,63,64,65,66-hexahydro-11H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide (21 mg, 100%) of its TFA salt as a yellow solid.

LCMS (ESI) calcd. for $C_{53}H_{70}FN_9O_7S$ $[M+H]^+$ m/z 995.5, found: 997.1.

Step 7: Synthesis of 1-acryloyl-N-((2S)-1-(((63S,4S,Z)-11-ethyl-12-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-61,62,63,64,65,66-hexahydro-11H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide

To a stirred solution of N-((2S)-1-(((6^{3}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide TFA salt (21 mg, 0.019 mmol) in DCM (2 mL) was added DIEA (10 mg, 0.076 mmol) and acryloyl chloride (4 mg, 0.038 mmol) at rt, the resulting mixture was stirred at rt overnight. The reaction mixture was concentrated to give the crude product. The crude product was purified by pre-HPLC (ACN/H_2O (0.5 % NH_4HCO_3) from 20% to 95% in 30 min) to give

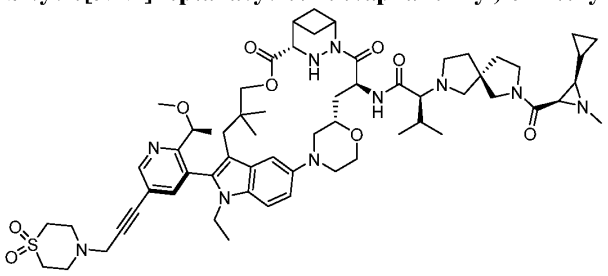
1-acryloyl-N-((2S)-1-(((6^{3}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyrid-
in-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide (6 mg, 30%) as a white solid.

LCMS (ESI) calcd. for $C_{56}H_{72}FN_9O_8S$ $[M+H]^+$ m/z 1049.5, found: 1051.1.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (d, J = 1.5 Hz, 1H), 8.48 – 8.42 (m, 2H), 7.85 – 7.78 (m, 2H), 7.74 (d, J = 7.7 Hz, 1H), 7.56 (d, J = 8.6 Hz, 1H), 6.89-6.80 (m, 1H), 6.15-6.10 (m, 1H), 5.69 (d, J = 11.2 Hz, 1H), 5.46-5.41 (m, 1H), 5.09 – 5.02 (m, 1H), 4.70 (d, J = 11.5 Hz, 1H), 4.38 – 4.15 (m, 6H), 4.12-3.94 (m, 3H), 3.60-3.54 (m, 8H), 3.24 (s, 3H), 3.07 (d, J = 5.3 Hz, 4H), 2.99 – 2.92 (m, 2H), 2.89-2.86 (m, 1H), 2.79-2.70 (m, 1H), 2.42-2.33 (m, 3H), 2.23-1.92 (m, 6H), 1.82-1.73 (m, 2H), 1.56-1.43 (m, 2H), 1.33 (d, J = 6.0 Hz, 3H), 1.01-1.98 (m, 1H), 0.94 – 0.81 (m, 9H), 0.76 (d, J = 6.4 Hz, 3H), 0.31 (s, 3H).

Example 40

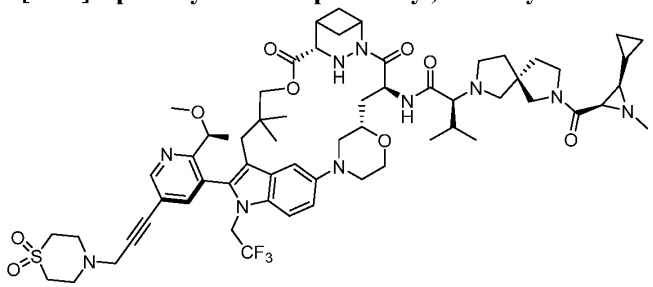
(2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{4}S,4S)-1^2-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1-(2,2,2-trifluoroethyl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide



Substituting 4-(prop-2-yn-1-yl)morpholine with 4-(prop-2-yn-1-yl)thiomorpholine 1,1-dioxide in the Step 1 of **Example 37**, the title compound was prepared by the same procedures as described for **Example 37**.

Example 41

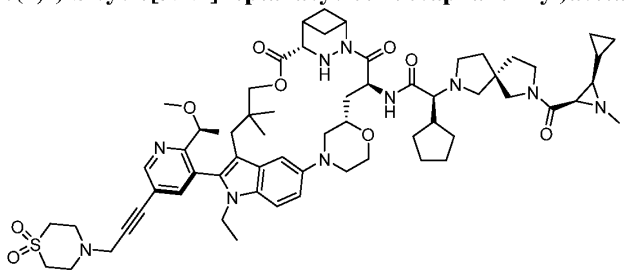
(2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{4}S,4S)-1^2-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide



Substituting 4-(prop-2-yn-1-yl)morpholine with 4-(prop-2-yn-1-yl)thiomorpholine 1,1-dioxide in the Step 1 of **Example 38**, the title compound was prepared by the same procedures as described for **Example 38**.

Example 42

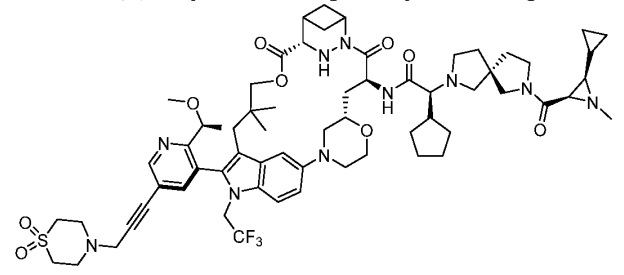
(2S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{4}S,4S)-1^2-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)acetamide



Substituting (S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-3-methylbutanoic acid with (S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)acetic acid in the Step 3 of **Example 41**, the title compound was prepared by the same procedures as described for **Example 41**.

Example 43

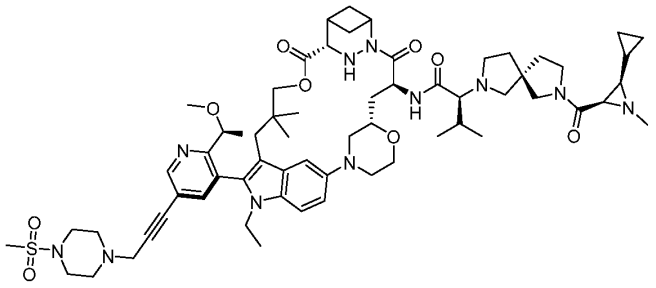
(2S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{4}S,4S)-1^2-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1-(2,2,2-trifluoroethyl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)acetamide



Substituting bromoethane with 2-bromo-1,1,1-trifluoroethane in the Step of **Example 42**, the title compound was prepared by the same procedures as described for **Example 42**.

Example 44

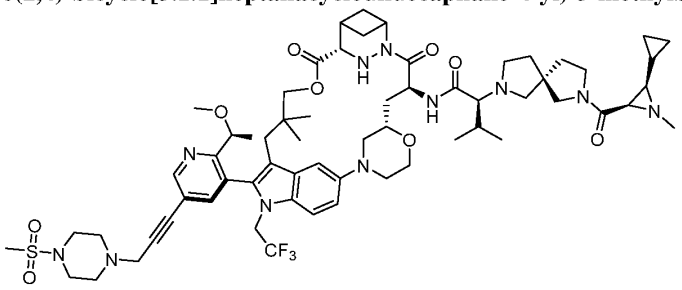
(2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-(4-(methylsulfonyl)piperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide



Substituting 4-(prop-2-yn-1-yl)morpholine with 1-(methylsulfonyl)-4-(prop-2-yn-1-yl)piperazine in the Step 1 of **Example 37**, the title compound was prepared by the same procedures as described for **Example 37**.

Example 45

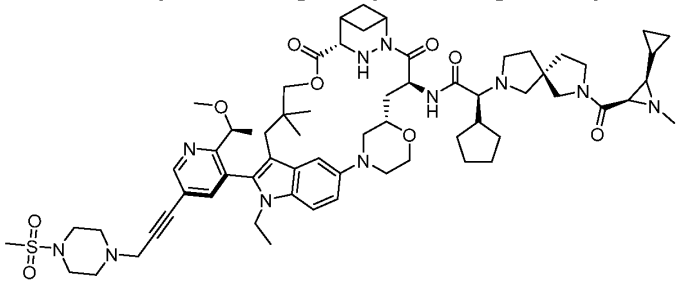
(2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{4}S,4S)-1^2-(2-((S)-1-methoxyethyl)-5-(3-(4-(methylsulfonyl)piperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1-(2,2,2-trifluoroethyl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide



Substituting bromoethane with 2-bromo-1,1,1-trifluoroethane in the Step of **Example 44**, the title compound was prepared by the same procedures as described for **Example 44**.

Example 46

(2S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-(4-(methylsulfonyl)piperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)acetamide

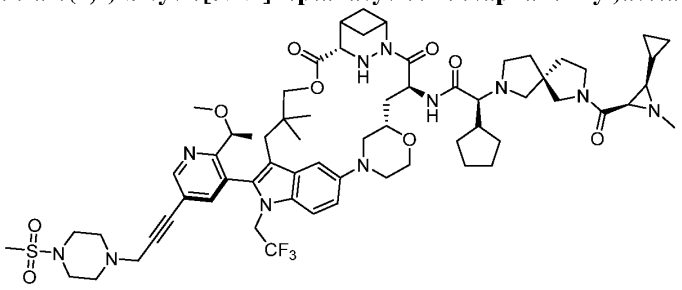


Substituting (S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-3-methylbutanoic acid with (S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nona

n-2-yl)acetic acid in the Step 3 of **Example 44**, the title compound was prepared by the same procedures as described for **Example 44**.

Example 47

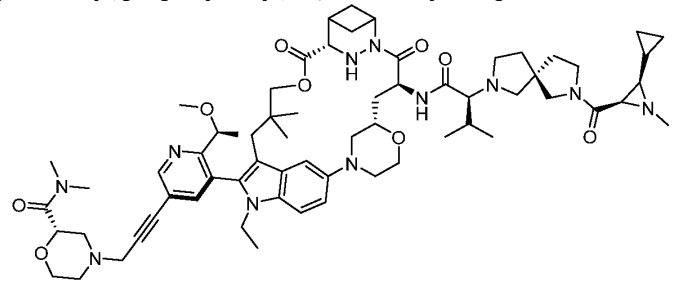
(2S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-(4-(methylsulfonyl)piperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)acetamide



Substituting bromoethane with 2-bromo-1,1,1-trifluoroethane in the Step of **Example 46**, the title compound was prepared by the same procedures as described for **Example 46**.

Example 48

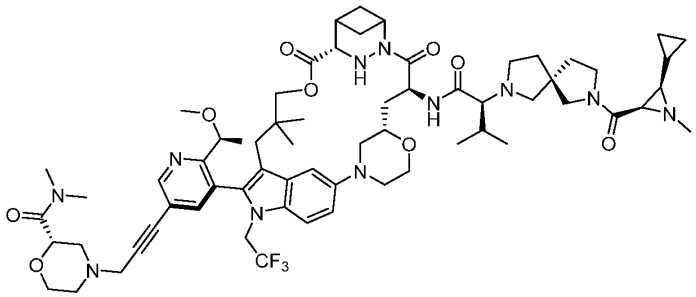
(2S)-4-(3-(5-((2^{2}S,6^{4}S,4S)-4-((S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-3-methylbutanamido)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-12-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)-N,N-dimethylmorpholine-2-carboxamide



Substituting 4-(prop-2-yn-1-yl)morpholine with (S)-N,N-dimethyl-4-(prop-2-yn-1-yl)morpholine-2-carboxamide in the Step 1 of **Example 37**, the title compound was prepared by the same procedures as described for **Example 37**.

Example 49

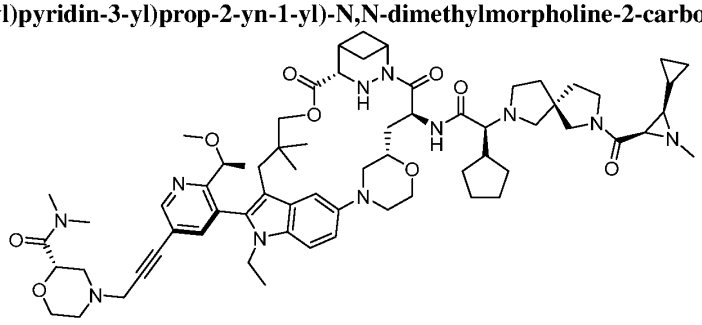
(2S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-(4-(methylsulfonyl)piperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)acetamide



Substituting bromoethane with 2-bromo-1,1,1-trifluoroethane in the Step of **Example 48**, the title compound was prepared by the same procedures as described for **Example 48**.

Example 50

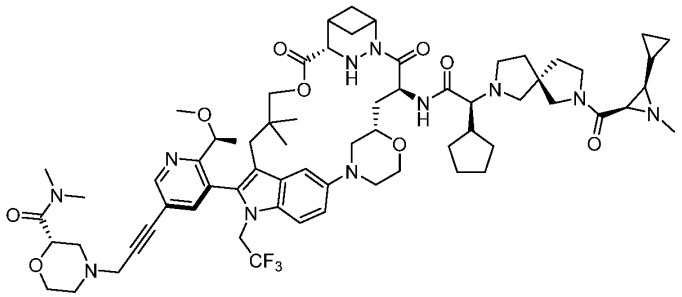
(2S)-4-(3-(5-((2^{2}S,6^{4}S,4S)-4-((S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)acetamido)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-12-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)-N,N-dimethylmorpholine-2-carboxamide



Substituting (S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-3-methylbutanoic acid with (S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)acetic acid in the Step 3 of **Example 48**, the title compound was prepared by the same procedures as described for **Example 48**.

Example 51

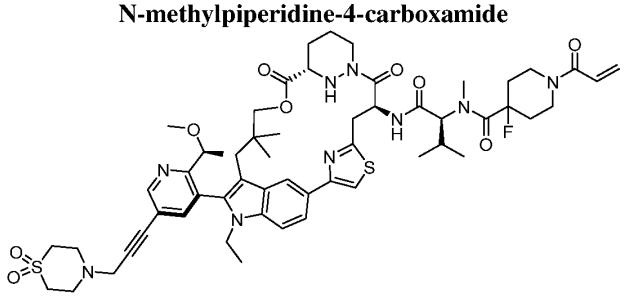
(2S)-4-(3-(5-((2^{2}S,6^{4}S,4S)-4-((S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)acetamido)-10,10-dimethyl-5,7-dioxo-1^1-(2,2,2-trifluoroethyl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)-N,N-dimethylmorpholine-2-carboxamide



Substituting bromoethane with 2-bromo-1,1,1-trifluoroethane in the Step of **Example 50**, the title compound was prepared by the same procedures as described for **Example 50**.

Example 52

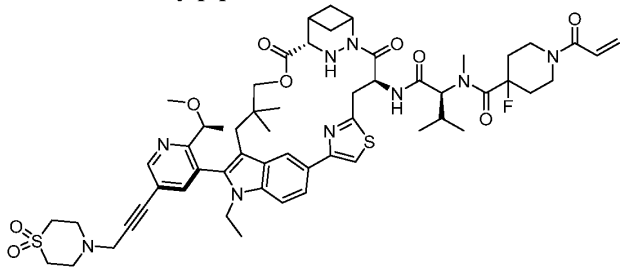
1-acryloyl-N-((2S)-1-(((6^{3}S,4S,Z)-1^2-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide



Substituting 4-(prop-2-yn-1-yl)morpholine with 4-(prop-2-yn-1-yl)thiomorpholine 1,1-dioxide in the Step of **Example 39**, the title compound was prepared by the same procedures as described for **Example 39**.

Example 53

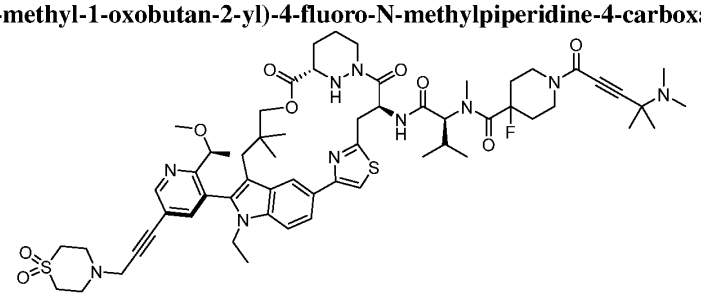
1-acryloyl-N-((2S)-1-(((6^{4}S,4S,Z)-1^2-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide



Substituting hexahydropyridazine-3-carboxylic acid with 2,3-diazabicyclo[3.1.1]heptane-4-carboxylic acid in the Step of **Example 52**, the title compound was prepared by the same procedures as described for **Example 52**.

Example 54

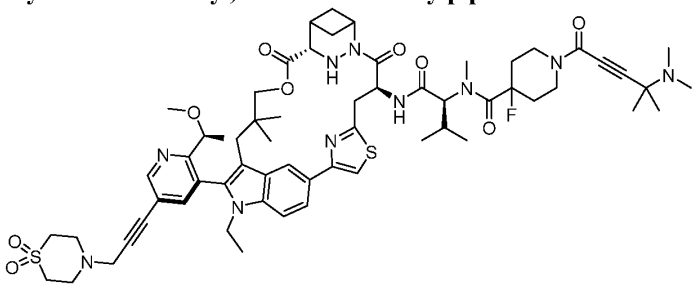
1-(4-(dimethylamino)-4-methylpent-2-ynoyl)-N-((2S)-1-(((6^{3}S,4S,Z)-1^2-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide



Substituting 4-(prop-2-yn-1-yl)morpholine with 4-(prop-2-yn-1-yl)thiomorpholine 1,1-dioxide in the Step and substituting acrylic acid with 4-(dimethylamino)-4-methylpent-2-ynoic acid in the Step 7 of **Example 39**, the title compound was prepared by the same procedures as described for **Example 39**.

Example 55

1-(4-(dimethylamino)-4-methylpent-2-ynoyl)-N-((2S)-1-(((6^{4}S,4S,Z)-1^2-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide

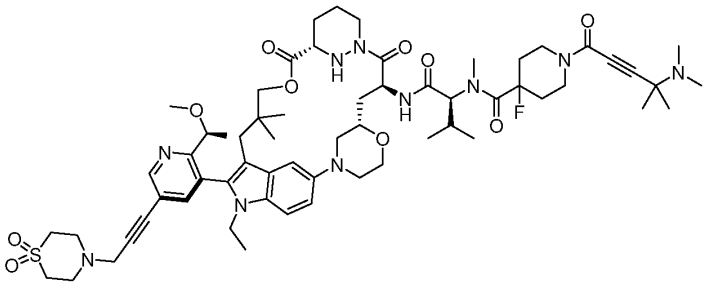


Substituting 4-(prop-2-yn-1-yl)morpholine with 4-(prop-2-yn-1-yl)thiomorpholine 1,1-dioxide in the Step 7 of **Example 53**, the title compound was prepared by the same procedures as described for **Example 53**.

Example 56

1-(4-(dimethylamino)-4-methylpent-2-ynoyl)-N-((2S)-1-(((2^{2}S,6^{3}S,4S)-1^2-(5-(3-(1,1-dioxidothiomorpholi-

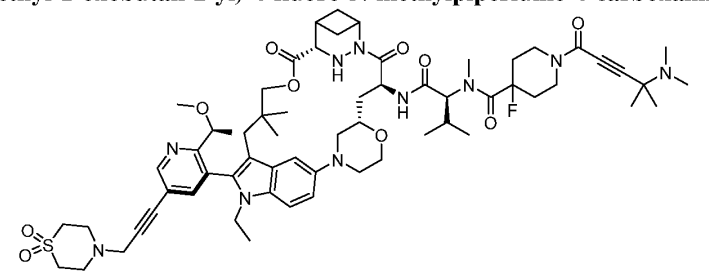
no)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-morpholina-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide



Substituting tert-butyl ((6^{3}S,4S,Z)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)carbamate with tert-butyl ((2^{2}S,6^{3}S,4S)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-morpholina-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)carbamate in the Step 1 of **Example 54**, the title compound was prepared by the same procedures as described for **Example 54**.

Example 57

1-(4-(dimethylamino)-4-methylpent-2-ynoyl)-N-((2S)-1-(((6^{4}S,4S,Z)-1^2-(5-(3-(1,1-dioxidothiomorpholino)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide

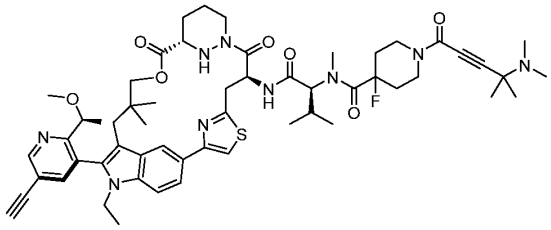


Substituting tert-butyl ((6^{4}S,4S,Z)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate with tert-butyl ((2^{2}S,6^{4}S,4S)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate in the Step 1 of **Example 55**, the title compound was prepared by the same procedures as described for **Example 55**.

Example 58

1-(4-(dimethylamino)-4-methylpent-2-ynoyl)-N-((2S)-1-(((6^{3}S,4S,Z)-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-thiazola-1(5,3)-indo-

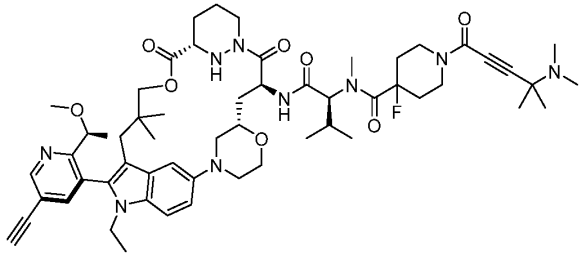
la-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpip eridine-4-carboxamide



Substituting tert-butyl ((6^{4}S,4S,Z)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate with tert-butyl ((6^{3}S,4S,Z)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)carbamate in the Step 1 of **Example 25**, the title compound was prepared by the same procedures as described for **Example 25**.

Example 59

1-(4-(dimethylamino)-4-methylpent-2-ynoyl)-N-((2S)-1-(((2^{2}S,6^{3}S,4S)-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyeth-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-morpholina-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide

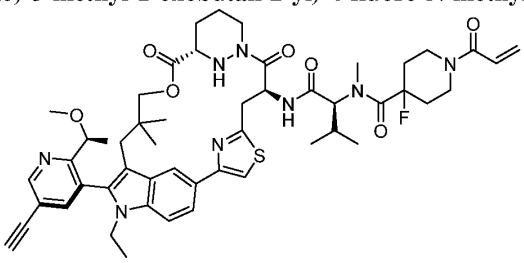


Substituting tert-butyl ((6^{4}S,4S,Z)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate with tert-butyl ((2^{2}S,6^{3}S,4S)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-morpholina-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)carbamate in the Step 1 of **Example 25**, the title compound was prepared by the same procedures as described for **Example 25**.

Example 60

1-acryloyl-N-((2S)-1-(((6^{3}S,4S,Z)-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacy

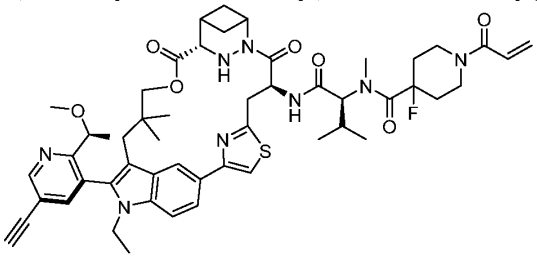
cloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide



Substituting tert-butyl ((6^{4}S,4S,Z)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate with tert-butyl ((6^{3}S,4S,Z)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)carbamate in the Step 1 and substituting acrylic acid with 4-(dimethylamino)-4-methylpent-2-ynoic acid in the Step 7 of **Example 25**, the title compound was prepared by the same procedures as described for **Example 25**.

