CGRP Antagonist Compounds

This application relates to novel compounds and their use as calcitonin gene-related peptide (CGRP) receptor antagonists. Compounds described herein may be useful in the treatment or prevention of diseases in which CGRP receptors are involved. Compounds described herein may be useful in the treatment or prevention of cerebrovascular or vascular disorders such as migraine. The application is also directed to pharmaceutical compositions comprising these compounds and the manufacture and use of these compounds and compositions in the prevention or treatment of such diseases in which CGRP receptors are involved.

BACKGROUND OF THE INVENTION

Migraine is a highly disabling neurovascular disorder characterized by attacks of moderate to severe headache that are often associated with nausea, vomiting, photophobia, and phonophobia. The attacks can last from 4 to 72 h, and the average attack frequency is 1 or 2 per month. About 20−30% of migraine patients experience transient focal neurologic symptoms known as aura, which are usually visual and can precede or accompany the headache. Migraine afflicts about 11% of adults worldwide and results in a significant socioeconomic burden, in terms of both quality of life and lost productivity.

Whilst the pathomechanism of migraine is still unclear, one of the leading hypotheses is based on activation of the trigeminovascular system (TS). Several neuropeptides participate in this activation, calcitonin gene-related peptide (CGRP) playing a crucial role among them. CGRP exerts various biological effects through the peripheral and central nervous system (CNS). The functional CGRP-receptor (CGRP-R) complex has been well characterized, and novel therapeutic approaches target CGRP itself and its receptors. This invention relates to the development of CGRP receptor antagonists (CGRP-RA).

CGRP, a 37-amino acid neuropeptide derived from the gene encoding calcitonin, is formed from the alternative splicing of the calcitonin/CGRP gene located on chromosome 11. In humans, CGRP has two isoforms: α- and β-CGRP. The β-isoform differs from the α-isoform in the amino acids located at positions 3, 22 and

25. The chemical structure of CGRP involves a disulphide bridge between residues 2 and 7 and an amidated C-terminus. The cyclic cysteine2-cysteine7 motif has a basic role in receptor activation. In the human trigeminal ganglia (TRIG), CGRP-immunoreactive neurons account for up to 50% of all neurons. It has been demonstrated through an in situ hybridization technique that 40% of all nerve cell bodies contain CGRP mRNA and CGRP.

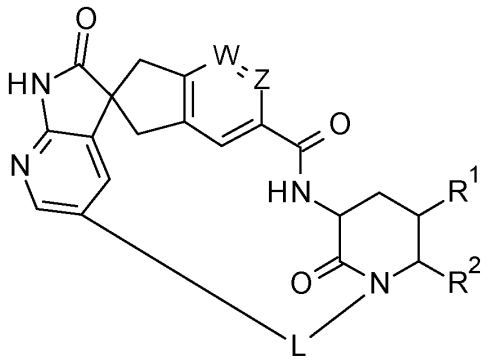
The functional CGRP-R consists of three proteins: i) Calcitonin Receptor Like Receptor (known as CRLR, CALCRL or CLR) is a seven-transmembrane spanning protein, which forms the ligand binding site with; ii) RAMP1, determining the specificity of the receptor; and iii) the CGRP-R component protein (RCP) couples the receptor to intracellular signal transduction pathways and to adenylyl cyclase.

Blockade of CGRP function as a treatment for migraine has been clinically validated for both antibody and small molecule agents. For example, antibody agents Erenumab (Aimovig), which targets the CGRP receptor, and Fremanezumab (Ajovy) and Galcanezumab (Emgality) which target the CGRP Protein are now approved medicines for treatment of migraine. Similarly small molecule antagonists of CGRP have also demonstrated efficacy against migraine. For example, both Ubrogepant and Rimegepant have demonstrated clinical efficacy and are now approved medicines for the treatment of migraine.

THE INVENTION

The present invention provides compounds having activity as calcitonin gene-related peptide (CGRP) receptor antagonists. Disclosed herein are novel compounds, and the first medical use of said compounds as CGRP receptor antagonists.

Accordingly, in one embodiment the invention provides a compound of Formula (1a):



(1a);

or a salt thereof, wherein;

W is CH or N;

Z is CH or N;

R^1 is an aryl or heteroaryl group optionally substituted with one or more halo groups or C_{1-3} alkyl groups which are themselves optionally substituted with one or more F atoms;

R^2 is H or C_{1-3} alkyl optionally substituted with one or more F atoms;

and L is a C_{4-15} linker group optionally substituted with one or more F atoms, wherein one, two or three, but not all, of the carbon atoms of the linker group may be optionally replaced by a heteroatom selected from O and N.