Example 61

1-acryloyl-N-((2S)-1-(((6^{3}S,4S,Z)-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide

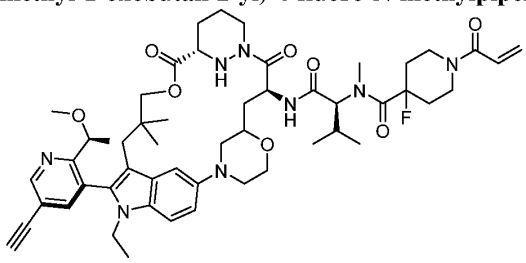


Substituting tert-butyl ((6^{3}S,4S,Z)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)carbamate with tert-butyl ((6^{4}S,4S,Z)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate in the Step 1 of **Example 60**, the title compound was prepared by the same procedures as described for **Example 60**.

Example 62

1-acryloyl-N-((2S)-1-(((6^{3}S,4S)-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-morpholina-1(5,3)-indola-6(1,3)-pyridazinacycloundeca-

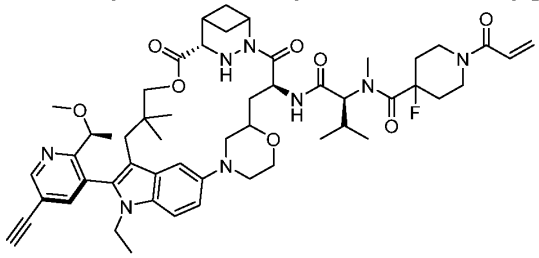
phane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide



Substituting tert-butyl ((6^{3}S,4S,Z)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)carbamate with tert-butyl ((2^{2}S,6^{3}S,4S)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-morpholina-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)carbamate in the Step 1 of **Example 60**, the title compound was prepared by the same procedures as described for **Example 60**.

Example 63

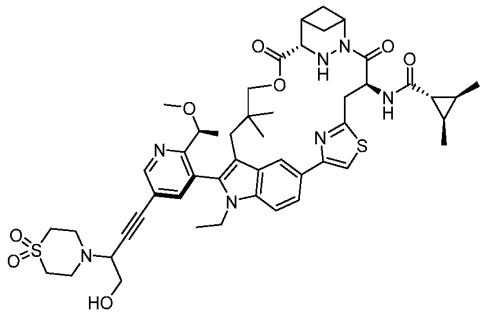
1-acryloyl-N-((2S)-1-(((6^{4}S,4S)-1^1-ethyl-1^2-(5-ethynyl-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-4-fluoro-N-methylpiperidine-4-carboxamide



Substituting tert-butyl ((6^{3}S,4S,Z)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)carbamate with tert-butyl ((2^{2}S,6^{4}S,4S)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate in the Step 1 of **Example 60**, the title compound was prepared by the same procedures as described for **Example 60**.

Example 64

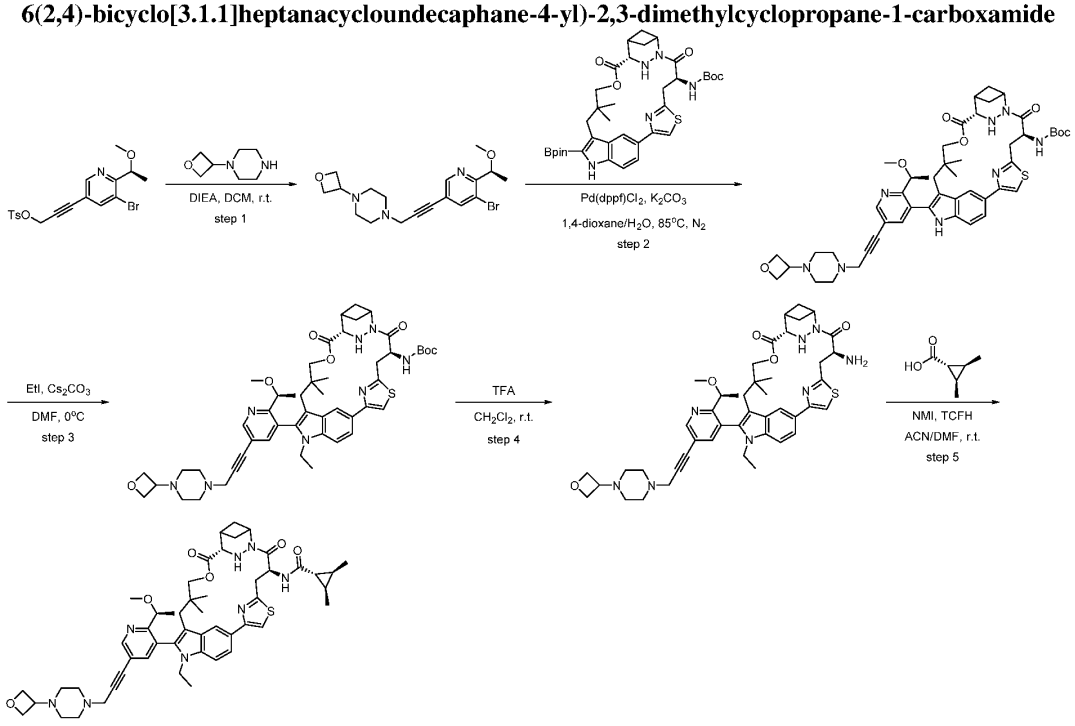
(1r,2R,3S)-N-((6^{4}S,4S,Z)-1^2-(5-(3-(1,1-dioxidothiomorpholino)-4-hydroxybut-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide



Substituting 4-(prop-2-yn-1-yl)morpholine with 4-(1-hydroxybut-3-yn-2-yl)thiomorpholine 1,1-dioxide in the Step 1 of **Example 16**, the title compound was prepared by the same procedures as described for **Example 16**.

Example 65

(1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-(4-(oxetan-3-yl)piperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide



Step 1: Synthesis of (S)-1-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)-4-(oxetan-3-yl)piperazine

To a stirred solution of (S)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl 4-methylbenzenesulfonate (300 mg, 0.71 mmol) in DCM (10 mL) was added 1-(oxetan-3-yl)piperazine (121 mg, 0.85 mmol) and DIEA (227 mg, 1.77 mmol) at r.t. , the resulting mixture was stirred at r.t. for 8 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with DCM/MeOH (30 mL, V:V = 10:1), washed with water (10 mL x 3) and saturated NaCl (10 x 2 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column (eluting with MeOH/DCM from 0% to 7%) to give

(S)-1-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)-4-(oxetan-3-yl)piperazine (227 mg, 81.6 %) as a yellow oil.

LCMS (ESI) calcd. for $C_{18}H_{24}BrN_3O_2$ $[M+H]^+$ m/z 394.1, found: 394.5.

Step 2: Synthesis of tert-butyl ((6⁴S,4S,Z)-1²-(2-((S)-1-methoxyethyl)-5-(3-(4-(oxetan-3-yl)piperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

To a stirred solution of tert-butyl ((6⁴S,4S,Z)-10,10-dimethyl-5,7-dioxo-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (200 mg, 0.28 mmol), (S)-1-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)-4-(oxetan-3-yl)piperazine (111 mg, 0.28 mmol) and K_2CO_3 (117 mg, 0.85 mmol) in 1,4-dioxane/H_2O (7 mL, V:V= 6:1) was added Pd(dppf)Cl_2 (20 mg, 0.03 mmol) at r.t.. The reaction mixture was stirred at 85°C under N_2 for 8 h. After completion under reduced pressure to obtain crude product which was purified by rsilica gel column (eluting with MeOH/DCM from 0% to 5%) to give tert-butyl ((6⁴S,4S,Z)-1²-(2-((S)-1-methoxyethyl)-5-(3-(4-(oxetan-3-yl)piperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (240 mg, 95.1 %) as a brown solid.

LCMS (ESI) calcd. for $C_{48}H_{60}N_8O_7S$ $[M+H]^+$ m/z 893.4, found: 893.9.

Step 3: Synthesis of tert-butyl ((6⁴S,4S,Z)-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-(3-(4-(oxetan-3-yl)piperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

To a stirred solution of tert-butyl ((6⁴S,4S,Z)-1²-(2-((S)-1-methoxyethyl)-5-(3-(4-(oxetan-3-yl)piperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (220 mg, 0.25 mmol) in DMF (5 mL) was added Cs_2CO_3 (241 mg, 0.74 mmol) and EtI (115 mg, 0.74 mmol) at 0°C., the resulting mixture was stirred at r.t. for 1 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with DCM/MeOH (11 mL, V:V = 10:1), washed with water (10 mL x 3) and saturated NaCl (10 x 2 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by rsilica gel column (eluting with MeOH/DCM from 0% to 5%) to give tert-butyl ((6⁴S,4S,Z)-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-(3-(4-(oxetan-3-yl)piperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (60 mg, 26.4 %) as a white solid.

LCMS (ESI) calcd. for $C_{50}H_{64}N_8O_7S$ $[M+H]^+$ m/z 921.5, found: 922.0.

Step 4: Synthesis of (6⁴S,4S,Z)-4-amino-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-(3-(4-(oxetan-3-yl)piperazin-1-yl)prop-1-yn-1-yl)pyri-

din-3-yl)-10,10-dimethyl-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptana cycloundecaphane-5,7-dione

To a stirred solution of tert-butyl ((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-(4-(oxetan-3-yl)piperazin-1-yl)prop-1-yn-1-yl)pyridi n-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (60 mg, 0.065 mmol) in dichloromethane (5 mL) was added TFA (1 mL) slowly at r.t., the resulting mixture was stirred at rt for 2 h. The reaction mixture was concentrated to give the crude product (6^{4}S,4S,Z)-4-amino-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(pyrimidin-5-ylethynyl)pyridin-3-yl)-10,10-dim ethyl-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5 ,7-dione (60 mg, crude) as a light yellow solid.

LCMS (ESI) calcd. for $C_{50}H_{64}N_8O_7S$ $[M+H]^+$ m/z 821.5, found: 822.0.

Step 5: Synthesis of (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-(4-(oxetan-3-yl)piperazin-1-yl)prop-1-yn -1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bi cyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

To a stirred solution of (6^{4}S,4S,Z)-4-amino-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(pyrimidin-5-ylethynyl)pyridin-3-yl)-10,10-dim ethyl-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5 ,7-dione (60 mg, 0.065 mmol) and (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid (10 mg, 0.085 mmol) and NMI (21 mg, 0.260 mmol) in ACN/DMF (3.5 mL, V:V= 6:1) was added TCFH (27 mg, 0.098 mmol) at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was concentrated to give the crude product. The crude product was purified by HPLC (ACN/H_2O (0.5 % NH_4HCO_3) from 40% to 95% in 30 min) to give (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-(4-(oxetan-3-yl)piperazin-1-yl)prop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4) -bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (19 mg, 31.9 %) as a white solid.

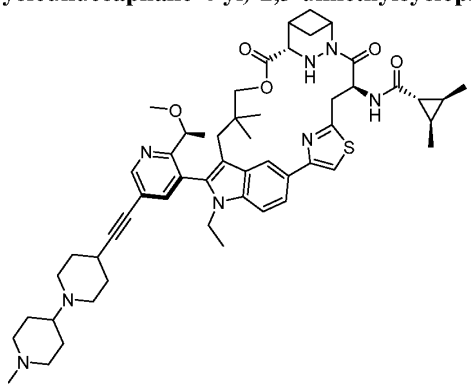
LCMS (ESI) calcd. for $C_{51}H_{64}N_8O_6S$ $[M+H]^+$ m/z 917.5, found: 918.0.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (d, J = 1.9 Hz, 1H), 8.41 (d, J = 10.7 Hz, 2H), 7.87 (d, J = 1.9 Hz, 1H), 7.82 (s, 1H), 7.75 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 8.7 Hz, 1H), 5.93 (d, J = 11.2 Hz, 1H), 5.38 (s, 1H), 4.66 (d, J = 11.2 Hz, 1H), 4.50 (dd, J = 13.0, 6.4 Hz, 3H), 4.40 (t, J = 6.0 Hz, 2H), 4.35 – 4.24 (m, 2H), 4.07 (dd, J = 14.7, 7.4 Hz, 1H), 3.61 – 3.51 (m, 4H), 3.39 (dd, J = 12.6, 6.1 Hz, 1H), 3.23 (s, 3H), 3.14 (dd, J = 14.7, 7.2 Hz, 1H), 2.94 (d, J = 14.3 Hz, 1H), 2.67 – 2.55 (m, 4H), 2.42 (d, J = 14.9 Hz, 2H), 2.36 – 2.12 (m, 6H), 1.57 (t, J = 9.1 Hz, 1H), 1.36 (d, J = 6.0 Hz, 3H), 1.24 (dt, J = 11.3, 5.8 Hz, 2H), 1.20 – 1.14 (m, 2H), 1.13 – 1.04 (m, 5H), 0.92 – 0.82 (m, 5H), 0.33 (s, 3H).

Example 66

(1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((1'-methyl-[1,4'-bipiperidin]-4-yl)ethy nyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-

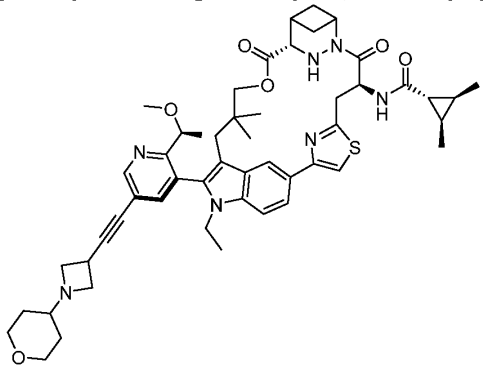
bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide



Substituting 4-(prop-2-yn-1-yl)morpholine with 4-ethynyl-1'-methyl-1,4'-bipiperidine in the Step 1 of **Example 16**, the title compound was prepared by the same procedures as described for **Example 16**.

Example 67

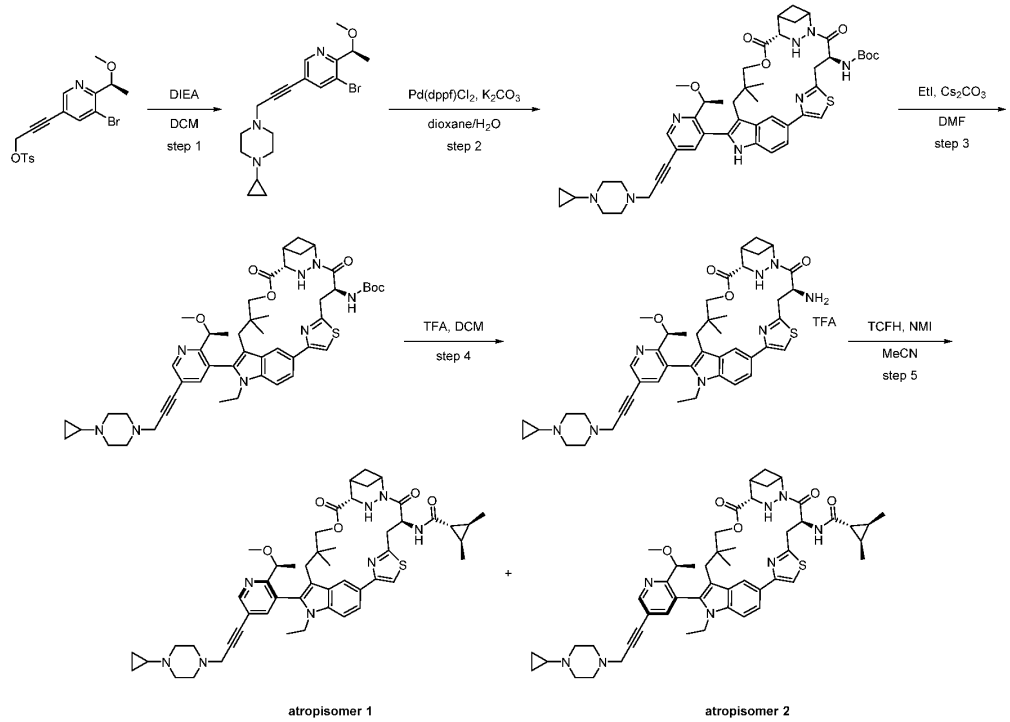
(1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((1-(tetrahydro-2H-pyran-4-yl)azetidin-3-yl)ethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide



Substituting 4-(prop-2-yn-1-yl)morpholine with 3-ethynyl-1-(tetrahydro-2H-pyran-4-yl)azetidine in the Step 1 of **Example 16**, the title compound was prepared by the same procedures as described for **Example 16**.

Example 68

(1r,2R,3S)-N-((64S,4S,Z)-12-(5-(3-(4-cyclopropylpiperazin-1-yl)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-11-ethyl-10,10-dimethyl-5,7-dioxo-11H-8-oxa-62,63-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide



Step 1: Synthesis of (S)-1-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)-4-cyclopropylpiperazine

To a solution of 1-cyclopropylpiperazine (126 mg, 1.00 mmol) in DCM (5 mL) were added DIEA (129 g, 1.00 mmol) and a solution of (S)-3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl 4-methylbenzenesulfonate (212 mg,0.500 mmol) in DCM (5 mL) at rt, the resulting mixture was stirred at rt for 2 h. After completion, the mixture was concentrated under reduced pressureto give a reside which was purified by silica gel column chromatography (eluting with EtOAc/PE from 0% to 40%) to obtain (S)-1-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)-4-cyclopropylpiperazine (180 mg, yield: 95%) as a yellow oil.

LCMS (ESI) calcd. for $C_{18}H_{24}BrN_3O$ [M+H]+ m/z 377.1, found 378.5.

Step 2: Synthesis of tert-butyl ((6⁴S,4S,Z)-1²-(5-(3-(4-cyclopropylpiperazin-1-yl)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

A mixture of (S)-1-(3-(5-bromo-6-(1-methoxyethyl)pyridin-3-yl)prop-2-yn-1-yl)-4-cyclopropylpiperazine (100 mg, 0.26 mmol), tert-butyl ((6⁴S,4S,Z)-10,10-dimethyl-5,7-dioxo-1²-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (200 mg, 0.286 mmol), K_2CO_3 (106 mg,0.78 mmol) and $Pd(dppf)Cl_2$ (20 mg, 0.026 mmol) in dioxane (4 mL) and H_2O (1 mL) was stirred at 85°C under N_2 for 8 h. After completion, the reaction mixture was concentrated to give the crude product which was purified by silica gel column (eluting with MeOH/DCM from 0% to

15%) to give tert-butyl ((6^{4}S,4S,Z)-1^2-(5-(3-(4-cyclopropylpiperazin-1-yl)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (120 mg, 53 %) as a yellow solid.

LCMS (ESI) calcd. for $C_{48}H_{60}N_8O_6S$ $[M+H]^+$ m/z 876.4, found: 877.9.

Step 3: Synthesis of tert-butyl ((64S,4S,Z)-12-(5-(3-(4-cyclopropylpiperazin-1-yl)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-11-ethyl-10,10-dimethyl-5,7-dioxo-11H-8-oxa-62,63-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

To a stirred solution of tert-butyl ((6^{4}S,4S,Z)-1^2-(5-(3-(4-cyclopropylpiperazin-1-yl)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (120 mg, 0.138 mmol) in DMF (3 mL) were added Cs_2CO_3 (90 mg, 0.276 mmol) and Iodoethane (42 mg, 0.276 mmol) at 0°C, the resulting mixture was stirred at rt overnight. After completion, the reaction mixture was diluted with EtOAc (20 mL), washed with water (10 mL x 2) and saturated NaCl (10 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column chromatography (eluting with EtOAc/PE from 0% to 100%) to give tert-butyl ((6^{4}S,4S,Z)-1^2-(5-(3-(4-cyclopropylpiperazin-1-yl)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (50 mg, 40%) as a yellow solid.

LCMS (ESI) calcd. for $C_{50}H_{64}N_8O_6S$ $[M+H]^+$ m/z 904.5, found: 906.0.

Step 4: Synthesis of (6^{4}S,4S,Z)-4-amino-1^2-(5-(3-(4-cyclopropylpiperazin-1-yl)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione

To a stirred solution of tert-butyl ((6^{4}S,4S,Z)-1^2-(5-(3-(4-cyclopropylpiperazin-1-yl)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (60 mg, 0.066 mmol) in dichloromethane (2 mL) was added TFA (1 mL) dropwisely at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was concentrated.The residue was dissolved in EtOAc (15 mL). The mixture was washed with sat.$NaHCO_3$ aquous (10 mL) and brine (10 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain (6^{4}S,4S,Z)-4-amino-1^2-(5-(3-(4-cyclopropylpiperazin-1-yl)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (50 mg, yield: 94%) as a yellow solid.

LCMS (ESI) calcd. for $C_{45}H_{56}N_8O_4S$ $[M+H]^+$ m/z 804.4, found: 805.9.

Step 5: Synthesis of

(1r,2R,3S)-N-((6^{4}S,4S,Z)-1^2-(5-(3-(4-cyclopropylpiperazin-1-yl)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

To a stirred solution of ((6^{4}S,4S,Z)-4-amino-1^2-(5-(3-(4-cyclopropylpiperazin-1-yl)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (50 mg, 0.062 mmol) and (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid (8 mg, 0.074 mmol) and 1-methyl-1H-imidazole (15 mg, 0.093 mmol) in ACN (2 mL) was added TCFH (26 mg, 0.093 mmol) at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was concentrated to give the crude product. The crude product was purified by pre-HPLC (ACN/H_2O (0.5 % NH_4HCO_3) from 20% to 95% in 30 min) to give (1r,2R,3S)-N-((6^{4}S,4S,Z)-1^2-(5-(3-(4-cyclopropylpiperazin-1-yl)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide as atropisomer 1 (16 mg, 29%) as a white solid and (1r,2R,3S)-N-((64S,4S,Z)-12-(5-(3-(4-cyclopropylpiperazin-1-yl)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-11-ethyl-10,10-dimethyl-5,7-dioxo-11H-8-oxa-62,63-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide as atropisomer 2 (i.e., compound of Example 68) (10 mg, 18%) as a white solid.

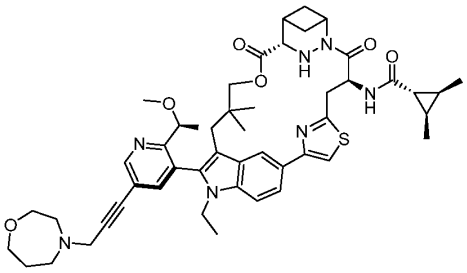
LCMS (ESI) calcd. for $C_{51}H_{64}N_8O_5S$ $[M+H]^+$ m/z 900.5, found: 901.9.

atropisomer 1: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (d, J = 1.8 Hz, 1H), 8.41-8.39 (m, 2H), 7.97 (d, J = 1.9 Hz, 1H), 7.80 (s, 1H), 7.72 (d, J = 8.6 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H), 5.87 (d, J = 11.1 Hz, 1H), 5.29 (t, J = 7.7 Hz, 1H), 4.71 (d, J = 10.9 Hz, 1H), 4.47 (dd, J = 9.9, 4.8 Hz, 1H), 3.95 – 3.87 (m, 2H), 3.84 – 3.77 (m, 1H), 3.59 – 3.47 (m, 4H), 3.23 (d, J = 14.8 Hz, 1H), 3.14 – 2.99 (m, 5H), 2.64-2.63 (m, 1H), 2.53 (s, 8H), 2.33-2.31 (m, 2H), 2.13-2.11 (m, 1H), 1.62-1.57 (m, 2H), 1.25 – 1.03 (m, 15H), 0.89 (s, 3H), 0.45 (s, 3H), 0.39-0.35 (m, 2H), 0.27 – 0.21 (m, 2H).

atropisomer 2 (i.e., compound of Example 68): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (d, J = 2.1 Hz, 1H), 8.40-8.37 (m, 2H), 7.83 (d, J = 1.9 Hz, 1H), 7.80 (s, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.56 (d, J = 8.7 Hz, 1H), 5.91 (d, J = 11.2 Hz, 1H), 5.36 (t, J = 8.4 Hz, 1H), 4.64 (d, J = 10.9 Hz, 1H), 4.46 (dd, J = 8.8, 3.6 Hz, 1H), 4.32 – 4.22 (m, 2H), 4.07-4.01 (m, 1H), 3.59 – 3.47 (m, 4H), 3.21 (s, 3H), 3.11 (dd, J = 14.7, 7.2 Hz, 2H), 2.91 (d, J = 14.4 Hz, 2H), 2.65-2.54 (m, 4H), 2.45-2.38 (m, 6H), 2.31-2.27 (m, 1H), 2.16 – 2.09 (m, 1H), 1.61-1.52 (m, 2H), 1.33 (d, J = 6.1 Hz, 3H), 1.25 – 0.98 (m, 10H), 0.87-0.86 (m, 6H), 0.37-0.24 (m, 7H).

Example 69

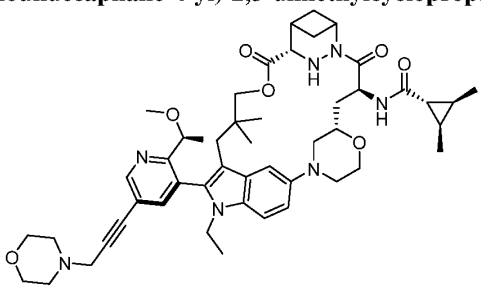
(1r,2R,3S)-N-((6^{4}S,4S,Z)-1^2-(5-(3-(1,4-oxazepan-4-yl)prop-1-yn-1-yl)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide



Substituting 4-(prop-2-yn-1-yl)morpholine with 4-(prop-2-yn-1-yl)-1,4-oxazepane in the Step 1 of **Example 16**, the title compound was prepared by the same procedures as described for **Example 16**.

Example 70

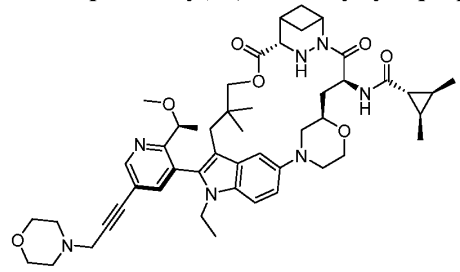
(1r,2R,3S)-N-((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide



Substituting tert-butyl ((6^{4}S,4S,Z)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate with tert-butyl ((2^{2}S,6^{4}S,4S)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate in the Step 1 of **Example 16**, the title compound was prepared by the same procedures as described for **Example 16**.

Example 71

(1r,2R,3S)-N-((2^{2}R,6^{4}S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

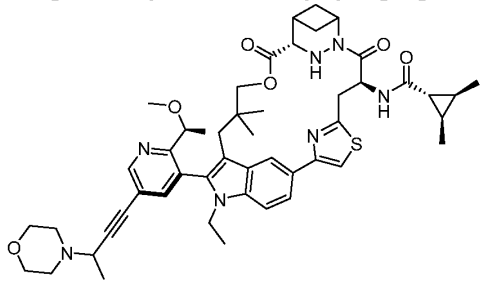


Substituting tert-butyl ((6^{4}S,4S,Z)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^{1}H-8-oxa

-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate with tert-butyl ((2^{2}R,6^{4}S,4S)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate in the Step 1 of **Example 16**, the title compound was prepared by the same procedures as described for **Example 16**.

Example 72

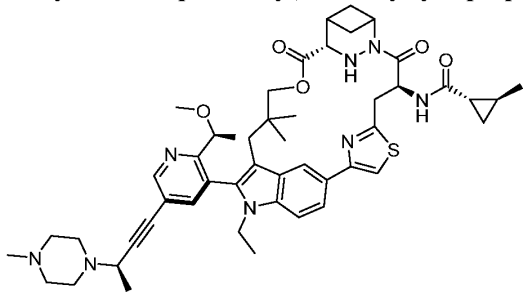
(1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinobut-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide



Substituting 4-(prop-2-yn-1-yl)morpholine with 4-(but-3-yn-2-yl)morpholine in the Step 1 of **Example 16**, the title compound was prepared by the same procedures as described for **Example 16**.

Example 73

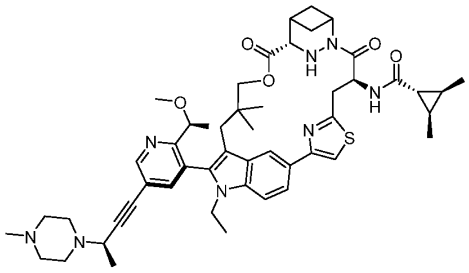
(1S,2S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((R)-3-(4-methylpiperazin-1-yl)but-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide



Substituting 4-(prop-2-yn-1-yl)morpholine with (R)-1-(but-3-yn-2-yl)-4-methylpiperazine in the Step 1 and substituting (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid with (1S,2S)-2-methylcyclopropane-1-carboxylic acid in the Step 4 of **Example 7**, the title compound was prepared by the same procedures as described for **Example 7**.

Example 74

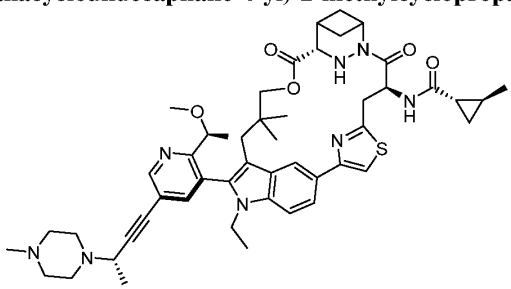
(1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((R)-3-(4-methylpiperazin-1-yl)but-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide



Substituting 4-(prop-2-yn-1-yl)morpholine with (R)-1-(but-3-yn-2-yl)-4-methylpiperazine in the Step 1 of **Example 7**, the title compound was prepared by the same procedures as described for **Example 7**.

Example 75

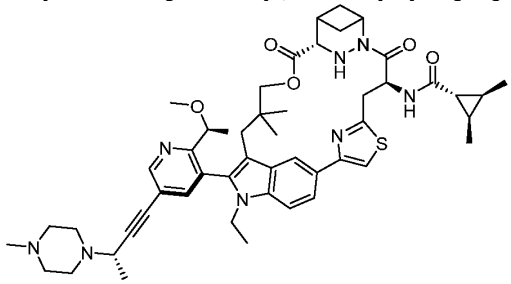
(1S,2S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((S)-3-(4-methylpiperazin-1-yl)but-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide



Substituting (R)-1-(but-3-yn-2-yl)-4-methylpiperazine with (S)-1-(but-3-yn-2-yl)-4-methylpiperazine in the Step 1 of **Example 73**, the title compound was prepared by the same procedures as described for **Example 73**.

Example 76

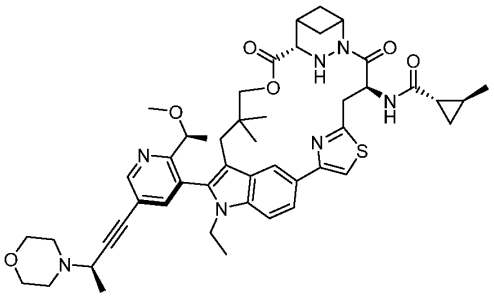
(1S,2S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((S)-3-(4-methylpiperazin-1-yl)but-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide



Substituting (R)-1-(but-3-yn-2-yl)-4-methylpiperazine with (S)-1-(but-3-yn-2-yl)-4-methylpiperazine in the Step 1 of **Example 74**, the title compound was prepared by the same procedures as described for **Example 74**.

Example 77

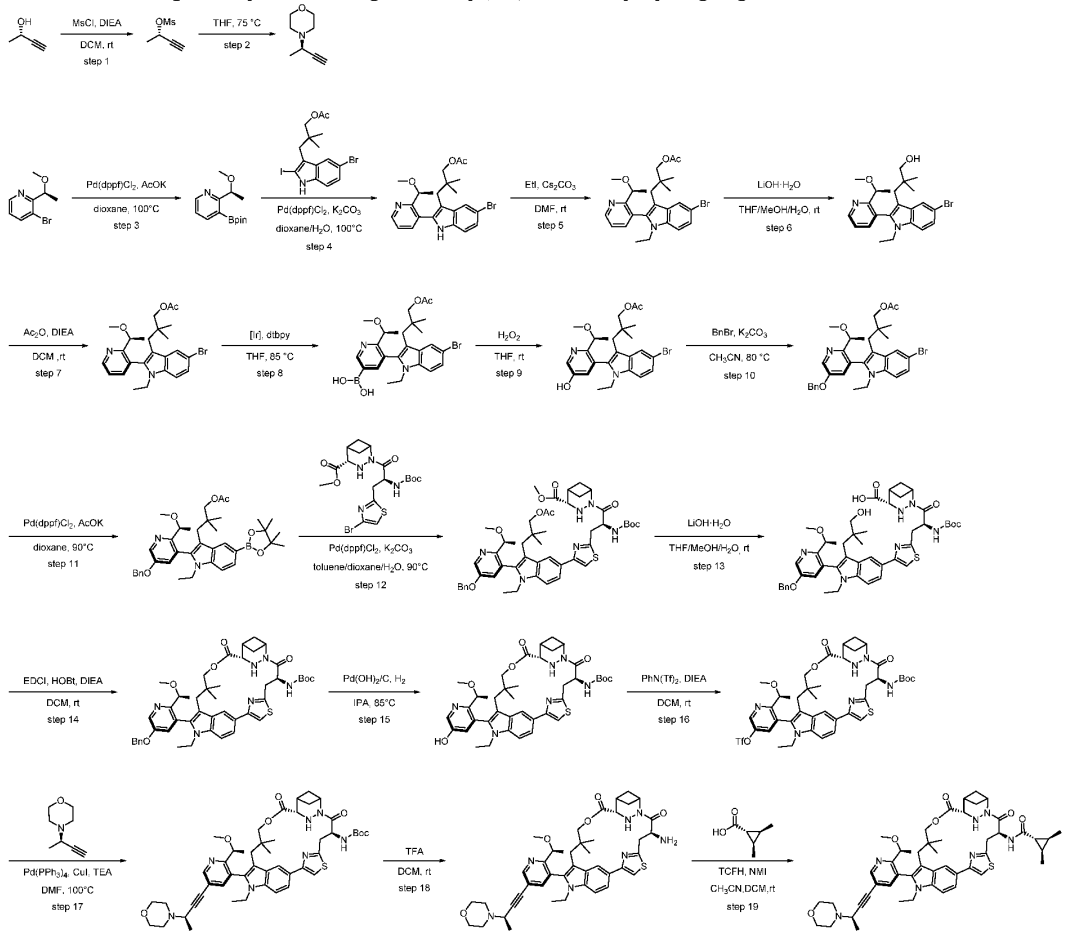
(1S,2S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((S)-3-(4-methylpiperazin-1-yl)but-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide



Substituting (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid with (1S,2S)-2-methylcyclopropane-1-carboxylic acid in the Step 19 of **Example 78**, the title compound was prepared by the same procedures as described for **Example 78**.

Example 78

(1r,2R,3S)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((R)-3-morpholinobut-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide



Step 1: Synthesis of (S)-but-3-yn-2-yl methanesulfonate

To a stirred solution of (S)-but-3-yn-2-ol 3 (300 mg, 4.28 mmol) in DCM (5mL) and DIEA (1.38g, 10.70 mmol) was added MsCl (736 mg, 6.42 mmol), the resulting mixture was stirred at rt for 5 h. The re-

action mixture was concentrated under reduced pressure to give the crude product which was purified by silica gel column (eluting with EtOAc/PE from 0% to 10%) to give (S)-but-3-yn-2-yl methanesulfonate (470 mg, 74.2%) as a brown oil.

Step 2: Synthesis of (R)-4-(but-3-yn-2-yl)morpholine

To a stirred solution of (S)-but-3-yn-2-yl methanesulfonate (230 mg, 1.55 mmol) in THF (4 mL) was addedmorpholine (677 mg, 7.77 mmol) dropwisely at rt, the resulting mixture was stirred at 75°C for 5 h. After completion, the reaction solution was concentrated under reduced pressure to give the residual, the residual was purified by silica gel column (eluting with EtOAc/PE from 0% to 80%) to afford (R)-4-(but-3-yn-2-yl)morpholine (69 mg, 32.0 %) as a yellow oil.

LCMS (ESI) calcd. for $C_8H_{13}NO$ $[M+H]^+$ m/z 140.1, found: 140.3.

Step 3: Synthesis of (S)-2-(1-methoxyethyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine

To a stirred solution of (S)-3-bromo-2-(1-methoxyethyl)pyridine (80.1 g, 370.83 mmol) and B_2Pin_2 (113.1 g, 445.00 mmol) in 1,4-dioxane (1000 mL) were added $Pd(dppf)Cl_2$ (23.1 g, 31.52 mmol) and KOAc (109.2 g, 1.11 mol). The reaction was stirred at 100°C for 18 h under N_2 atmosphere. The reaction was monitored by LCMS. After completion, the reaction solution was concentrated under reduced pressure to give the residual which was purified by neutral Al_2O_3 column (eluting with EtOAc/PE from 0% to 100%) to afford (S)-2-(1-methoxyethyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (130.8 g) as a brown oil.

LCMS (ESI) calcd. for $C_{14}H_{22}BNO_3$ $[M+H]^+$ m/z 264.2, found: 264.5.

Step 4: Synthesis of (S)-3-(5-bromo-2-(2-(1-methoxyethyl)pyridin-3-yl)-1H-indol-3-yl)-2,2-dimethylpropyl acetate

To a stirred solution of 3-(5-bromo-2-iodo-1H-indol-3-yl)-2,2-dimethylpropyl acetate (12.2 g, 27.17 mmol), (S)-2-(1-methoxyethyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (11.4 g, 43.47 mmol) and K_2CO_3 (11.3 g, 81.51 mmol) in 1,4-dioxane (180 mL) and H_2O (45 mL) was added $Pd(dppf)Cl_2$ (2.0 g, 2.72 mmol) at rt. The reaction mixture was stirred at 90°C under N_2 for 18 h. After completion, the reaction solution was concentrated under reduced pressure to remove 1,4-dioxane to give the residual which was purified by silica gel column (eluting with EtOAc/PE from 0% to 80%) to afford (S)-3-(5-bromo-2-(2-(1-methoxyethyl)pyridin-3-yl)-1H-indol-3-yl)-2,2-dimethylpropyl acetate (10.5 g, 84.1 %) as a yellow solid.

LCMS (ESI) calcd. for $C_{23}H_{27}BrN_2O_3$ $[M+H]^+$ m/z 459.1, found: 459.5.

Step 5: Synthesis of (S)-3-(5-bromo-1-ethyl-2-(2-(1-methoxyethyl)pyridin-3-yl)-1H-indol-3-yl)-2,2-dimethylpropyl acetate

To a stirred solution of (S)-3-(5-bromo-2-(2-(1-methoxyethyl)pyridin-3-yl)-1H-indol-3-yl)-2,2-dimethylpropyl acetate (12.4 g, 27.10 mmol) in DMF (120 mL) were added Cs_2CO_3 (17.6 g, 54.19 mmol) and Iodoethane (6.3 g, 40.64 mmol) at 0°C, the resulting mixture was stirred at rt for 18 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with EtOAc (200 mL), washed with water (1000 mL x 2) and saturated NaCl (1000 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column (eluting with EtOAc/PE from 0% to 60%)

to afford (S)-3-(5-bromo-1-ethyl-2-(2-(1-methoxyethyl)pyridin-3-yl)-1H-indol-3-yl)-2,2-dimethylpropyl acetate (10.4 g, 79.0 %) as a brown solid.

LCMS (ESI) calcd. for $C_{25}H_{31}BrN_2O_3$ $[M+H]^+$ m/z 487.2, found: 487.6.

Step 6: Synthesis of (S)-3-(5-bromo-1-ethyl-2-(2-(1-methoxyethyl)pyridin-3-yl)-1H-indol-3-yl)-2,2-dimethylpropan-1-ol

To a solution of (S)-3-(5-bromo-1-ethyl-2-(2-(1-methoxyethyl)pyridin-3-yl)-1H-indol-3-yl)-2,2-dimethylpropyl acetate (10.4 g, 21.42 mmol) in THF (100 mL), MeOH (50 mL)and H_2O (50 mL) was added LiOH (2.7 g, 64.26 mmol) at 0-10°C, the resulting mixture was stirred at 0-10°C for 20 h. The reaction was monitored by LCMS. After completion, the reaction mixture was concentrated to give the residue. The residue was diluted with H_2O and acidified to pH = 4-5 with 2 N HCl. The resulting mixture was extracted with EtOAc (100 mL x 2), the combined organic phase was washed with saturated NaCl (100 mL), then dried over Na_2SO_4 and concentrated to give the crude product which was purified by silica gel column (eluting with EtOAc/PE from 0% to 80%) to afford (S)-3-(5-bromo-1-ethyl-2-(2-(1-methoxyethyl)pyridin-3-yl)-1H-indol-3-yl)-2,2-dimethylpropan-1-ol (5.0 g, 52.0 %) as a yellow solid.

LCMS (ESI) calcd. for $C_{23}H_{29}BrN_2O_2$ $[M+H]^+$ m/z 445.2, found: 445.6.

Step 7: Synthesis of (S)-3-(5-bromo-1-ethyl-2-(2-(1-methoxyethyl)pyridin-3-yl)-1H-indol-3-yl)-2,2-dimethylpropyl acetate

To a stirred solution of (S)-3-(5-bromo-1-ethyl-2-(2-(1-methoxyethyl)pyridin-3-yl)-1H-indol-3-yl)-2,2-dimethylpropan-1-ol (5.0 g, 11.15 mmol) in DCM (50 mL) were added DIEA (2.9 g, 22.30 mmol), DMAP (136 mg, 1.11 mmol) and Ac_2O (1.20 g, 11.71 mmol) at rt , t he resulting mixture was stirred at rt for 18 h. The reaction was monitored by LCMS. After completion, the reaction mixture was concetrated to give the crude product which was purified by silica gel column (eluting with EA/PE from 0% to 50%) to give (S)-3-(5-bromo-1-ethyl-2-(2-(1-methoxyethyl)pyridin-3-yl)-1H-indol-3-yl)-2,2-dimethylpropyl acetate (5.1 g, 94.3 %) as a pale yellow solid.

LCMS (ESI) calcd. for $C_{25}H_{31}BrN_2O_3$ $[M+H]^+$ m/z 487.2, found: 487.6.

Step 8: Synthesis of (S)-(5-(3-(3-acetoxy-2,2-dimethylpropyl)-5-bromo-1-ethyl-1H-indol-2-yl)-6-(1-methoxyethyl)pyridin-3-yl)boronic acid

To a stirred solution of (S)-3-(5-bromo-1-ethyl-2-(2-(1-methoxyethyl)pyridin-3-yl)-1H-indol-3-yl)-2,2-dimethylpropyl acetate (5.1 g, 10.51 mmol), B_2Pin_2 (4.0 g, 15.77 mmol)in THF (100 mL) was added $[Ir(COD)Cl]_2$ (353 mg, 0.53 mmol) and dtbpy (423 mg, 1.58 mmol) at rt , the resulting mixture was stirred at 85°C under N_2 for 24 h. The reaction was monitored by LCMS. After completion, the reaction mixture was concentrated to give the crude product which was used to next step without purification.

Step 9: Synthesis of (S)-3-(5-bromo-1-ethyl-2-(5-hydroxy-2-(1-methoxyethyl)pyridin-3-yl)-1H-indol-3-yl)-2,2-dimethylpropyl

acetate

To a stirred solution of crude (S)-(5-(3-(3-acetoxy-2,2-dimethylpropyl)-5-bromo-1-ethyl-1H-indol-2-yl)-6-(1-methoxyethyl)pyridin-3-yl)boronic acid (4.5 g, 8.40 mmol) in THF (300 mL) was added H_2O_2 (4.8 g, 41.98 mmol) at r.t. The reaction mixture was stirred at r.t. for 2 h. After completion, reaction mixture was diluted with EtOAc (60 mL), washed with water (50 mL x 2) and saturated NaCl (50 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain the crude (S)-3-(5-bromo-1-ethyl-2-(5-hydroxy-2-(1-methoxyethyl)pyridin-3-yl)-1H-indol-3-yl)-2,2-dimethylpropyl acetate (3.4 g, 80.9 %) as a yellow solid.

LCMS (ESI) calcd. for $C_{25}H_{31}BrN_2O_4$ $[M+H]^+$ m/z 503.2, found: 503.7.

Step 10: Synthesis of (S)-3-(2-(5-(benzyloxy)-2-(1-methoxyethyl)pyridin-3-yl)-5-bromo-1-ethyl-1H-indol-3-yl)-2,2-dimethylpropyl acetate

To a stirred solution of crude (S)-3-(5-bromo-1-ethyl-2-(5-hydroxy-2-(1-methoxyethyl)pyridin-3-yl)-1H-indol-3-yl)-2,2-dimethylpropyl acetate (3.4 g, 6.79 mmol) in CH_3CN (68 mL) were added K_2CO_3 (2.8 g, 20.38 mmol) and BnBr (1.7 g, 10.19 mmol), the resulting mixture was stirred at 85°C for 16 h. The reaction mixture was concentrated to give the crude product which was purified by silica gel column (eluting with EA/PE from 0% to 30%) to give (S)-3-(2-(5-(benzyloxy)-2-(1-methoxyethyl)pyridin-3-yl)-5-bromo-1-ethyl-1H-indol-3-yl)-2,2-dimethylpropyl acetate (3.2 g, 79.4 %) as a yellow foam.

LCMS (ESI) calcd. for $C_{32}H_{37}BrN_2O_4$ $[M+H]^+$ m/z 593.2, found: 593.6.

Step 11: Synthesis of (S)-3-(2-(5-(benzyloxy)-2-(1-methoxyethyl)pyridin-3-yl)-1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3-yl)-2,2-dimethylpropyl acetate

To a stirred solution of (S)-3-(2-(5-(benzyloxy)-2-(1-methoxyethyl)pyridin-3-yl)-5-bromo-1-ethyl-1H-indol-3-yl)-2,2-dimethylpropyl acetate (3.2 g, 5.39 mmol) and B_2Pin_2 (2.1 g, 8.08 mmol) in 1,4-dioxane (45 mL) were added $Pd(dppf)Cl_2$ (395 mg, 0.54 mmol) and KOAc (1.6 g, 16.17 mol). The reaction mixture was stirred at 90°C for 5 h under N_2 atmosphere. The reaction was monitored by LCMS. After completion, the reaction solution was concentrated under reduced pressure to give the residual which was purified by silica gel column (eluting with EtOAc/PE from 0% to 30%) to afford (S)-3-(2-(5-(benzyloxy)-2-(1-methoxyethyl)pyridin-3-yl)-1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3-yl)-2,2-dimethylpropyl acetate (3.7 g) as a yellow oil.

LCMS (ESI) calcd. for $C_{38}H_{49}BrN_2O_6$ $[M+H]^+$ m/z 641.4, found: 641.9.

Step 12: Synthesis of methyl (S)-2-((S)-3-(4-(3-(3-acetoxy-2,2-dimethylpropyl)-2-(5-(benzyloxy)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-1H-indol-5-yl)thiazol-2-yl)-2-((tert-butoxycarbonyl)amino)propanoyl)-2,3-diazabicyclo[3.1.1]heptane-4-carboxylate

To a stirred solution of methyl (S)-2-((S)-3-(4-bromothiazol-2-yl)-2-((tert-butoxycarbonyl)amino)propanoyl)-2,3-diazabicyclo[3.1.1]heptane-4-carboxylate (11.9 g, 24.31 mmol), (S)-3-(2-(5-(benzyloxy)-2-(1-methoxyethyl)pyridin-3-yl)-1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3-yl)-2,2-dimethylpropyl acetat (15.6 g, 24.31 mmol) and K_2CO_3 (10.1 g, 73.19 mmol) in toluene/1,4-dioxane/H_2O (350 mL, V:V:V = 3:1:1) was added $Pd(dppf)Cl_2$ (1.8 g, 2.46 mmol) at rt. The reaction mixture was stirred at 90°C under N_2 for 22 h. After completion, the reaction solution was concentrated under reduced pressure to remove 1,4-dioxane and toluene, the residual was diluted with H_2O and extracted with EtOAc (100 mL x 2), the combined organic phase was washed with saturated NaCl (200 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column (eluting with EtOAc/PE from 0% to 80%) to afford methyl (S)-2-((S)-3-(4-(3-(3-acetoxy-2,2-dimethylpropyl)-2-(5-(benzyloxy)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-1H-indol-5-yl)thiazol-2-yl)-2-((tert-butoxycarbonyl)amino)propanoyl)-2,3-diazabicyclo[3.1.1]heptane-4-carboxylate (17.2 g, 76.8 %) as a brown foam.

LCMS (ESI) calcd. for $C_{50}H_{62}N_6O_9S$ $[M+H]^+$ m/z 923.4, found: 924.7.

Step 13: Synthesis of (S)-2-((S)-3-(4-(2-(5-(benzyloxy)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1H-indol-5-yl)thiazol-2-yl)-2-((tert-butoxycarbonyl)amino)propanoyl)-2,3-diazabicyclo[3.1.1]heptane-4-carboxylic acid

To a solution of methyl (S)-2-((S)-3-(4-(3-(3-acetoxy-2,2-dimethylpropyl)-2-(5-(benzyloxy)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-1H-indol-5-yl)thiazol-2-yl)-2-((tert-butoxycarbonyl)amino)propanoyl)-2,3-diazabicyclo[3.1.1]heptane-4-carboxylate (17.4 g, 18.66 mmol) in THF (170 mL), MeOH (45 mL)and H_2O (85 mL) was added LiOH (3.9 g, 93.28 mmol) at 0-10°C, the resulting mixture was stirred at rt for 17 h. The reaction was monitored by LCMS. After completion, the reaction mixture was concentrated to give the residue. The residue was diluted with H_2O and acidified to pH = 4-5 with 2 N HCl. The resulting mixture was extracted with EtOAc (200 mL x 2), the combined organic phase was washed with saturated NaCl (200 mL), then dried over Na_2SO_4 and concentrated to give crude (S)-2-((S)-3-(4-(2-(5-(benzyloxy)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1H-indol-5-yl)thiazol-2-yl)-2-((tert-butoxycarbonyl)amino)propanoyl)-2,3-diazabicyclo[3.1.1]heptane-4-carboxylic acid (17.4 g) as a brown foam.

LCMS (ESI) calcd. for $C_{47}H_{58}N_6O_8S$ $[M+H]^+$ m/z 867.4, found: 868.6.

Step 14: Synthesis of tert-butyl ((6^{4}S,4S,Z)-1^2-(5-(benzyloxy)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

To a solution of crude (S)-2-((S)-3-(4-(2-(5-(benzyloxy)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethyl

pro-
pyl)-1H-indol-5-yl)thiazol-2-yl)-2-((tert-butoxycarbonyl)amino)propanoyl)-2,3-diazabicyclo[3.1.1]heptane -4-carboxylic acid (13.0 g, 15.01 mmol), HOBt (10.1 g, 75.06 mmol) and DIEA (64.0 g, 495.38 mmol) in DCM (1300 mL) under ice-water bath was added EDCI (80.6 g, 420.32 mmol) in batches. The reaction was gradually improved temperature to room temperature and stirred for 22 h, the reaction was monitored by LCMS. After completion, the reaction was washed with H_2O (700 mL x 3) and NH_4Cl (aq) (700 mL x 3), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column (eluting with EtOAc/PE from 0% to 65%) to afford tert-butyl ((6^{4}S,4S,Z)-1^2-(5-(benzyloxy)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H -8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carba mate (6.4 g, 50.3 %) as a yellow foam.

LCMS (ESI) calcd. for $C_{47}H_{56}N_5O_6S$ $[M+H]^+$ m/z 849.4, found: 850.2.

Step 15: Synthesis of tert-butyl ((6^{4}S,4S,Z)-1^1-ethyl-1^2-(5-hydroxy-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-ox a-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamat e

To a stirred solution of tert-butyl ((6^{4}S,4S,Z)-1^2-(5-(benzyloxy)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H -8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carba mate (6.2 g, 7.28 mmol) in IPA (180 mL) was added $Pd(OH)_2/C$ (10%, 1.2 g) at rt , the resulting mixture was stirred at 85°C for 60 h. The reaction was monitored by LCMS. After completion, the reaction mixture was filtered and the filtrate was concentrated to give crude tert-butyl ((6^{4}S,4S,Z)-1^1-ethyl-1^2-(5-hydroxy-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbama te (6.6 g) as a white solid.

LCMS (ESI) calcd. for $C_{40}H_{50}IN_6O_7S$ $[M+H]^+$ m/z 759.4, found: 760.2.

Step 16: Synthesis of 5-((6^{4}S,4S,Z)-4-((tert-butoxycarbonyl)amino)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4 ,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-12-yl)-6-((S)-1-methoxyethyl)py ridin-3-yl trifluoromethanesulfonate

To a solution of crude tert-butyl ((6^{4}S,4S,Z)-1^1-ethyl-1^2-(5-hydroxy-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbama te (6.60 g, 8.71 mmol) in DCM (130 mL) were added DIEA (2.2 g, 17.41 mmol) and $PhN(Tf)_2$ (3.1 g, 8.71 mmol) at 0-10°C. The resulting mixture was stirred at rt for 2 h. The reaction was monitored by LCMS. After completion, the reaction mixture was concentrated under reduced pressure to obtain crude product which was purified by silica gel column eluting with (EtOAc/PE from 0% to 60%) to afford 5-((6^{4}S,4S,Z)-4-((tert-butoxycarbonyl)amino)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-12-yl)-6-((S)-1-methoxyethyl)p

yridin-3-yl trifluoromethanesulfonate (4.8 g, 61.9 %) as a white foam.

LCMS (ESI) calcd. for $C_{41}H_{49}F_3N_6O_9S_2$ $[M+H]^+$ m/z 891.3, found: 892.2.

Step 17: Synthesis of tert-butyl ((6⁴S,4S,Z)-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-((R)-3-morpholinobut-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

A mixture of 5-((6⁴S,4S,Z)-4-((tert-butoxycarbonyl)amino)-1¹-ethyl-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-12-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate (256 mg, 0.29 mmol), (R)-4-(but-3-yn-2-yl)morpholine (60 mg, 0.43 mmol), CuI (9 mg, 0.043 mmol), TEA (87 mg, 0.86 mmol) and $Pd(PPh_3)_2Cl_2$ (50 mg, 0.043 mmol) in DMF (4 mL) was stirred at 100°C for 1 h under N_2 atmosphere, the reaction was monitored by LCMS. After completion, the mixture was filtered and the filtrate was concentrated, the residue was purified by silica gel column chromatography (eluting with MeOH/DCM from 0% to 10%) to obtain tert-butyl ((6⁴S,4S,Z)-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-((R)-3-morpholinobut-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (120 mg, 47.1%) as a brown foam.

LCMS (ESI) calcd. for $C_{48}H_{61}N_7O_7S$ $[M+H]^+$ m/z 880.4, found: 881.4.

Step 18: Synthesis of (6⁴S,4S,Z)-4-amino-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-((R)-3-morpholinobut-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione

To a stirred solution of tert-butyl ((6⁴S,4S,Z)-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-((R)-3-morpholinobut-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (120 mg, 0.14 mmol) in dichloromethane (2 mL) was added TFA (0.6 mL) dropwisely at rt, the resulting mixture was stirred at rt for 2 h. The reaction mixture was concentrated to give crude (6⁴S,4S,Z)-4-amino-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-((R)-3-morpholinobut-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione which was used to next step without purification.

LCMS (ESI) calcd. for $C_{43}H_{53}N_7O_5S$ $[M+H]^+$ m/z 780.4, found: 781.4.

Step 19: Synthesis of (1r,2R,3S)-N-((6⁴S,4S,Z)-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-((R)-3-morpholinobut-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide

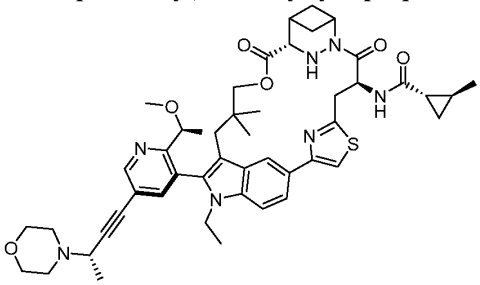
To a stirred solution of crude (6^4S,4S,Z)-4-amino-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((R)-3-morpholinobut-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-5,7-dione (106 mg, 0.14 mmol) and (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid (16 mg, 0.14 mmol) and NMI (112 mg, 1.37 mmol) in ACN (1.5 mL) and DCM (1.5 mL) was added TCFH (58 mg, 0.20 mmol) at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was concentrated to give the crude product. The crude product was purified by pre-HPLC (eluting with CH_3CN/H_2O(0.1% NH_4HCO_3) from 20% to 80%) to give (1r,2R,3S)-N-((6^4S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((R)-3-morpholinobut-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide (26.8 mg) as a white solid.

LCMS (ESI) calcd. for $C_{49}H_{61}N_7O_6S$ $[M+H]^+$ m/z 876.4, found: 876.5.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 1H), 8.40 (d, J = 6.5 Hz, 2H), 7.89 (s, 1H), 7.81 (s, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.57 (d, J = 8.7 Hz, 1H), 5.92 (d, J = 11.1 Hz, 1H), 5.35 (s, 1H), 4.65 (d, J = 10.9 Hz, 1H), 4.46 (d, J = 4.7 Hz, 1H), 4.37 – 4.20 (m, 2H), 4.05 (dd, J = 14.7, 7.6 Hz, 1H), 3.89 (s, 2H), 3.64 – 3.46 (m, 6H), 3.24 (d, J = 16.8 Hz, 3H), 3.12 (dd, J = 15.1, 7.1 Hz, 1H), 2.92 (d, J = 13.9 Hz, 1H), 2.61 (d, J = 5.7 Hz, 1H), 2.45 – 2.36 (m, 2H), 2.30 (d, J = 5.5 Hz, 1H), 2.13 (t, J = 9.7 Hz, 1H), 1.56 (s, 1H), 1.48 (s, 5H), 1.34 (d, J = 5.9 Hz, 3H), 1.22 (s, 2H), 1.16 (s, 2H), 1.06 (dd, J = 10.5, 5.8 Hz, 5H), 0.85 (d, J = 8.2 Hz, 5H), 0.30 (s, 3H).

Example 79

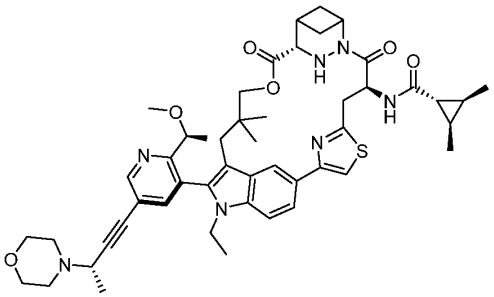
(1S,2S)-N-((6^4S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((S)-3-morpholinobut-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide



Substituting (R)-4-(but-3-yn-2-yl)morpholine with (S)-4-(but-3-yn-2-yl)morpholine in the Step 17 and substituting (1r,2R,3S)-2,3-dimethylcyclopropane-1-carboxylic acid with (1S,2S)-2-methylcyclopropane-1-carboxylic acid in the Step 19 of **Example 78**, the title compound was prepared by the same procedures as described for **Example 78**.

Example 80

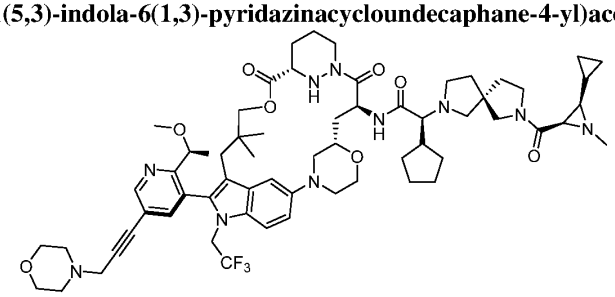
(1r,2R,3S)-N-((6^4S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((S)-3-morpholinobut-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-2,3-dimethylcyclopropane-1-carboxamide



Substituting (R)-4-(but-3-yn-2-yl)morpholine with (S)-4-(but-3-yn-2-yl)morpholine in the Step 17 of **Example 78**, the title compound was prepared by the same procedures as described for **Example 78**.

Example 81

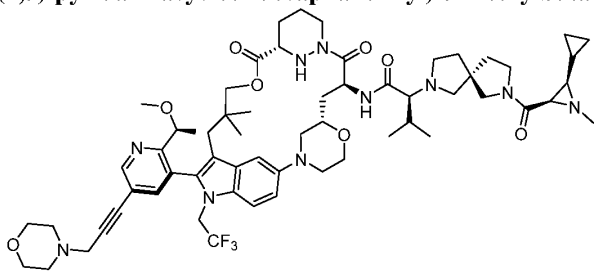
(2S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{3}S,4S)-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1-(2,2,2-trifluoroethyl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-morpholina-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)acetamide



Substituting tert-butyl ((2^{2}S,6^{4}S,4S)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate with tert-butyl ((2^{2}S,6^{3}S,4S)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-morpholina-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)carbamate in the Step 1 of **Example 23**, the title compound was prepared by the same procedures as described for **Example 23**.

Example 82

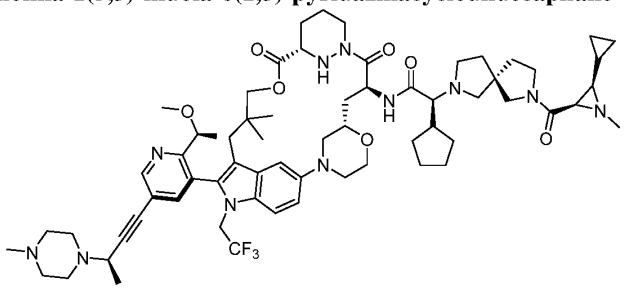
(2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{3}S,4S)-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1-(2,2,2-trifluoroethyl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-morpholina-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)-3-methylbutanamide



Substituting (S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)acetic acid with (S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-3-methylbutanoic acid in the Step 4 of **Example 81**, the title compound was prepared by the same procedures as described for **Example 81**.

Example 83

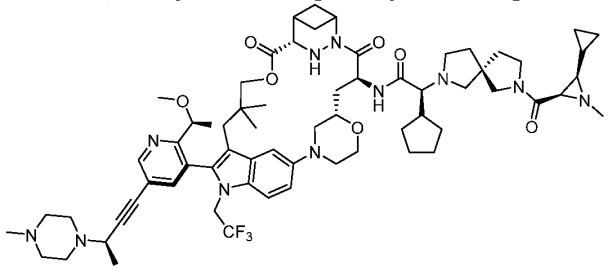
(2S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{3}S,4S)-1^2-(2-((S)-1-methoxyethyl)-5-((R)-3-(4-methylpiperazin-1-yl)but-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1-(2,2,2-trifluoroethyl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-morpholina-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)acetamide



Substituting 4-(prop-2-yn-1-yl)morpholine with (R)-1-(but-3-yn-2-yl)-4-methylpiperazine in the Step 1 of **Example 81**, the title compound was prepared by the same procedures as described for **Example 81**.

Example 84

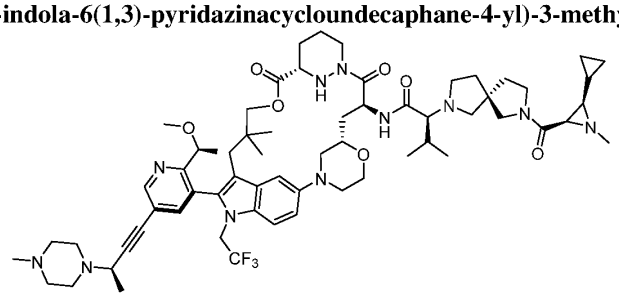
(2S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{4}S,4S)-1^2-(2-((S)-1-methoxyethyl)-5-((R)-3-(4-methylpiperazin-1-yl)but-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1-(2,2,2-trifluoroethyl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)acetamide



Substituting tert-butyl ((2^{2}S,6^{3}S,4S)-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^1-(2,2,2-trifluoroethyl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-morpholina-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)carbamate with tert-butyl ((2^{2}S,6^{4}S,4S)-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^1-(2,2,2-trifluoroethyl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate in the Step 1 of **Example 83**, the title compound was prepared by the same procedures as described for **Example 83**.

Example 85

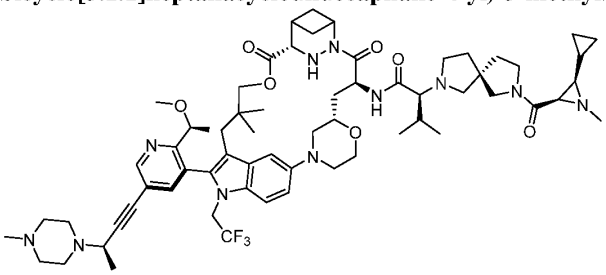
(2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{3}S,4S)-1^2-(2-((S)-1-methoxyethyl)-5-((R)-3-(4-methylpiperazin-1-yl)but-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1-(2,2,2-trifluoroethyl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-morpholina-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)-3-methylbutanamide



Substituting 4-(prop-2-yn-1-yl)morpholine with (R)-1-(but-3-yn-2-yl)-4-methylpiperazine in the Step 4 of **Example 82**, the title compound was prepared by the same procedures as described for **Example 82**.

Example 86

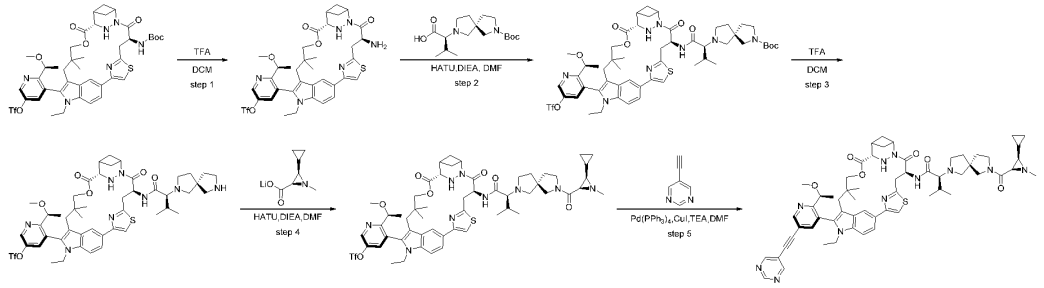
(2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{4}S,4S)-1^2-(2-((S)-1-methoxyethyl)-5-((R)-3-(4-methylpiperazin-1-yl)but-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^1-(2,2,2-trifluoroethyl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide



Substituting (S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)acetic acid with (S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-3-methylbutanoic acid in the Step 4 of **Example 84**, the title compound was prepared by the same procedures as described for **Example 84**.

Example 87

(2S)-2-(7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(pyrimidin-5-ylethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide



Step 1: Synthesis of 5-((6⁴S,4S,Z)-4-amino-1¹-ethyl-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1²-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate

To a stirred solution of 5-((6⁴S,4S,Z)-4-((tert-butoxycarbonyl)amino)-1¹-ethyl-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1²-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate (330 mg, 0.37 mmol) in dichloromethane (10 mL) was added TFA (3 mL) dropwisely at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was washed with sat. $NaHCO_3$ (10 mL), brine (10 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product 5-((6⁴S,4S,Z)-4-amino-1¹-ethyl-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1²-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate (293 mg) as a yellow solid.

LCMS (ESI) calcd. for $C_{36}H_{41}F_3N_6O_7S_2[M+H]^+$ m/z 791.2, found: 792.5.

Step 2: Synthesis of tert-butyl 7-((2S)-1-(((6⁴S,4S,Z)-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-(((trifluoromethyl)sulfonyl)oxy)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2,7-diazaspiro[4.4]nonane-2-carboxylate

To a solution of (2S)-2-(7-(tert-butoxycarbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-3-methylbutanoic acid (121 mg, 0.37 mmol) in DMF (6 mL) were added HATU (183 mg, 0.37 mmol) and DIEA (239 mg, 1.85 mmol) at 0-10°C. The resulting mixture was stirred at RT for 30 min. Then 5-((6⁴S,4S,Z)-4-amino-1¹-ethyl-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1²-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate (293 mg, 0.37 mmol) was added into the reaction mixture, the resulting mixture was stirred at rt for 2 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with brine and extracted with EtOAc (2 x 30 mL), the combined organic phase was washed with saturated NaCl (50 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column eluting with EtOAc/PE from 0% to 100% to afford tert-butyl 7-((2S)-1-(((6⁴S,4S,Z)-1¹-ethyl-1²-(2-((S)-1-methoxyethyl)-5-(((trifluoromethyl)sulfonyl)oxy)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2,7-diazaspiro[4.4]nonane-2-carboxylate (280

mg, 69 %) as a yellow solid.

LCMS (ESI) calcd. for $C_{53}H_{69}F_3N_8O_{10}S_2$ $[M+H]^+$ m/z 1099.5, found: 1101.0.

Step 3: Synthesis of 5-((6^{4}S,4S,Z)-1^1-ethyl-10,10-dimethyl-4-((2S)-3-methyl-2-(2,7-diazaspiro[4.4]nonan-2-yl)butanamido)-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate

To a stirred solution of tert-butyl 7-((2S)-1-(((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(((trifluoromethyl)sulfonyl)oxy)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2,7-diazaspiro[4.4]nonane-2-carboxylate (280 mg, 0.25 mmol) in dichloromethane (2 mL) was added TFA (0.5 mL) dropwisely at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was washed with sat. $NaHCO_3$ (10 mL), brine (10 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product 5-((6^{4}S,4S,Z)-1^1-ethyl-10,10-dimethyl-4-((2S)-3-methyl-2-(2,7-diazaspiro[4.4]nonan-2-yl)butanamido)-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate (255 mg) as a yellow solid.

LCMS (ESI) calcd. for $C_{48}H_{61}F_3N_8O_8S_2$ $[M+H]^+$ m/z 999.4, found: 1000.1.

Step 4: Synthesis of 5-((6^{4}S,4S,Z)-4-((2S)-2-(7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-3-methylbutanamido)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate

To a solution of lithium (2R,3R)-3-cyclopropyl-1-methylaziridine-2-carboxylate (75 mg, 0.51 mmol) in DMF (3 mL) were added HATU (116 mg, 0.31 mmol) and DIEA (329 mg, 2.5 mmol) at 0-10°C. The resulting mixture was stirred at RT for 30 min. Then 5-((6^{4}S,4S,Z)-1^1-ethyl-10,10-dimethyl-4-((2S)-3-methyl-2-(2,7-diazaspiro[4.4]nonan-2-yl)butanamido)-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate (255 mg, 0.25 mmol) was added into the reaction mixture, the resulting mixture was stirred at rt for 2 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with brine and extracted with EtOAc (2 x 30 mL), the combined organic phase was washed with saturated NaCl (50 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column eluting with MeOH/DCM from 0% to 7% to afford 5-((6^{4}S,4S,Z)-4-((2S)-2-(7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-3-methylbutanamido)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate (160 mg, 56 %) as an orange oil.

LCMS (ESI) calcd. for $C_{53}H_{69}F_3N_8O_{10}S_2$ $[M+H]^+$ m/z 1122.5, found: 1123.2.

Step 5: Synthesis of

(2S)-2-(7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(pyrimidin-5-ylethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide

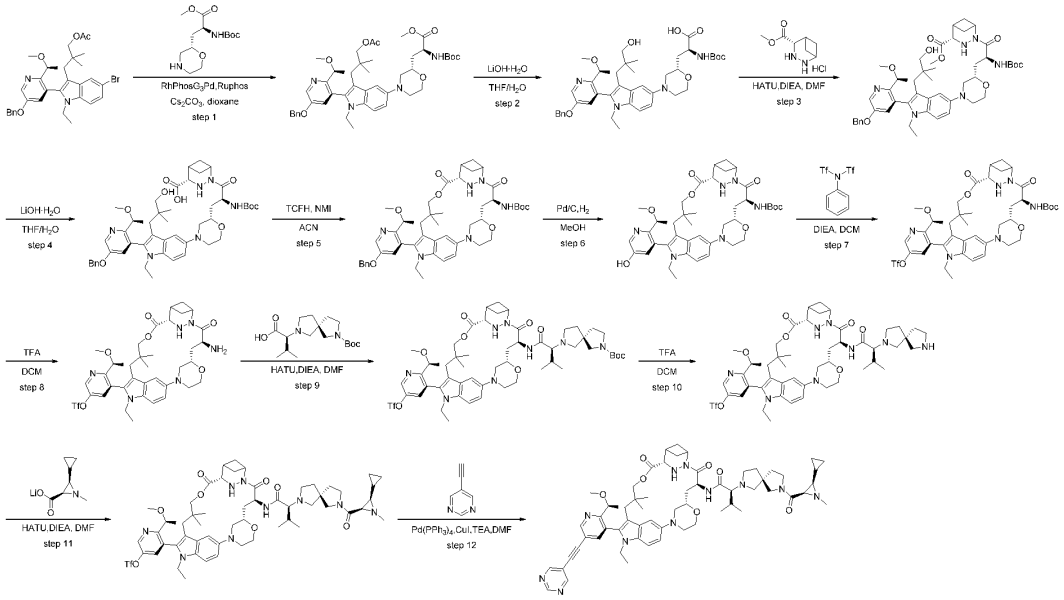
To a stirred solution of 5-((6^{4}S,4S,Z)-4-((2S)-2-(7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-3-methylbutanamido)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate (80 mg, 0.071 mmol) and 5-ethynylpyrimidine (15 mg, 0.14 mmol), CuI (2 mg, 0.011 mmol), TEA (0.5 mL) and $Pd(PPh_3)_4$ (12 mg, 0.011 mmol) in DMF (2 mL) was stirred at 90°C for 1 h under N_2 atmosphere, the reaction was monitored by LCMS. After completion, the mixture was filtered and the filtrate was concentrated, the residue was purified by pre-HPLC (eluting with CH_3CN/H_2O(0.1% NH_4HCO_3) from 20% to 70%) to give (2S)-2-(7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(pyrimidin-5-ylethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide (28 mg, 36 %) as a white solid.

LCMS (ESI) calcd. for $C_{60}H_{73}N_{11}O_6S$ $[M+H]^+$ m/z 1076.6, found:1077.5.

^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.24 (s, 1H), 9.08 (s, 1H), 8.99 (s, 1H), 8.43 (s, 1H), 8.37 – 8.14 (m, 2H), 8.09 (s, 1H), 7.88 (d, *J* = 9.7 Hz, 1H), 7.76 (t, *J* = 12.4 Hz, 1H), 7.64 – 7.55 (m, 1H), 6.01 – 5.89 (m, 1H), 5.34 (dd, *J* = 13.5, 8.1 Hz, 1H), 4.76 (d, *J* = 11.3 Hz, 1H), 4.50 (s, 1H), 4.41-4.35 (m, 2H), 4.04 (dt, *J* = 63.0, 19.2 Hz, 2H), 3.76 – 3.36 (m, 5H), 3.29 (s, 4H), 3.13 – 2.55 (m, 8H), 2.53 (s, 5H), 2.46 – 2.06 (m, 6H), 2.04 – 1.54 (m, 6H), 1.49 – 1.18 (m, 5H), 1.07 – 0.71 (m, 9H), 0.62-0.55 (m, 2H), 0.39 – 0.21 (m, 4H), 0.19-0.15 (m, 1H).

Example 88

(2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(pyrimidin-5-ylethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide



Step 1: Synthesis of methyl (S)-3-((S)-4-(3-(3-acetoxy-2,2-dimethylpropyl)-2-(5-(benzyloxy)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-1H-indol-5-yl)morpholin-2-yl)-2-((tert-butoxycarbonyl)amino)propanoate

To a stirred solution of (S)-3-(2-(5-(benzyloxy)-2-(1-methoxyethyl)pyridin-3-yl)-5-bromo-1-ethyl-1H-indol-3-yl)-2,2-dimethylpropyl acetate (2.6 g, 4.4 mmol), methyl (S)-2-((tert-butoxycarbonyl)amino)-3-((S)-morpholin-2-yl)propanoate (1.3 g, 4.4 mmol) and Cs_2CO_3 (3.6 g, 11 mmol) in 1,4-dioxane (50 mL) were added $RuphosG_3Pd$ (367 mg, 0.4 mmol) and Ruphos (410 mg, 0.9 mmol at rt. The reaction mixture was stirred at 100 °C under N_2 for 18 h. After completion, the reaction solution was concentrated under reduced pressure to remove 1,4-dioxane to give the residual which was purified by silica gel column (eluting with EtOAc/PE from 0% to 80%) to afford methyl (S)-3-((S)-4-(3-(3-acetoxy-2,2-dimethylpropyl)-2-(5-(benzyloxy)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-1H-indol-5-yl)morpholin-2-yl)-2-((tert-butoxycarbonyl)amino)propanoate (2 g, 57 %) as a yellow oil.

LCMS (ESI) calcd. for $C_{45}H_{60}N_4O_9$ $[M+H]^+$ m/z 801.4, found: 802.6.

Step 2: Synthesis of (S)-3-((S)-4-(2-(5-(benzyloxy)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1H-indol-5-yl)morpholin-2-yl)-2-((tert-butoxycarbonyl)amino)propanoic acid

To a solution of methyl (S)-3-((S)-4-(3-(3-acetoxy-2,2-dimethylpropyl)-2-(5-(benzyloxy)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-1H-indol-5-yl)morpholin-2-yl)-2-((tert-butoxycarbonyl)amino)propanoate (1.7 g, 2.1 mmol) in THF (18 mL) and H_2O (6 mL) was added $LiOHH_2O$ (267 mg, 6.4 mmol) at 0-10°C , the resulting mixture was stirred at RT for 16 h. The reaction was monitored by LCMS. After completion, the reaction mixture was acidified to pH = 3-4 with 2 N HCl. The resulting mixture was extracted with EtOAc (300 mL x 2), the combined organic phase was washed with saturated NaCl (500 mL), then dried over Na_2SO_4 and concen-

trated to give (S)-3-((S)-4-(2-(5-(benzyloxy)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1H-indol-5-yl)morpholin-2-yl)-2-((tert-butoxycarbonyl)amino)propanoic acid (1.58 g, 100 %) as a light yellow solid.

LCMS (ESI) calcd. for $C_{42}H_{56}N_4O_8$ $[M+H]^+$ m/z 745.4, found: 746.3.

Step 3: Synthesis of methyl (S)-2-((S)-3-((S)-4-(2-(5-(benzyloxy)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1H-indol-5-yl)morpholin-2-yl)-2-((tert-butoxycarbonyl)amino)propanoyl)-2,3-diazabicyclo[3.1.1]heptane-4-carboxylate

To a solution of (S)-3-((S)-4-(2-(5-(benzyloxy)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1H-indol-5-yl)morpholin-2-yl)-2-((tert-butoxycarbonyl)amino)propanoic acid (1.58 g, 2.1 mmol) in DMF (20 mL) were added HATU (1.05 g, 2.8 mmol) and DIEA (1.37 g, 10.6 mmol) at 0-10°C. The resulting mixture was stirred at 0-10°C for 10 min. Then methyl (S)-2,3-diazabicyclo[3.1.1]heptane-4-carboxylate hydrochloride (531 mg, 2.8 mmol) was added into the reaction mixture, the resulting mixture was stirred at rt for 2 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with brine and extracted with EtOAc (2 x 30 mL), the combined organic phase was washed with saturated NaCl (100 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column eluting with EtOAc/PE from 0% to 100% to afford methyl (S)-2-((S)-3-((S)-4-(2-(5-(benzyloxy)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1H-indol-5-yl)morpholin-2-yl)-2-((tert-butoxycarbonyl)amino)propanoyl)-2,3-diazabicyclo[3.1.1]heptane-4-carboxylate (750 mg, 40 %) as a light yellow solid.

LCMS (ESI) calcd. for $C_{49}H_{66}N_6O_9$ $[M+H]^+$ m/z 883.5, found: 884.2.

Step 4: Synthesis of (S)-2-((S)-3-((S)-4-(2-(5-(benzyloxy)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1H-indol-5-yl)morpholin-2-yl)-2-((tert-butoxycarbonyl)amino)propanoyl)-2,3-diazabicyclo[3.1.1]heptane-4-carboxylic acid

To a solution of (S)-2-((S)-3-((S)-4-(2-(5-(benzyloxy)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1H-indol-5-yl)morpholin-2-yl)-2-((tert-butoxycarbonyl)amino)propanoyl)-2,3-diazabicyclo[3.1.1]heptane-4-carboxylate (750 mg, 0.85 mmol) in THF (6 mL) and H_2O (2 mL) was added $LiOH·H_2O$ (107 mg, 2.55 mmol) at 0-10°C , the resulting mixture was stirred at RT for 16 h. The reaction was monitored by LCMS. After completion, the reaction mixture was acidified to pH = 3-4 with 2 N HCl. The resulting mixture was extracted with EtOAc (30 mL x 2), the combined organic phase was washed with saturated NaCl

(50 mL), then dried over Na_2SO_4 and concentrated to give (S)-2-((S)-3-((S)-4-(2-(5-(benzyloxy)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1H-indol-5-yl)morpholin-2-yl)-2-((tert-butoxycarbonyl)amino)propanoyl)-2,3-diazabicyclo[3.1.1]heptane-4-carboxylic acid (700 mg, 95 %) as a light yellow solid.

LCMS (ESI) calcd. for $C_{48}H_{64}N_6O_9$ $[M+H]^+$ m/z 869.5, found: 870.6.

Step 5: Synthesis of tert-butyl ((2²S,6⁴S,4S)-1²-(5-(benzyloxy)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1¹-ethyl-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

To a solution of TCFH (905 mg, 3.2 mmol) and NMI (528 mg, 6.4 mmol) in ACN (100 mL) was added a solution of (S)-2-((S)-3-((S)-4-(2-(5-(benzyloxy)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1H-indol-5-yl)morpholin-2-yl)-2-((tert-butoxycarbonyl)amino)propanoyl)-2,3-diazabicyclo[3.1.1]heptane-4-carboxylic acid (700 mg, 0.8 mmol) in ACN (40 mL) at 0-10°C, the reaction was gradually improved temperature to room temperature and stirred for 2 h. The reaction was monitored by LCMS. After completion, the reaction was concentrated under reduced pressure to give crude product which was purified by silica gel column (eluting with EtOAc/PE from 0% to 100% to afford tert-butyl ((2²S,6⁴S,4S)-1²-(5-(benzyloxy)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1¹-ethyl-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (310 mg, 45 %) as a white solid.

LCMS (ESI) calcd. for $C_{48}H_{62}N_6O_8$ $[M+H]^+$ m/z 851.5, found: 852.4.

Step 6: Synthesis of tert-butyl ((2²S,6⁴S,4S)-1¹-ethyl-1²-(5-hydroxy-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate

To a stirred solution of tert-butyl ((2²S,6⁴S,4S)-1²-(5-(benzyloxy)-2-((S)-1-methoxyethyl)pyridin-3-yl)-1¹-ethyl-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (310 mg, 0.36 mmol) in MeOH (10 mL) was added Pd/C (10%, 31 mg) at rt , the resulting mixture was stirred at RT for 12 h. The reaction was monitored by LCMS. After completion, the reaction mixture was filtered and the filtrate was concentrated to give crude tert-butyl ((2²S,6⁴S,4S)-1¹-ethyl-1²-(5-hydroxy-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (270 mg) as a light yellow solid.

LCMS (ESI) calcd. for $C_{41}H_{56}N_6O_8$ $[M+H]^+$ m/z 761.4, found: 762.5.

Step 7: Synthesis of 5-((2²S,6⁴S,4S)-4-((tert-butoxycarbonyl)amino)-1¹-ethyl-10,10-dimethyl-5,7-dioxo-1¹H-8-oxa-6²,6³-diaza-2

(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate

To a solution of crude tert-butyl ((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(5-hydroxy-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate (270 mg, 0.35 mmol) in DCM (5 mL) were added DIEA (137 mg, 1.06 mmol) and $PhN(Tf)_2$ (152 mg, 0.43 mmol) at 0-10°C. The resulting mixture was stirred at rt for 2 h. The reaction was monitored by LCMS. After completion, the reaction mixture was concentrated under reduced pressure to obtain crude product which was purified by silica gel column eluting with (EtOAc/PE from 0% to 100%) to afford 5-((2^{2}S,6^{4}S,4S)-4-((tert-butoxycarbonyl)amino)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate (290 mg, 91 %) as a white foam.

LCMS (ESI) calcd. for $C_{42}H_{55}F_3N_6O_{10}S$ $[M+H]^+$ m/z 893.4, found: 894.3.

Step 8: Synthesis of 5-((2^{2}S,6^{4}S,4S)-4-amino-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate

To a stirred solution of 5-((2^{2}S,6^{4}S,4S)-4-((tert-butoxycarbonyl)amino)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate (80 mg, 0.09 mmol) in dichloromethane (3 mL) was added TFA (1 mL) dropwise at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was washed with sat. $NaHCO_3$ (3 mL), brine (3 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product 5-((2^{2}S,6^{4}S,4S)-4-amino-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate (91 mg, crude) as a yellow solid.

LCMS (ESI) calcd. for $C_{37}H_{47}F_3N_6O_8S$ $[M+H]+$ m/z 793.3, found: 794.3.

Step 9: Synthesis of tert-butyl (5S)-7-((2S)-1-(((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(((trifluoromethyl)sulfonyl)oxy)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2,7-diazaspiro[4.4]nonane-2-carboxylate

To a solution of (S)-2-((S)-7-(tert-butoxycarbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-3-methylbutanoic acid (44 mg, 0.13 mmol) in DMF (2 mL) were added HATU (51 mg, 0.13 mmol) and DIEA (58 mg, 0.45 mmol) at 0-10 °C. The resulting mixture was stirred at 0-10°C for 10 min. Then 5-((2^{2}S,6^{4}S,4S)-4-amino-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate (71 mg, 0.89 mmol) was added into the reaction mixture, the resulting mixture was

stirred at rt for 2 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with brine and extracted with EtOAc (2 x 30 mL), the combined organic phase was washed with saturated NaCl (100 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column eluting with EtOAc/PE from 0% to 100% to afford tert-butyl (5S)-7-((2S)-1-(((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(((trifluoromethyl)sulfonyl)oxy)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2,7-diazaspiro[4.4]nonane-2-carboxylate (70 mg, 71 %) as a light yellow solid.

LCMS (ESI) calcd. for $C_{54}H_{75}F_3N_8O_{11}S$ [M+H]+ m/z 1101.5, found: 1102.4.

Step 10: Synthesis of 5-((2^{2}S,6^{4}S,4S)-1^1-ethyl-10,10-dimethyl-4-((S)-3-methyl-2-((S)-2,7-diazaspiro[4.4]nonan-2-yl)butanamido)-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate

To a stirred solution of tert-butyl (5S)-7-((2S)-1-(((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(((trifluoromethyl)sulfonyl)oxy)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2,7-diazaspiro[4.4]nonane-2-carboxylate (70 mg, 0.06 mmol) in dichloromethane (3 mL) was added TFA (1 mL) dropwise at rt, the resulting mixture was stirred at rt for 1 h. The reaction mixture was washed with sat. $NaHCO_3$ (3 mL), brine (3 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product 5-((2^{2}S,6^{4}S,4S)-1^1-ethyl-10,10-dimethyl-4-((S)-3-methyl-2-((S)-2,7-diazaspiro[4.4]nonan-2-yl)butanamido)-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate (63 mg, crude) as a yellow solid.

LCMS (ESI) calcd. for $C_{49}H_{67}F_3N_8O_9S$ [M+H]+ m/z 1001.5, found: 1002.3.

Step 11: Synthesis of (2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(5-hydroxy-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide trifluoromethanesulfonate

To a solution of lithium (2R,3R)-3-cyclopropyl-1-methylaziridine-2-carboxylate (19 mg, 0.13 mmol) in DMF (2 mL) were added HATU (29 mg, 0.08 mmol) and DIEA (81 mg, 0.63 mmol) at 0-10°C. The resulting mixture was stirred at 0-10°C for 10 min. Then 5-((2^{2}S,6^{4}S,4S)-1^1-ethyl-10,10-dimethyl-4-((S)-3-methyl-2-((S)-2,7-diazaspiro[4.4]nonan-2-yl)butanamido)-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-1^2-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate (63 mg, 0.06 mmol) was added into the reaction mixture, the resulting mixture was stirred at rt for 2 h. The reaction was monitored by LCMS. After completion, the reaction mixture was diluted with brine and extracted with EtOAc (2 x 30

mL), the combined organic phase was washed with saturated NaCl (100 mL), then dried over Na_2SO_4, following with concentration under reduced pressure to obtain crude product which was purified by silica gel column eluting with EtOAc/PE from 0% to 100% to afford tert-butyl (2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2 ^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(5-hydroxy-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide trifluoromethanesulfonate (25 mg, 31 %) as a light yellow solid.

LCMS (ESI) calcd. for $C_{56}H_{76}F_3N_9O_{10}S$ [M+H]+ m/z 1124.5, found: 1125.4.

Step 12: Synthesis of (2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(pyrimidin-5-ylethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide

A mixture of (2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2 ^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(5-hydroxy-2-((S)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide trifluoromethanesulfonate (25 mg, 0.022 mmol), 5-ethynylpyrimidine (4.6 mg, 0.044 mmol), CuI (0.6 mg, 0.003 mmol) and $Pd(PPh_3)_4$ (3.9 mg, 0.003 mmol) in TEA/DMF (0.5 mL/2 mL) was stirred at 100°C for 1 h under N_2 atmosphere, the reaction was monitored by LCMS. After completion, the mixture was filtered and the filtrate was concentrated, the residue was purified by pre-HPLC (ACN/H_2O (0.5 % NH_4HCO_3) from 20% to 95% in 30 min) to give (2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2 ^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(pyrimidin-5-ylethynyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide (3 mg, 12.5%) as a white solid.

LCMS (ESI) calcd. for $C_{61}H_{79}N_{11}O_7$ $[M+H]^+$ m/z 1078.6, found: 1079.4.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.15 (t, *J* = 1.7 Hz, 1H), 8.79 (d, *J* = 1.8 Hz, 2H), 8.36 (d, *J* = 12.1 Hz, 1H), 8.31 (d, *J* = 2.0 Hz, 1H), 8.04 (d, *J* = 2.0 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.21 (d, *J* = 2.2 Hz, 1H), 7.01 (dd, *J* = 7.9, 2.2 Hz, 1H), 5.24 (q, *J* = 5.4 Hz, 1H), 4.90 (d, *J* = 8.6 Hz, 1H), 4.47 (q, *J* = 11.9 Hz, 1H), 4.15 (q, *J* = 4.4 Hz, 2H), 4.12 – 4.06 (m, 1H), 4.06 – 4.03 (m, 2H), 3.99 – 3.89 (m, 2H), 3.89 – 3.82 (m, 2H), 3.82 – 3.78 (m, 1H), 3.68 (d, *J* = 6.0 Hz, 1H), 3.65 – 3.55 (m, 5H), 3.45 (dd, *J* = 7.4, 4.8 Hz, 1H), 3.37 (d, *J* = 1.3 Hz, 2H), 3.33 (s, 3H), 3.09 (s, 2H), 2.99 – 2.92 (m, 1H), 2.88 – 2.79 (m, 3H), 2.79 – 2.66 (m, 2H), 2.41 (t, *J* = 1.5 Hz, 3H), 2.25 – 1.91 (m, 9H), 1.89 – 1.81 (m, 3H), 1.67 (d, *J* = 5.3 Hz, 3H), 1.37 (t, *J* = 4.4 Hz, 3H), 1.21 (dd, *J* = 7.9, 4.9 Hz, 2H), 1.15 (s, 3H), 1.10 (s, 3H), 1.05 (dd, *J* = 7.6, 5.0 Hz, 2H), 0.95 (d, *J* = 5.7 Hz, 3H), 0.90 (d, *J* = 5.5 Hz, 3H).

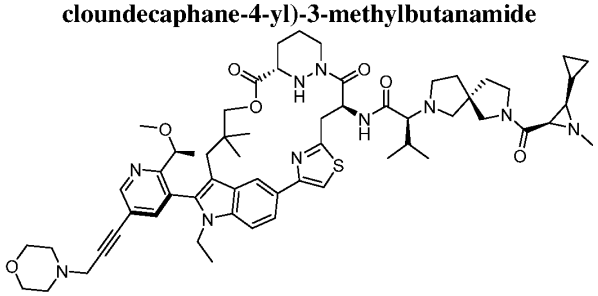
Example 89

(2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((6^{3}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-d

ime-

thyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacy

cloundecaphane-4-yl)-3-methylbutanamide



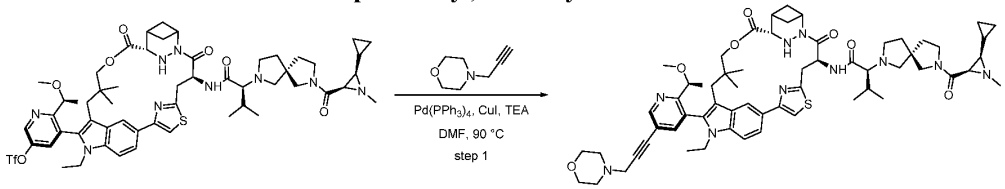
Substituting tert-butyl ((6^{4}S,4S,Z)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate with tert-butyl ((6^{3}S,4S,Z)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)carbamate in the Step 1 of **Example 90**, the title compound was prepared by the same procedures as described for **Example 90**.

Example 90

(2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dime-

thyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacyclou

ndecaphane-4-yl)-3-methylbutanamide



Step 1: Synthesis of (2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide

To a stirred solution of 5-((6^{4}S,4S,Z)-4-((2S)-2-(7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-3-methylbutanamido)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-12-yl)-6-((S)-1-methoxyethyl)pyridin-3-yl trifluoromethanesulfonate (80 mg, 0.071 mmol) and 4-(prop-2-yn-1-yl)morpholine (18 mg, 0.14 mmol), CuI (2 mg, 0.011 mmol), TEA (22 mg, 0.21 mmol) and $Pd(PPh_3)_4$ (12 mg, 0.011 mmol) in DMF (2 mL) was stirred at 90°C for 1 h under N_2 atmosphere, the reaction was monitored by LCMS. After completion, the

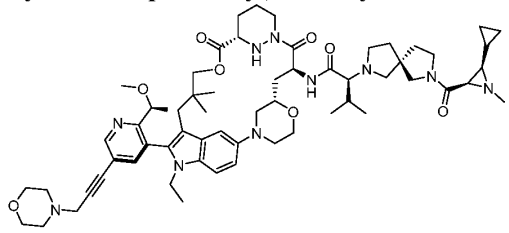
mixture was filtered and the filtrate was concentrated, the residue was purified by pre-HPLC (eluting with CH_3CN/H_2O(0.1% NH_4HCO_3) from 20% to 70%) to give (2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((6^{4}S,4S,Z)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide (19.1mg) as a white solid.

LCMS (ESI) calcd. for $C_{61}H_{80}N_{10}O_7S$ $[M+H]^+$ m/z 1097.6, found: 1098.4.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.40 (s, 1H), 8.35 – 8.18 (m, 1H), 7.86 (s, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H), 5.93 (s, 1H), 5.32 (s, 1H), 4.73 (d, J = 10.2 Hz, 1H), 4.49 (s, 1H), 4.37 – 4.20 (m, 2H), 4.07 (d, J = 7.3 Hz, 1H), 3.53 (dd, J = 26.3, 13.2 Hz, 5H), 3.25 (s, 3H), 2.88 – 2.69 (m, 3H), 2.67 – 2.50 (m, 4H), 2.36 (d, J = 14.5 Hz, 2H), 2.27 – 2.09 (m, 3H), 2.02 – 1.76 (m, 3H), 1.66 (dd, J = 33.9, 16.1 Hz, 3H), 1.34 (d, J = 5.8 Hz, 3H), 1.21 (s, 1H), 0.99 – 0.79 (m, 7H), 0.58 (s, 1H), 0.31 (d, J = 17.6 Hz, 3H), 0.14 (s, 1H).

Example 91

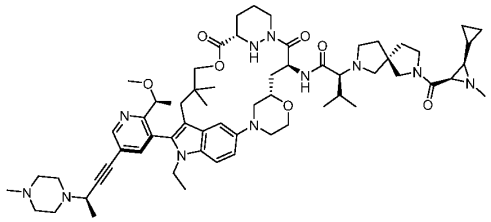
(2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{3}S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-morpholina-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)-3-methylbutanamide



Substituting tert-butyl ((6^{4}S,4S,Z)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-thiazola-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate with tert-butyl ((2^{2}S,6^{3}S,4S)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-morpholina-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)carbamate in the Step 1 of **Example 90**, the title compound was prepared by the same procedures as described for **Example 90**.

Example 92

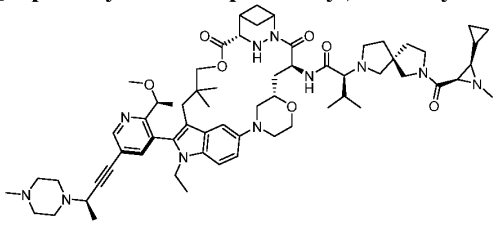
(2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{3}S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((R)-3-(4-methylpiperazin-1-yl)but-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-morpholina-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)-3-methylbutanamide



Substituting 4-(prop-2-yn-1-yl)morpholine with (R)-1-(but-3-yn-2-yl)-4-methylpiperazine in the Step 1 of **Example 91**, the title compound was prepared by the same procedures as described for **Example 91**.

Example 93

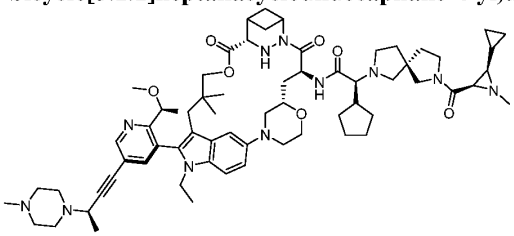
(2S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((R)-3-(4-methylpiperazin-1-yl)but-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)-3-methylbutanamide



Substituting tert-butyl ((2^{2}S,6^{3}S,4S)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-morpholina-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)carbamate with tert-butyl ((2^{2}S,6^{4}S,4S)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate in the Step 1 of **Example 92**, the title compound was prepared by the same procedures as described for **Example 92**.

Example 94

(2S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((R)-3-(4-methylpiperazin-1-yl)but-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)acetamide

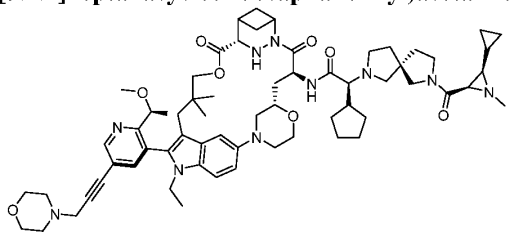


Substituting (S)-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-3-methylbutanoic acid with (S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nona

n-2-yl)acetic acid in the Step 1 of **Example 93**, the title compound was prepared by the same procedures as described for **Example 93**.

Example 95

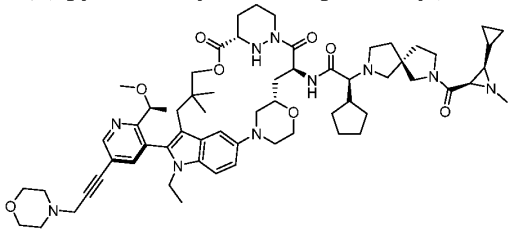
(2S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{4}S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)acetamide



Substituting (R)-1-(but-3-yn-2-yl)-4-methylpiperazine with 4-(prop-2-yn-1-yl)morpholine in the Step 1 of **Example 94**, the title compound was prepared by the same procedures as described for **Example 94**.

Example 96

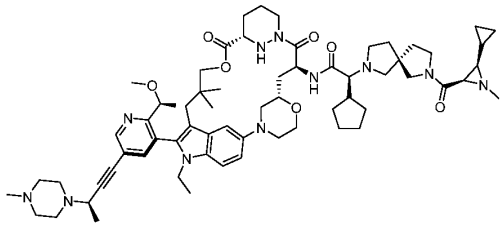
(2S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{3}S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-(3-morpholinoprop-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-morpholina-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)acetamide



Substituting tert-butyl ((2^{2}S,6^{4}S,4S)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1^{1}H-8-oxa-6^2,6^3-diaza-2(4,2)-morpholina-1(5,3)-indola-6(2,4)-bicyclo[3.1.1]heptanacycloundecaphane-4-yl)carbamate with tert-butyl ((2^{2}S,6^{3}S,4S)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-1^2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-morpholina-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)carbamate in the Step 1 of **Example 95**, the title compound was prepared by the same procedures as described for **Example 95**.

Example 97

(2S)-2-cyclopentyl-2-((S)-7-((2R,3R)-3-cyclopropyl-1-methylaziridine-2-carbonyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-((2^{2}S,6^{3}S,4S)-1^1-ethyl-1^2-(2-((S)-1-methoxyethyl)-5-((R)-3-(4-methylpiperazin-1-yl)but-1-yn-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^{1}H-8-oxa-2(4,2)-morpholina-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)acetamide



Substituting 4-(prop-2-yn-1-yl)morpholine with (R)-1-(but-3-yn-2-yl)-4-methylpiperazine in the Step 1 of **Example 96**, the title compound was prepared by the same procedures as described for **Example 96**.

The following exemplary compounds was synthesized from different starting materials according to the method above (such as method for Example 1-30)

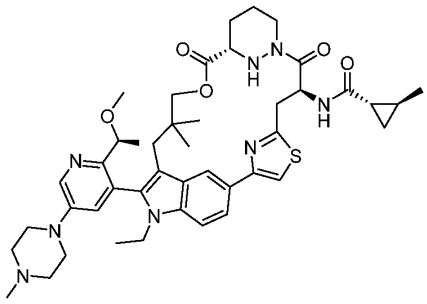
Table 4A. Exemplary Compounds Prepared by Methods of the Present Invention

Code	LCMS $[M+H]^+$	Code	LCMS $[M+H]^+$	Code	LCMS $[M+H]^+$	Code	LCMS $[M+H]^+$
Example 31	940.4	Example 48	1270.7	Example 65	917.5	Example 82	1141.6
Example 32	940.2	Example 49	1224.5	Example 66	943.6	Example 83	1194.7
Example 33	1044.4	Example 50	1196.6	Example 67	902.5	Example 84	1206.7
Example 34	1001.3	Example 51	1250.7	Example 68	901.5	Example 85	1168.7
Example 35	1055.3	Example 52	1098.5	Example 69	876.4	Example 86	1180.7
Example 36	1081.3	Example 53	1110.5	Example 70	864.5	Example 87	1077.5
Example 37	1100.6	Example 54	1181.6	Example 71	864.5	Example 88	1078.6
Example 38	1154.4	Example 55	1194.5	Example 72	876.4	Example 89	1085.6
Example 39	1051.3	Example 56	1184.5	Example 73	875.5	Example 90	1097.6
Example 40	1148.5	Example 57	1196.5	Example 74	889.5	Example 91	1087.7
Example 41	1201.6	Example 58	1134.6	Example 75	875.5	Example 92	1114.7
Example 42	1174.5	Example 59	1136.6	Example 76	889.5	Example 93	1126.8
Example 43	1127.6	Example 60	951.5	Example 77	862.5	Example 94	1152.6
Example 44	1176.7	Example 61	963.6	Example 78	876.4	Example 95	1125.7
Example 45	1230.6	Example 62	953.5	Example 79	862.5	Example 96	1113.7
Example 46	1202.7	Example 63	965.5	Example 80	876.4	Example 97	1140.7
Example 47	1256.6	Example 64	940.6	Example 81	1167.7	Example 98	1156.7

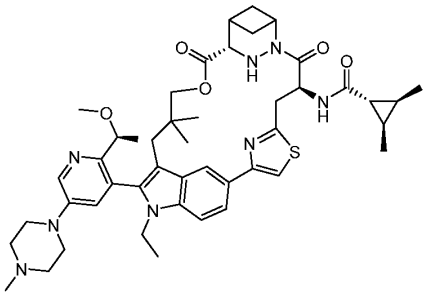
Note: values may differ slightly from values found elsewhere in this application due to different measurements and rounding.

BIOLOGICAL ACTIVITY RESULTS

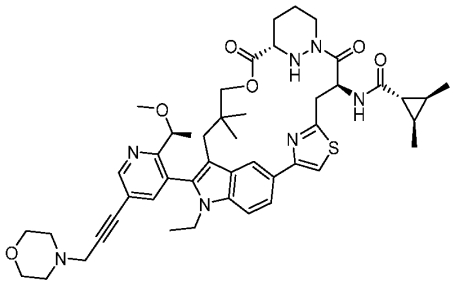
The following were used as reference compounds.



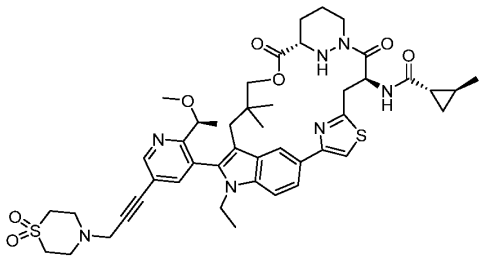
Ref.1



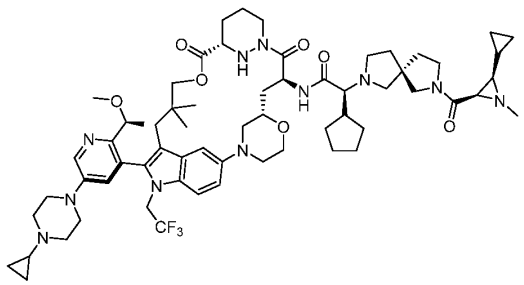
Ref.2



Ref.3



Ref.4



Ref.5

Ras: RAF1 HTRF Assay

This example is to verify the binding between RAS protein and its interacting protein (SOS1 or RAF1). When RAS exists with SOS1 or RAF, the two interact to make the energy donor and receptor bound to it close enough, and then when the donor is excited by an external light source, energy resonance transfer occurs, thereby exciting the receptor and emitting a specific wavelength of emitted light, the FRET signal is detected.

Specific experimental methods: 20 nM purified RAS protein (e.g. KRAS-G12C, G12D, G12V, G12S, WT) was incubated with the drug to be screened (the drug was diluted in a 3-fold gradient to a final concentration of 1000 nM) at room temperature for 1 h. Subsequently, 30 nM purified SOS1-Cat was added and incubated at room temperature for 0.5-1 h. After adding the detection antibody (PerkinElmer, Cisbio, HTRF antibody), the value was measured according to the manufacturer's instructions.

The representative compound results

The reference compound (Ref.1) and the representative Compound A (Example 16) significantly inhibited the interaction of RAF1 with active RAS^{Mutant} protein or RAS^{WT} protein, and the result is shown in Figure 1.

The inhibitory IC_{50} of the compounds of the examples of the present invention was shown in Table 5.

Table 5. RAS-GTP & Raf Disruption/HTRF Assay

Code	$KRAS^{G12C}$ IC_{50}(nM)	$KRAS^{G12D}$ IC_{50}(nM)	$KRAS^{G12V}$ IC_{50}(nM)	$KRAS^{G12S}$ IC_{50}(nM)	KRA^{WT} IC_{50}(nM)
Ref.1	B*	B	B	B	B
Example 1	B	C	B	B	C
Example 2	A	B	A	B	B
Example 3	B	B	B	B	B
Example 4	A	B	A	A	A
Example 5	A	B	A	A	A
Example 6	B	C	B	B	B
Example 7	B	C	B	B	C
Example 8	A	B	A	B	A
Example 9	A	B	A	A	A
Example 10	A	B	B	B	B
Example 11	A	A	A	A	A
Example 12	A	A	A	A	A
Example 13	B	B	A	A	B
Example 14	B	B	A	A	A
Example 15	A	B	A	A	A
Example 16	A	A	A	A	A
Example 17	A	A	A	A	A
Example 18	A	A	A	A	A
Example 19	A	A	A	A	A
Example 20	B	C	B	B	C
Example 27	A	A	E	E	E
Example 28	B	A	E	E	E
Example 29	A	B	E	E	E
Example 30	A	B	E	E	E
Example 31	A	A	A	A	A
Example 32	A	A	A	A	A
Example 33	A	C	B	B	B
Example 64	B	B	B	B	B
Example 65	A	B	B	B	B
Example 66	B	B	B	B	B
Example 67	B	B	B	B	B
Example 68	B	B	C	C	C
Example 69	A	A	B	B	B
Example 70	B	B	C	C	C
Example 71	C	C	C	C	C

Example 72	A	A	B	B	B
Example 73	A	B	A	A	A
Example 74	A	B	A	A	A
Example 75	B	B	B	B	B
Example 76	B	B	B	B	B
Example 77	A	B	A	A	A
Example 78	A	B	A	A	A
Example 79	B	B	B	B	B
Example 80	B	B	B	B	B

*Key: A: 1 nM <IC_{50} ≤ 10 nM; B: 10 nM < IC_{50} ≤ 100 nM; C: 100 nM < IC_{50} ≤ 1000 nM; D: IC_{50} > 1000 nM; E: not tested.

Cell viability assay

Selective screening using RAS-driven and RAS-non-driven cells: (1) RAS-driven cells, including cells with persistent RAS activation due to RAS mutations and upstream EGFR activation. Cells that are continuously activated due to RAS mutations, such as KRAS G12D (AsPC-1, HPAC, AGS, etc.) mutant cells, KRAS G12C (NCI-H358, MIAPaCa-2, etc.) KRAS G13D (LOVO, HCT15, etc.) mutant cells, etc. Cells with continuous activation of RAS due to EGFR mutations, such as EGFREx19del (PC-9, etc.) mutant cells, EGFRT790M/L858R (NCI-H1975, etc.) mutant cells, etc.; (2) Non-RAS driven cells, including BRAFV600E (A375, SK,) -MEL-3, etc.) mutant cells, RASWT (BxPC-3, etc.) cells, etc.

Specific experimental methods: The above cells were seeded in a 96-well plate at a density of 1000-10000 per well. Drugs were diluted in DMSO to make a 10 mM stock solution. Subsequently, the drug was diluted in a 3-fold gradient to a final concentration of 1000 nM. The cells were treated with the drug for 5 days. Cell viability was then detected by the MTS method.

The representative compound results

The reference compound (Ref.1) and the representative Compound A (Example 16) significantly inhibited the cell viability of KRAS mutant cells: MIA PACA-2(KRAS G12C), NCI-H358 (KRAS G12C), NCI-H2122 (KRAS G12C) HPAF II (KRAS G12D), AGS (KRAS G12D), ASPC-1(KRAS G12D), HPAC (KRAS G12D), LS174T (KRAS G12D), SW480 (KRAS G12V), SW620 (KRAS G12V), CAL-62 (KRAS G12R), LOVO (KRAS G13D) Calu6 (KRAS Q61K) and HCC827 (EGFR). The result is shown in Figure 2.

The inhibitory IC_{50} of the compounds of the examples of the present invention was shown in Table 6.

Table 6. Activity of Compounds of present invention in KRAS Cell viability assay

Code	$KRAS^{G12V}$ IC_{50}(nM)	$KRAS^{G12C}$ IC_{50}(nM)	$KRAS^{G12D}$ IC_{50}(nM)		
	SW620	NCI-H358	ASPC-1	HPAC	AGS
Ref.1	A*	AA	A	A	A
Ref.2	AA	A	A	A	A
Ref.3	AA	AA	AA	A	AA
Ref.4	AA	AA	AA	A	AA

Ref.5	E	E	B	B	B
Example 1	B	A	B	B	B
Example 2	A	A	A	B	A
Example 3	A	A	B	B	B
Example 4	AA	AA	A	A	A
Example 5	AA	AA	A	A	A
Example 6	A	A	B	B	A
Example 7	A	A	B	B	B
Example 8	A	A	B	B	A
Example 9	A	A	A	A	A
Example 10	AA	AA	A	A	A
Example 11	AA	AA	A	A	A
Example 12	AA	AA	A	A	A
Example 13	AA	AA	A	A	A
Example 14	A	A	A	A	A
Example 15	A	A	A	B	A
Example 16	AA	AA	AA	A	AA
Example 17	AA	AA	AA	AA	AA
Example 18	AA	AA	AA	AA	AA
Example 19	AA	AA	AA	AA	AA
Example 20	AA	AA	A	A	A
Example 21	E	E	A	A	A
Example 22	E	E	A	A	A
Example 23	E	E	A	A	A
Example 24	E	B	E	E	E
Example 25	E	A	E	E	E
Example 26	C	A	C	C	C
Example 27	A	A	A	B	A
Example 28	A	A	A	B	A
Example 29	A	A	A	B	A
Example 30	A	A	A	B	A
Example 31	AA	A	A	A	A
Example 32	AA	AA	AA	AA	AA
Example 33	AA	A	A	A	A
Example 34	E	E	B	B	B
Example 35	E	E	B	B	B
Example 36	E	E	B	B	B
Example 37	E	E	B	B	B

Example 38	E	E	A	A	A
Example 39	E	A	E	E	E
Example 40	E	E	A	A	A
Example 41	E	E	A	A	A
Example 42	E	E	B	B	B
Example 43	E	E	A	A	A
Example 44	E	E	A	A	A
Example 45	E	E	B	B	B
Example 46	E	E	A	A	A
Example 47	E	E	A	A	A
Example 48	E	E	A	A	A
Example 49	E	E	A	A	A
Example 50	E	E	B	B	B
Example 51	E	E	A	A	A
Example 52	E	B	E	E	E
Example 53	E	B	E	E	E
Example 54	E	A	E	E	E
Example 55	E	A	E	E	E
Example 56	E	A	E	E	E
Example 57	E	A	E	E	E
Example 58	E	A	E	E	E
Example 59	E	A	E	E	E
Example 60	E	B	E	E	E
Example 61	E	B	E	E	E
Example 62	E	B	E	E	E
Example 63	E	B	E	E	E
Example 64	A	B	B	B	B
Example 65	A	A	A	A	A
Example 66	A	B	B	B	B
Example 67	B	C	C	C	C
Example 68	B	C	C	C	C
Example 69	AA	AA	AA	AA	AA
Example 70	B	C	D	D	D
Example 71	C	C	D	D	D
Example 72	AA	AA	A	A	A
Example 73	E	A	A	E	E
Example 74	E	A	A	E	E
Example 75	E	A	A	E	E

Example 76	E	A	A	E	E
Example 77	E	A	A	E	E
Example 78	E	A	A	E	E
Example 79	E	A	A	E	E
Example 80	E	A	A	E	E
Example 81	E	E	A	A	A
Example 82	E	E	A	A	A
Example 83	E	E	A	A	A
Example 84	E	E	A	A	A
Example 85	E	E	B	B	B
Example 86	E	E	B	B	B
Example 87	E	E	A	B	A
Example 88	E	E	A	B	A
Example 89	E	E	A	A	A
Example 90	E	E	A	B	A
Example 91	E	E	C	C	C
Example 92	E	E	B	B	B
Example 93	E	E	B	B	B
Example 94	E	E	B	B	B
Example 95	E	E	B	B	B
Example 96	E	E	B	B	B
Example 97	E	E	C	C	C

*Key: AA: $IC_{50} \leq 1$ nM; A: 1 nM $< IC_{50} \leq 10$ nM; B: 10 nM $< IC_{50} \leq 100$ nM; C: 100 nM $< IC_{50} \leq 1000$ nM; D: $IC_{50} > 1000$ nM; E: not tested.

Anti-proliferation IC_{50} Values of each cell line

Methods: The purpose of this cellular assay was to determine the effects of test compounds on the proliferation of human cancer cell lines NCI-H358 cells, AGS cells, HPAC cells, AsPC-1 cells, SW620 cells, and A375 cells over a 5-day treatment using Cell Counting Kit-8 (CCK8). Cells were seeded at 2000 cells/well (NCI-H358), 1000 cells/well (AGS), 1500 cells/well (HAPC), 3000 cells/well (AsPC-1), 2000 cells/well (SW620), 2000 cells/well (A375) in 96-well assay plates and incubated overnight. On the day of the assay, diluted compounds were then added in a final concentration of 0.5% DMSO. After 5 days incubation, a tenth of the volume of cell counting kit 8 (Dnjindo-CK04) was added into each well. Read the signal (OD450) using Biotek synergy H1 plate reader after incubation. IC_{50} was determined by Graphpad 8.0.

Table 6A. Anti-proliferation IC_{50} Values of reference compounds and Optimized compounds in each cell line

Cell Viability (IC_{50}, nM)

Code	NCI-H358 ($KRAS^{G12C}$)	AGS ($KRAS^{G12D}$)	HPAC ($KRAS^{G12D}$)	AsPC-1 ($KRAS^{G12D}$)	SW620 ($KRAS^{G12V}$)	A375 ($BRAF^{V600E}$)
Ref.1	5.017	5.513	7.253	11.81	0.4233	>1000
Ref.2	1.753	1.442	1.361	4.421	0.1601	>1000
Ref.3	0.2651	0.1116	1.031	0.2086	0.044	>1000
Ref.4	0.6982	0.328	1.043	0.8654	0.1535	>1000
Example 16	0.09764	0.05339	0.442	0.1341	0.05155	>1000
Example 17	0.06482	0.01911	0.3929	0.09446	0.03637	>1000
Example 18	0.05751	0.006379	0.1301	0.06333	0.02079	>1000

Results: Results from in vitro cell proliferation assays showed that Example 16, Example 17 and Example 18 exhibited a more potent inhibitory effect on cell growth compared to Ref.1 and Ref.2. Besides, the activity of Example 16 was more potent than Ref.3; the activity of Example 17 was more potent than Ref.4

In vivo efficacy and PD studies

After multiple batches of cell screening and activity testing, Compound A and B (Example 16 and Example 17) were selected for in vitro efficacy experiments with reference compounds Ref.1 and Ref.2 in this disclosure, and the differences and advantages of the disclosed compounds and clinical compounds were further compared.

Experimental Animal Models 1: Ref.1 and Compound A in PDAC Tumor ($HPAC^{G12D}$)

Methods: Subcutaneous inoculation of 3×10^6 HPAC cells in 0.1 mL DPBS (Dulbecco's Phosphate-Buffered Saline) was performed in the right cervical dorsal region of each Balb/c nude mice. Experimental animals were marked with ear tag numbers during inoculation as the sole identification for subsequent experiments. The in vivo efficacy study commenced with group administration on day 20 post-cell inoculation, with 5 mice per group receiving continuous treatment for 21 days. Tumor volume and body weight were measured twice weekly. T/C % = T/C × 100; TGI (%) = [1-(Treatending day - Treatgrouping day)/(Vehicleending day - Vehiclegrouping day)] × 100.

Results: On day 21 drug administration, tumor-bearing mice in the vehicle group exhibited a mean tumor volume of 723 mm^3. Significant antitumor efficacy with statistical differences was observed in the following treatment groups: Ref.1 5 mg/kg (tumor volume = 183 mm^3, TGI = 89.32%, T/C = 25.37%, $p < 0.0001$); Compound A 0.1 mg/kg (tumor volume = 167 mm^3, TGI = 92.02%, T/C = 23.10%, $p < 0.0001$), Compound A 0.5 mg/kg (tumor volume = 26 mm^3, TGI = 115.38%, T/C = 3.53%, $p < 0.0001$), Compound A 1 mg/kg (tumor volume = 20 mm^3, TGI = 116.27%, T/C = 2.81%, $p < 0.0001$). Notably, Compound A demonstrated a clear dose-dependent relationship in tumor growth inhibition. The result is shown in Figure 3.

Experimental Animal Models 2: Ref.2 and Compound A in PDAC Tumor ($PK59^{G12D}$)

Methods: Subcutaneous inoculation of 5×10^6 PK59 cells in 0.1 mL DPBS (Dulbecco's Phosphate-Buffered Saline) was performed in the right cervical dorsal region of each Balb/c nude mice. Experimental animals were marked with ear tag numbers during inoculation as the sole identification for subsequent experiments. The in vivo efficacy study commenced with group administration on day 17

post-cell inoculation, with 5 mice per group receiving continuous treatment for 21 days. Tumor volume and body weight were measured twice weekly. T/C % = T/C × 100; TGI (%) = [1-(Treatending day - Treatgrouping day)/(Vehicleending day - Vehiclegrouping day)] × 100.

Results: On day 21 drug administration, tumor-bearing mice in the vehicle group exhibited a mean tumor volume of 915 mm^3. Significant antitumor efficacy with statistical differences was observed in the following treatment groups: Ref.2 0.1 mg/kg (tumor volume = 224 mm^3, TGI = 86.68%, T/C = 24.46%, $p < 0.0001$); Compound A 0.02 mg/kg (tumor volume = 303 mm^3, TGI = 76.82%, T/C = 33.05%, $p < 0.0001$), Compound A 0.05 mg/kg (tumor volume = 110 mm^3, TGI = 100.92%, T/C = 12.05%, $p < 0.0001$), Compound A 0.1 mg/kg (tumor volume = 16 mm^3, TGI = 112.79%, T/C = 1.70%, $p < 0.0001$), Compound A 0.3 mg/kg (tumor volume = 7 mm^3, TGI = 113.82%, T/C = 0.81%, $p < 0.0001$). Notably, Compound A demonstrated a clear dose-dependent relationship in tumor growth inhibition. The result is shown in Figure 4.

Experimental Animal Models 3: Ref.1, Ref.2, Compound A and Compound B in PDAC Tumor ($PK59^{G12D}$)

Methods: Subcutaneous inoculation of 5×10^6 HPAC cells in 0.1 mL DPBS (Dulbecco's Phosphate-Buffered Saline) mixed with 50% Matrigel was performed in the right cervical dorsal region of each Balb/c nude mice. Experimental animals were marked with ear tag numbers during inoculation as the sole identification for subsequent experiments. The in vivo efficacy study commenced with group administration on day 17 post-cell inoculation, with 5 mice per group receiving continuous treatment for 23 days. Tumor volume and body weight were measured twice weekly. T/C % = T/C × 100; TGI (%) = [1-(Treatending day - Treatgrouping day)/(Vehicleending day - Vehiclegrouping day)] × 100.

Results: On day 23 drug administration, tumor-bearing mice in the vehicle group exhibited a mean tumor volume of 1678 mm^3. Significant antitumor efficacy with was observed across treatment groups except for Ref.2 0.1 mg/kg (tumor volume = 1495 mm^3, TGI = 11.93%): Ref.1 5 mg/kg (tumor volume = 674 mm^3, TGI = 65.12%); Ref.1 25 mg/kg (tumor volume = 50 mm^3, TGI = 105.49%);, Ref.2 0.3 mg/kg (tumor volume = 527 mm^3, TGI = 74.51%), Compound A 0.1 mg/kg (tumor volume = 392 mm^3, TGI = 83.41%), Compound A 0.3 mg/kg (tumor volume = 70 mm^3, TGI = 104.13%), Compound B 0.1 mg/kg (tumor volume = 374 mm^3, TGI = 84.48%), Compound B 0.3 mg/kg (tumor volume = 82 mm^3, TGI = 103.45%). The result is shown in Figure 5.

Experimental Animal Models 4: Ref.1, Ref.3, Ref.4, Compound A and Compound B in NSCLC Tumor ($LU99^{G12C}$)

Methods: Subcutaneous inoculation of 5×10^6 LU99 cells in 0.1 mL DPBS (Dulbecco's Phosphate-Buffered Saline) mixed with 50% Matrigel was performed in the right cervical dorsal region of each Balb/c nude mice. Experimental animals were marked with ear tag numbers during inoculation as the sole identification for subsequent experiments. The in vivo efficacy study commenced with group administration on day 8 post-cell inoculation, with 6 mice per group receiving continuous treatment for 14 days. Tumor volume and body weight were measured twice weekly. T/C % = T/C × 100; TGI (%) = [1-(Treatending day - Treatgrouping day)/(Vehicleending day - Vehiclegrouping day)] × 100.

Results: On day 14 drug administration, tumor-bearing mice in the vehicle group exhibited a mean

tumor volume of 1069 mm^3. Antitumor efficacy of Compound A (TGI=32.11%, Compound A 0.01 mg/kg; TGI=109.42%, Compound A 0.05 mg/kg) was more potent than that of Ref.3 (TGI=13.37%, Ref.3 0.01 mg/kg; TGI=87.45%, Ref.3 0.05 mg/kg); Antitumor efficacy of Compound B (TGI=57.43%, Compound B 0.05 mg/kg) was more potent than that of Ref.4 (TGI=33.62%, Ref.4 0.05 mg/kg). The result is shown in Figure 6.

Brain metastasis intracranial model

The purpose of this assay is to determine whether brain exposure of the compounds of current invention was sufficient to mediate regression of tumors in experimental Brain Metastases (BM) models.

Methods: Female BALB/c nude mice were anesthetized with xylazine hydrochloride (8 mg/kg) and Zoletil 50 (35 mg/kg), receiving pre- and post-operative analgesia through butorphanol tartrate (1 mg/kg). Following head fixation in a stereotaxic apparatus, surgical sites were disinfected with 70% ethanol and draped sterilely. A 1 cm sagittal incision exposed the parietal and occipital bones, which were cleaned with 3% hydrogen peroxide. A burr hole was drilled 2 mm right of the bregma and 0.5 mm posterior to the coronal suture using a dental drill. The cell suspension containing 3×10□ NCI-H1373-luc cells in 3 μL DPBS with 20% Matrigel Matrix was carefully loaded into a Hamilton syringe, with external surfaces wiped with ethanol to prevent ectopic tumor formation. The needle was vertically inserted to 3 mm depth for controlled infusion over 1 minute (0.05 μL/sec), followed by 1-minute dwell time before slow withdrawal. The injection site was sealed with cyanoacrylate glue, and the scalp was repositioned and sutured. Postoperative analgesia with meloxicam was administered for three days, with ear tags applied for identification. The efficacy study commenced on day 4 post-implantation, utilizing five mice per group for 21-day treatment.

Results: On day 21 post-grouping, tumor-bearing mice in the vehicle control group demonstrated a mean tumor bioluminescence intensity of 5.12×10□ photons/sec. Significant antitumor efficacy with statistical significance ($p < 0.0001$) was observed across treatment groups: Ref.1 25 mg/kg (2.45×10□ photons/sec, TGI=113.40%, T/C=4.79%), Compound A 0.1 mg/kg (5.68×10□ photons/sec, TGI=105.86%, T/C=11.09%), Compound A 0.5 mg/kg (8.86×10□ photons/sec, TGI=117.06%, T/C=1.73%), and Compound A 1 mg/kg (1.05×10□ photons/sec, TGI=116.63%, T/C=2.05%). The result is shown in Figure 7 and Figure 8.

Metabolic Stability *In Vitro*

The purpose of this experiment was to investigate the metabolic stability of the test compounds in liver microsomes and plasma of human, mouse, rat, canine and cynomolgus monkey.

Liver microsomal stability assay

The original stock solution of the test compound and the positive compound (prepared with 1 mg/mL DMSO) was diluted with DMSO to prepare a 0.25 mM working solution. General formula: mg/mL = (1000/M) mmol/L, M is the relative molecular mass of the compound. The metabolic stability of compounds in liver microsomes was evaluated by incubation them with liver microsomes of different species *in vitro*. After the chemical was incubated with liver microsomes for different times (0 min, 5 min, 15 min, 30 min, 45 min, 60 min), the reaction was terminated by precooled acetonitrile (containing internal standard). After sample processed (protein precipitation method), it was loaded into LC-MS for quantitative analysis of the compounds.

The elimination rate constant and clearance rate of the test compound in liver microsomes were calculated using the following formula:

a) Residual Rate (%) = peak area ratio of compound to internal standard at any time point/peak area ratio of compound to internal standard at 0 min*100%;

b) $T_{1/2} = 0.693/k_e$, where k_e is the elimination rate constant and $T_{1/2}$ is the half-life;

c) Liver Microsomal Intrinsic Clearance ($CL_{int,\ in\ vitro}$) = $0.693/T_{1/2}$/microsomal protein concentration (mg/mL);

The representative compound results

The results of liver microsome stability (Table 7) showed that the intrinsic clearance rate of most of the compounds of the present invention in different species (human, mouse, rat, dog, cynomolgus monkey) was generally lower than that of the reference compound (Ref.1), indicating that it had better stability in the liver microsomes of the above species.

Table 7. Liver Microsome Stability Data for Selected Compounds

Code	Species	Liver Microsomes		Code	Species	Liver Microsomes	
		$T_{1/2}$ (min)	$CL_{int,\ in\ vitro}$ (μL/min/mg protein)			$T_{1/2}$ (min)	$CL_{int,\ in\ vitro}$ (μL/min/mg protein)
Ref.1	Human	16.59	83.6	Ref.2	Human	28.9	47.9
	Mouse	33.35	41.6		Mouse	44.1	31.4
	Rat	54.57	25.4		Rat	>120	8.6
	Dog	68.48	20.2		Dog	>120	11.1
	Monkey	8.85	156.6		Monkey	8.0	173.9
Ref.3	Human	23.9	58.1	Ref.4	Human	108.0	12.8
	Mouse	74.3	18.7		Mouse	>120	3.5
	Rat	40.0	34.6		Rat	39.7	34.9
	Dog	27.4	50.7		Dog	115.3	12.0
	Monkey	7.9	174.5		Monkey	21.2	65.4
Example 5	Human	>120	/*	Example 16	Human	34.38	40.3
	Mouse	>120	/		Mouse	>120	9.7
	Rat	>120	/		Rat	>120	11.0
	Dog	>120	/		Dog	40.38	34.3
	Monkey	72.63	19.1		Monkey	11.61	119.4
Example 17	Human	105.8	13.1	Example 18	Human	59.08	23.5
	Mouse	>120	4.1		Mouse	>120	0.4
	Rat	>120	8.9		Rat	48.67	28.5
	Dog	50.6	27.4		Dog	/	/
	Monkey	11.9	116.9		Monkey	/	/
Example 19	Human	10.88	127.4				
	Mouse	>120	/				

	Rat	75.47	18.4				
	Dog	64.53	21.5				
	Monkey	13.81	100.4				

*/: not tested

Plasma stability assay

The compounds were incubated with the plasma of different species (human, CD-1 mouse, SD rat, beagle dog and cynomolgus monkey) to evaluate the metabolic stability of the compounds in plasma. After the compound was incubated with plasma for different time (0 min, 3 min, 5 min, 15 min, 30 min, 60 min, 120 min), the reaction was terminated by precooling acetonitrile (including internal standard). The terminated reaction solution was purified by protein precipitation method, and the compounds were quantitatively analyzed by LC-MS.

The results of plasma stability (Table 8) showed that the metabolism of Ref.1 in rat plasma was relatively unstable ($T_{1/2}$=20.66 min), while the compound of the present invention was $T_{1/2}$>120 min in rat plasma, and at the same time, the $T_{1/2}$ of the compounds of the present invention in the plasma of different species (human, CD-1 mouse, SD rat, beagle dog and cynomolgus monkey) were greater than 120 min.

Notably, the $T_{1/2}$ of Example 16 and Example 17 in human, mouse, rat, monkey and dog plasma were >120 min, which indicates that Example 16 and Example 17 are metabolically stable in the plasma of different species. Example 16 exhibits superior stability compared to Ref.3 in liver microsomal metabolic systems of all species (human, CD-1 mouse, SD rat, beagle dog and cynomolgus monkey). Example 16 exhibits superior stability compared to Ref.2 in liver microsomal metabolic systems of human, CD-1 mouse, and cynomolgus monkey (Table 8). Example 17 exhibits superior stability compared to Ref.4 in liver microsomal metabolic systems of SD rats (Table 8)

In summary, it showed that the compounds of the present invention had good plasma stability of multiple genera, and at the same time, compared with the reference compound (Ref.1), it had more excellent plasma stability of rats.

Table 8. Plasma Stability Data for Selected Compounds

Code	Species	Plasma $T_{1/2}$(min)	Code	Species	Plasma $T_{1/2}$(min)
Ref.1	Human	>120	Ref.2	Human	>120
	Mouse	>120		Mouse	>120
	Rat	20.66		Rat	>120
	Dog	>120		Dog	>120
	Monkey	>120		Monkey	>120
Ref.3	Human	>120	Ref.4	Human	>120
	Mouse	>120		Mouse	>120
	Rat	>120		Rat	99.24
	Dog	>120		Dog	>120
	Monkey	>120		Monkey	>120
Example 5	Human	>120	Example 16	Human	>120

	Mouse	>120		Mouse	>120
	Rat	>120		Rat	>120
	Dog	/*		Dog	>120
	Monkey	/		Monkey	>120
Example 17	Human	>120	Example 18	Human	>120
	Mouse	>120		Mouse	>120
	Rat	>120		Rat	>120
	Dog	>120		Dog	/
	Monkey	>120		Monkey	/
Example 19	Human	>120			
	Mouse	>120			
	Rat	>120			
	Dog	/			
	Monkey	/			

*/: not tested

Pharmacokinetic study

Oral bioavailability (F) of Ref.1, Ref.2, Ref.3, Ref.4, Example 5, Example 16 and Example 17 was compared in ICR mice.

The above compounds were administered via caudal vein at a dose of 2 mg/kg, and orally at a dose of 10 mg/kg. Whole blood was collected from cheek veins at 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 8 h, 24 h, and 48 h after administration. And plasma samples were also prepared for the pharmacokinetics study of Ref.1, Example 5, Example 16.

The established and verified LC-MS method was used to quantitatively analyze the above compounds in plasma or blood. The mobile phase system of H_2O (B) and acetonitrile (D) was utilized. The compounds were eluted by HPLC gradient with a rate of 0.8 $mL \cdot min^{-1}$. And the detection of the ions was carried out in the negative ESI mode and Selected Ion Record (SIR) mode. MS conditions are as follows: Capillary voltage, 1.5 kV; Cone voltage, 50 V; Desolvation temperature, 400℃; Desolvation Gas, 800 L/Hr. Pharmacokinetic parameters were calculated by WinNonlin.

The representative compound results

The plasma pharmacokinetic parameters of Ref.1, Example 5 and Example 16 after single-dose administration in mice were shown in Table 9. After a single oral dose, $T_{1/2}$, C_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and bioavailability (F) of Example 5 were 10 times, 3 times, 11 times, 10 times and 1 times of that of Ref.1, respectively; $T_{1/2}$, C_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and bioavailability (F) of Example 16 were 9 times, 4 times, 24 times, 23 times and 1 times of that of Ref.1, respectively.

Compared with Ref.1, Example 5 and Example 16 exhibited better pharmacokinetics in mice.

Table 9. Plasma PK Parameters of Compounds in ICR Mice

Code	Dose and Route	2 mg/kg, i.v.	10 mg/kg, p.o.
Ref.1	$t_{1/2}$ (hr)	1.42	2.77

	T_{max} (hr)	0.08	1.08
	C_{max} (ng/mL)	136.13	95.91
	AUC_{0-t} (hr*ng/mL)	151.22	358.66
	$AUC_{0-\infty}$ (hr*ng/mL)	183.64	474.87
	V_d (mL/kg)	24009	
	CL (mL/hr/kg)	11347.08	
	MRT_{0-t} (hr)	1.16	2.75
	F (%)	47.44	
Example 5	$t_{1/2}$ (hr)	10.92	12.44
	T_{max} (hr)	0.08	3
	C_{max} (ng/mL)	380.56	335.59
	AUC_{0-t} (hr*ng/mL)	1637.29	4894.62
	$AUC_{0-\infty}$ (hr*ng/mL)	1803.61	5274.94
	V_d (mL/kg)	17521.51	
	CL (mL/hr/kg)	1111.48	
	MRT_{0-t} (hr)	8.95	12.07
	F (%)	59.79	
Example 16	$t_{1/2}$ (hr)	8.78	9.18
	T_{max} (hr)	0.08	1.67
	C_{max} (ng/mL)	1524.94	1197.58
	AUC_{0-t} (hr*ng/mL)	3668.11	11732.32
	$AUC_{0-\infty}$ (hr*ng/mL)	4294.72	11996
	V_d (mL/kg)	5925.5	
	CL (mL/hr/kg)	466.9	
	MRT_{0-t} (hr)	6.37	11.07
	F (%)	63.97	

The boold pharmacokinetic parameters of Ref.1, Ref.2, Ref.3, Ref.4 and Example 17 after single-dose administration in mice were shown in Table 9A.

After a single vein dose, C_{max}, $AUC_{(0-\infty)}$ of Example 16 were 2.3 times, 1.2 times of those of Ref.2, respectively. And after a single oral dose, C_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and F of Example 16 were 1.7 times, 1.9 times, 1.8 times and 1.9 times of those of Ref.2, respectively. And after a single vein dose, $T_{1/2}$ and Vd of Example 16 were 1.9 times and 2.5 times of those of Ref.3, after a single oral dose, $T_{1/2}$ were 1.9 times of that of Ref.3. The above data indicate that Example 16 (Plasma PK, Example 16 is evenly distributed in whole blood and plasma) has a higher peak concentration, higher exposure, higher bioavailability than Ref.2 and a longer elimination half-life than Ref.3 after a single dose administration in mice.

After a single vein dose, $T_{1/2}$, C_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ of Example 17 were 1.8 times, 1.5 times, 2.2 times and 2.3 times of those of Ref.4; And after a single oral dose, $T_{1/2}$, C_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and F of Example 17 were 2.1 times, 1.1 times, 2.7 times, 2.8 times and 1.2 times of those of Ref.4. The above data

indicate that Example 17 has a higher peak concentration, higher exposure, higher bioavailability and a longer elimination half-life than Ref.4.

Table 9A. The Blood Pharmacokinetic Parameters of Compounds after Single-dose Administration in Mice.

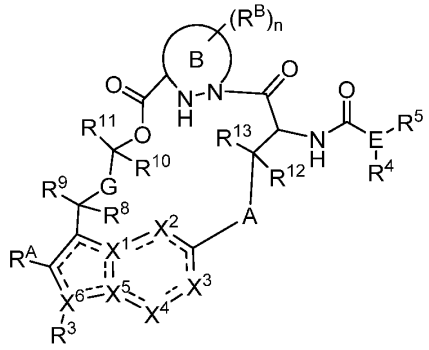
Code	Dose and Route	2 mg/kg, i.v.	10 mg/kg, p.o.
Ref.1	$t_{1/2}$ (hr)	2.06	6.83
	T_{max} (hr)	0.08	0.50
	C_{max} (ng/mL)	1252.6	328.6
	AUC_{0-t} (hr*ng/mL)	1460.3	2203.0
	$AUC_{0-\infty}$ (hr*ng/mL)	1558.6	2465.4
	V_d (mL/kg)	3804.4	
	CL (mL/hr/kg)	1283.2	
	MRT_{0-t} (hr)	1.90	5.9
	F (%)	30.2	
Ref.2	$t_{1/2}$ (hr)	8.80	12.43
	T_{max} (hr)	0.08	2.00
	C_{max} (ng/mL)	677.40	717.40
	AUC_{0-t} (hr*ng/mL)	3640.80	6117.90
	$AUC_{0-\infty}$ (hr*ng/mL)	3726.90	6595.50
	V_d (mL/kg)	6814.10	
	CL (mL/hr/kg)	536.60	
	MRT_{0-t} (hr)	11.40	10.41
	F (%)	33.61	
Ref.3	$t_{1/2}$ (hr)	4.65	4.90
	T_{max} (hr)	0.08	1.00
	C_{max} (ng/mL)	1600.00	1897.00
	AUC_{0-t} (hr*ng/mL)	5735.00	17835.00
	$AUC_{0-\infty}$ (hr*ng/mL)	5744.00	17848.00
	V_d (mL/kg)	2330.00	
	CL (mL/hr/kg)	348.00	
	MRT_{0-t} (hr)	4.82	9.22
	F (%)	62.20	
Ref.4	$t_{1/2}$ (hr)	3.18	4.86
	T_{max} (hr)	0.25	1.00
	C_{max} (ng/mL)	961.00	811.00
	AUC_{0-t} (hr*ng/mL)	1739.00	2575.00
	$AUC_{0-\infty}$ (hr*ng/mL)	1744.00	2608.00
	V_d (mL/kg)	5270.00	

	CL (mL/hr/kg)	1150.00	
	MRT_{0-t} (hr)	3.23	2.71
	F (%)	29.61	
Example 17	$t_{1/2}$ (hr)	5.71	10.09
	T_{max} (hr)	0.08	2.00
	C_{max} (ng/mL)	1416.0	873.6
	AUC_{0-t} (hr*ng/mL)	3817.3	7021.0
	$AUC_{0-\infty}$ (hr*ng/mL)	3980.0	7376.3
	V_d (mL/kg)	4138.1	
	CL (mL/hr/kg)	502.5	
	MRT_{0-t} (hr)	4.60	8.3
	F (%)	36.78	

All literatures mentioned in the present application are incorporated herein by reference, as though each one is individually incorporated by reference. Additionally, it should be understood that after reading the above teachings, those skilled in the art can make various changes and modifications to the present invention. These equivalents also fall within the scope defined by the appended claims.

Claims

1. A compound, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I);



(I)

wherein

n is 0, 1, 2, or 3;

A is optionally substituted 5 to 6-membered heterocycloalkylene, optionally substituted 5 to 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

B is selected from optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 3 to 6-membered heterocycloalkenylene, optionally substituted 4 to 11-membered bicyclic cycloalkylene, or optionally substituted 4 to 11-membered bicyclic heterocycloalkylene;

G is optionally substituted C_{1-6} alkylene;

R^8 and R^9 are each independently selected from hydrogen, deuterium, halogen, hydroxy, cyano, optionally substituted C_{1-3} alkyl, or R^8 and R^9 combine with the atoms to which they are attached to form an optionally substituted C_{3-6} cycloalkyl or a carbonyl;

R^{10} and R^{11} are each independently selected from hydrogen, deuterium, halogen, hydroxy, cyano, optionally substituted C_{1-3} alkyl, or R^{10} and R^{11} combine with the atoms to which they are attached to form an optionally substituted C_{3-6} cycloalkyl or a carbonyl;

R^{12} and R^{13} are each independently selected from hydrogen, deuterium, halogen, hydroxy, optionally substituted C_{1-3} alkyl, -O(C_{1-6} alkyl), -S(C_{1-6} alkyl) or -N(C_{1-6} alkyl)(C_{1-6} alkyl); furthermore, the C_{1-6} alkyl may be further optionally substituted;

R^A is optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl (or 4 to 7-membered heterocycloalkyl), optionally substituted 5 to 8-membered aryl, optionally substituted 5 to 8-membered heteroaryl, optionally substituted 8 to 10-membered fused bicyclic aryl or optionally substituted 8 to 10-membered fused bicyclic heteroaryl;

R^B is selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, optionally substituted C_{3-6} cycloalkyl, or optionally substituted C_{3-6} heterocycloalkyl (or 4 to 7- membered heterocycloalkyl); or provided that when n exceeds 1, any two of R^B combine with the atoms to which they are attached to form a 3 to 6-membered ring, wherein the ring can be optionally substituted with halogen, hydroxy, and

C_{1-3} alkyl;

X^1 is N or C;

X^2 is N or -CR^a-;

X^3 is N or -CR^b-;

X^4 is N or -CR^c-;

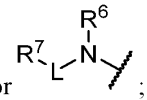
X^5 is N or C;

X^6 is S, O, N, or -CH-;

R^a, R^b, and R^c are each independently hydrogen, halogen, cyano, C_{1-3} alkyl, C_{1-3} alkoxyl, C_{1-3} haloalkyl, C_{1-3} haloalkoxyl, C_{3-6} cycloalkyl, or C_{3-6} heterocycloalkyl (or 4 to 7-membered heterocycloalkyl);

R^3 is absent, or selected from hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl, provided that when X^6 is O or S, R^3 is absent;

E is a bond, or selected from N, or -CR^d-, wherein R^d is selected from hydrogen, halogen, hydroxy, cyano, carboxyl, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkoxyl, C_{1-6} aminoalkyl, C_{1-6} hydroxyalkyl, or -NR^eR^f; wherein R^e and R^f are independently selected from hydrogen, or optionally substituted C_{1-6} alkyl;

R^4 is hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{3-10} cycloalkenyl, optionally substituted C_{3-10} heterocycloalkyl (or 4 to 12-membered heterocycloalkyl), optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or ;

R^5 is hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl, furthermore, the C_{1-6} alkyl or C_{3-6} cycloalkyl may be further optionally substituted;

or R^4 and R^5 combine with the atoms to which they are attached to form a ring, wherein the ring is selected from optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 4 to 11-membered bicyclic cycloalkyl, optionally substituted 4 to 11-membered bicyclic heterocycloalkyl;

wherein

L is absent, or selected from -CH_2-, -C(O)-, -CHR^g- or -$C(R^g)_2$-, wherein R^g is optionally substituted C_{1-6} alkyl;

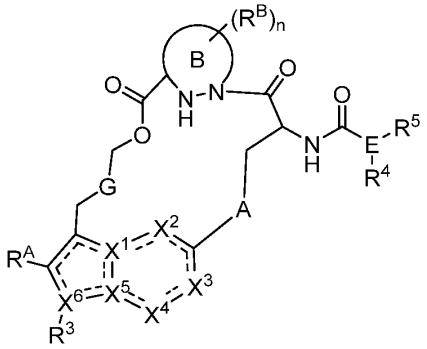
R^6 is hydrogen, or optionally substituted C_{1-6} alkyl;

R^7 is optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{3-10} heterocycloalkyl (or 3 to 10-membered heterocycloalkyl), optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl;

or L, R^6 and R^7 combine with the atoms to which they are attached to form a ring, wherein the ring is selected from optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 4 to 11-membered bicyclic cycloalkyl, optionally substituted 4 to 11-membered bicyclic heterocycloalkyl.

2. The compound according to claim 1, or a stereoisomer thereof, a pharmaceutically acceptable salt

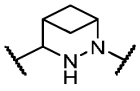
thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is a compound of formula (I-1)

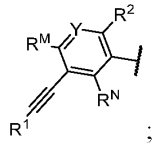


(I-1)

wherein X^1, X^2, X^3, X^4, X^5, X^6, A, B, E, G, R^A, R^B, R^3, R^4, R^5 and n are as defined in claim 1.

3. The compound according to claim 1, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein

B is optionally substituted  ; and

R^A is  ;

wherein

R^1 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl, optionally substituted 5 to 8-membered aryl, optionally substituted 5 to 8-membered heteroaryl, optionally substituted 8 to 10-membered fused bicyclic aryl, optionally substituted 8 to 10-membered fused bicyclic heteroaryl, optionally substituted -C_{1-2} alkylene-C_{3-6} cycloalkyl, optionally substituted -C_{1-2} alkylene-C_{3-6} heterocycloalkyl, optionally substituted -C_{1-2} alkylene-5 to 8-membered aryl, optionally substituted -C_{1-2} alkylene-5 to 8-membered heteroaryl, optionally substituted -C_{1-2} alkylene-8 to 10-membered fused bicyclic aryl, and optionally substituted -C_{1-2} alkylene-8 to 10-membered fused bicyclic heteroaryl; furthermore, the C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, C_{1-6} hydroxyalkyl may be further optionally substituted;

in R^1, when the C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, or C_{1-6} hydroxyalkyl is further substituted, the substituent is selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl, optionally substituted 5 to 8-membered aryl, optionally substituted 5 to 8-membered heteroaryl, optionally substituted 8 to 10-membered fused bicyclic aryl, optionally substituted 8 to 10-membered fused bicyclic heteroaryl; preferably, the substituent is selected from the group consist-

ing of optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl, optionally substituted 5 to 8-membered aryl, optionally substituted 5 to 8-membered heteroaryl, optionally substituted 8 to 10-membered fused bicyclic aryl, optionally substituted 8 to 10-membered fused bicyclic heteroaryl; more preferably, the substituent is optionally substituted C_{3-6} heterocycloalkyl;

Y is -CH- or N;

R^2 is optionally substituted C_{1-6} alkoxy, or optionally substituted C_{1-6} alkyl; preferably, R^2 is optionally substituted C_{1-6} alkyl; and

R^M and R^N are each independently selected from hydrogen, halogen, hydroxy, cyano, carboxyl, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl; furthermore, the C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxyl, C_{1-6} hydroxyalkyl may be further optionally substituted. In some embodiments, R^M and R^N are each independently selected from hydrogen, and C_{1-6} alkyl.

4. The compound according to claim 3, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein

R^1 is optionally substituted C_{1-6} alkyl;

and, in R^1, the C_{1-6} alkyl is further substituted, and the substituent is selected from optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{3-6} heterocycloalkyl, optionally substituted 5 to 8-membered aryl, optionally substituted 5 to 8-membered heteroaryl, optionally substituted 8 to 10-membered fused bicyclic aryl, optionally substituted 8 to 10-membered fused bicyclic heteroaryl.

5. The compound according to claim 3, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein

R^1 is optionally substituted C_{1-6} alkyl;

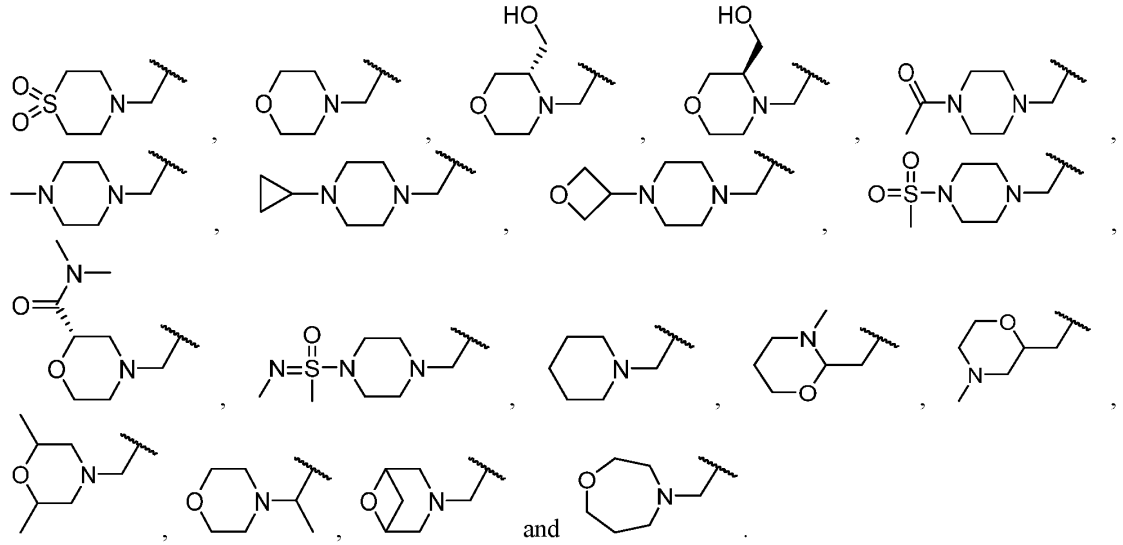
in R^1, the C_{1-6} alkyl is further substituted, and the substituent is optionally substituted C_{3-6} heterocycloalkyl.

6. The compound of claim 3, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein R^1 is C_1 alkyl; and the C_1 alkyl is further substituted with optionally substituted C_{3-6} heterocycloalkyl, wherein the heterocycloalkyl is saturated and the heterocycloalkyl is attached to the rest of the molecule via the N atom on the ring.

7. The compound of claim 3, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein R^1 is C_1 alkyl; and the C_1 alkyl is further substituted with optionally substituted C_{3-6} heterocycloalkyl, wherein the heterocycloalkyl is saturated and the heterocycloalkyl is attached to the rest of the molecule via the N atom on the ring.and the C_{3-6} heterocycloalkyl is 5 to 7 menbered heterocycloalkyl and has l to 2 heteroatoms.

8. The compound according to claim 3, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein

R^1 is selected from the group consisting of

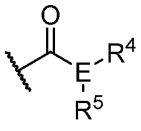


and

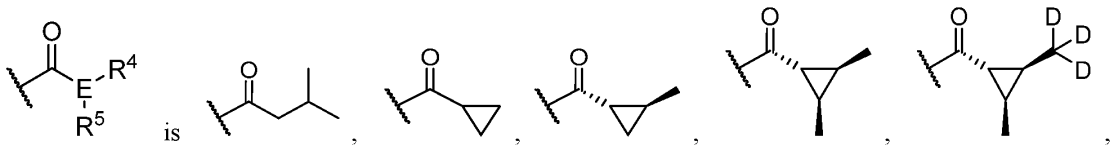
9. The compound according to claim 3, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein R^1 is C_1 alkyl substituted by C_6 heterocycloalkyl, optionally wherein the C_6 heterocycloalkyl is piperazine or morpholine.

10. The compound of claim 1, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein R^4 and R^5 combine with the atoms to which they are attached to form a ring, wherein the ring is optionally substituted 3 to 10-membered cycloalkyl; preferably, is optionally substituted 3 to 6-membered cycloalkyl; more preferably, optionally substituted cyclopropyl.

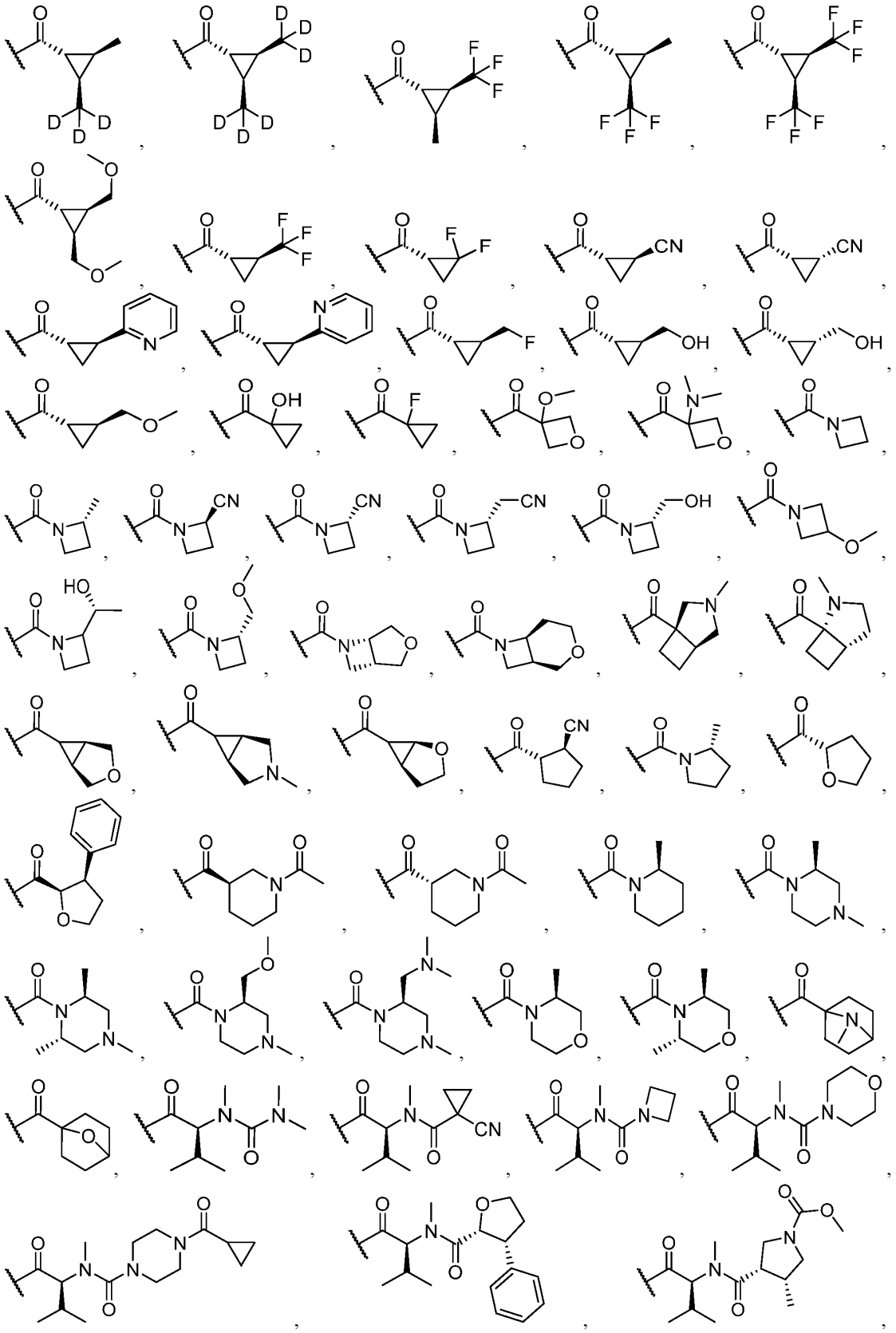
11. The compound according to claim 1, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein

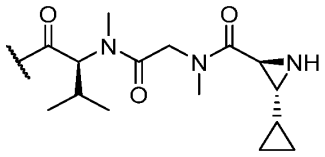
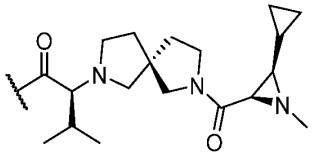
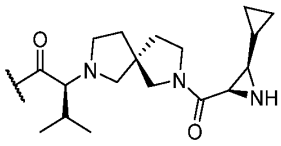
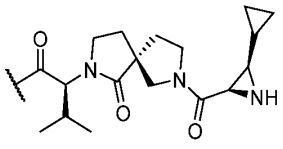
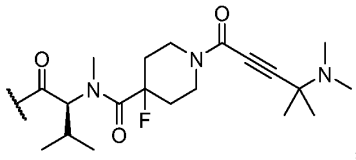
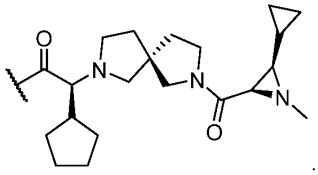


is selected from the group consisting of:



is



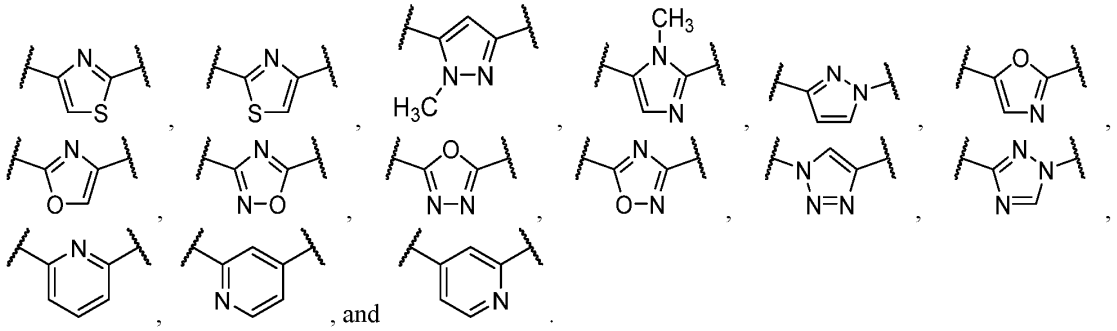

,

,

or

,

,

.

12. The compound according to claim 1, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein

A is optionally substituted 5 to 6-membered heteroarylene, the heteroatom is independently selected from one or two of N, O and S, and the number of the heteroatom is independently 1 to 3

preferably, A is optionally substituted 5-membered heteroarylene, the heteroatom is independently selected from N, O and S, and the number of the heteroatom is independently 1 to 2; preferably, one of the heteroatom is N, and the other, if present, is O or S;

more preferably, A is selected from the group consisting of


, and
.

13. The compound according to claim 1, or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, a metabolite thereof, a prodrug thereof, a solvate thereof or a solvate of the pharmaceutically acceptable salt thereof, wherein

X^1 is C, and/or X^2 is -CR^a-, and/or X^3 is -CR^b, and/or X^4 is –CR^c-, and/or X^5 is -C-.

14. The compound according to claim 1, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, the metabolite thereof, the prodrug thereof, the solvate thereof or the solvate of the pharmaceutically acceptable salt thereof, wherein, the compound is selected from any one of the compounds in Table 1.

15. The compound according to claim 14, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, the metabolite thereof, the prodrug thereof, the solvate thereof or the solvate of the pharmaceutically acceptable salt thereof, wherein, the compound is selected from compounds of Examples 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 27, 28, 29, 30, 31, 32, 33, 37,38, 39, 40,41, 42, 43, 44, 45, 46,

47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 84, 86, 87, 88, and 90 in Table 1.

16. A pharmaceutical composition comprising the compound according to any one of claims 1 to 15, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, the metabolite thereof, the prodrug thereof, the solvate thereof or the solvate of the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

17. A use of the compound according to any one of claims 1 to 15, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, the metabolite thereof, the prodrug thereof, the solvate thereof or the solvate of the pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 16 in the preparation of a medicament used for the treatment of cancer.

18. The use according to claim 17, wherein the cancer is selected from the group consisting of small cell lung cancer (SCLC), colorectal cancer (CRC), pancreatic cancer, and cholangiocarcinoma, pancreatic cancer, appendiceal cancer, small bowel cancer, colorectal cancer, ampullary cancer, non-small cell lung cancer, cervical cancer, lung cancer, endometrial cancer, acute myeloid leukemia, gastrointestinal neuroendocrine tumor, uterine endometrioid carcinoma, oesophagogastric cancer, bladder cancer, ovarian cancer, melanoma, multiple myeloma, thyroid gland adenocarcinoma, a myelodysplastic syndrome, and squamous cell lung carcinoma, or combinations thereof.

19. The use according to claim 17, wherein the cancer is selected from the group consisting of non-small cell lung cancer, small cell lung cancer, colorectal cancer, pancreatic cancer, and cholangiocarcinoma.

20. The compound according to any one of claims 1 to 15, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, the metabolite thereof, the prodrug thereof, the solvate thereof or the solvate of the pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprising the same for use in treating cancer.

21. A method for treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound according to any one of claims 1 to 15, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, the metabolite thereof, the prodrug thereof, the solvate thereof or the solvate of the pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprising the same.