The compounds may be used as CGRP receptor antagonists. The compounds may be used in the manufacture of medicaments. The compounds or medicaments may be for use in treating, preventing, ameliorating, controlling or reducing the risk of diseases or disorders in which CGRP receptors are involved including cerebrovascular or vascular disorders such as migraine.

DETAILED DESCRIPTION OF THE INVENTION

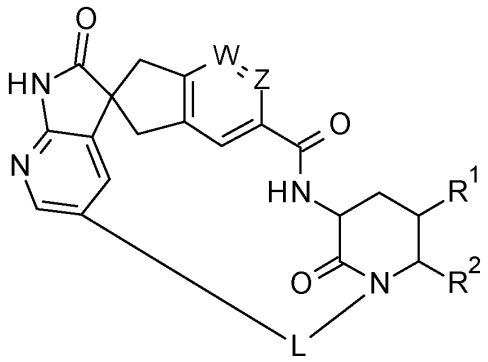
The invention relates to novel compounds. The invention also relates to the use of novel compounds as antagonists of the CGRP receptor. The invention further relates to the use of novel compounds in the manufacture of medicaments for use as CGRP receptor antagonists.

The invention further relates to compounds, compositions and medicaments for the treatment of cerebrovascular or vascular disorders including migraine (with or without

aura), chronic migraine, pure menstrual migraine, frequent episodic migraine, menstrually-related migraine, migraine with aura, familial hemiplegic migraine, sporadic hemiplegic migraine, basilar-type migraine, cyclical vomiting, abdominal migraine, benign paroxysmal vertigo of childhood, retinal migraine, status migrainosus, cluster headache, dialysis headache, chronic headaches of unknown origin, tension/stress induced headaches, allergy induced headaches, paroxysmal hemicrania, osteoarthritis and associated osteoporotic fracture pain, hot flashes associated with menopause or medically induced menopause due to surgery or drug treatment, hemicrania continua, cyclic vomiting syndrome, opiate withdrawal syndrome, morphine tolerance, neurodegenerative disease, epilepsy, allergic rhinitis, rosacea, dental pain, earache, middle ear inflammation, sunburn, joint pain associated with osteoarthritis and rheumatoid arthritis and gout, cancer pain, neuropathic pain (including but not limited to cancer pain in all its various forms including of unexplained origin), dystonic pain, inflammatory pain, post-operative incision pain, sciatica, fibromyalgia, trigeminal neuralga, diabetic neuropathy, complex regional pain syndrome, Behçet's disease, endometriosis pain, back pain, phantom limb pain, menstrual period pain, pain associated with labour, pain resulting from burns to skin, or visceral pain associated with inflammatory bowel disease (including Crohn's disease, ileitis and ulcerative colitis), gastro-esophageal reflux disease, dyspepsia, irritable bowel syndrome, renal colic, cystitis, gout, pancreatitis and prostatitis.

The compounds, compositions and medicaments of the invention may also be beneficial in the treatment of inflammatory and immune associated disorders including chronic fatigue syndrome, skin diseases, neurogenic cutaneous redness, skin rosaceousness, erythema, bronchial hyperreactivity, asthma, mast cell activation syndrome, mastocytosis, mast cell degranulation disorder, vascular disorders, shock, sepsis, non-insulin dependent diabetes mellitus, and infectious diseases including those of a respiratory and gastrointestinal origin.

In one embodiment the invention provides a compound of Formula (1a):



(1a);

or a salt thereof, wherein;

W is CH or N;

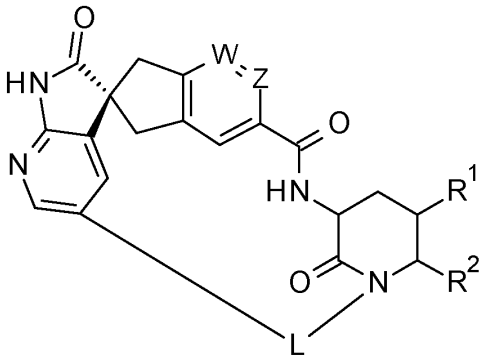
Z is CH or N;

R^1 is an aryl or heteroaryl group optionally substituted with one or more halo groups or C_{1-3} alkyl groups which are themselves optionally substituted with one or more F atoms;

R^2 is H or C_{1-3} alkyl optionally substituted with one or more F atoms;

and L is a C_{4-15} linker group optionally substituted with one or more F atoms, wherein one, two or three, but not all, of the carbon atoms of the linker group may be optionally replaced by a heteroatom selected from O and N.

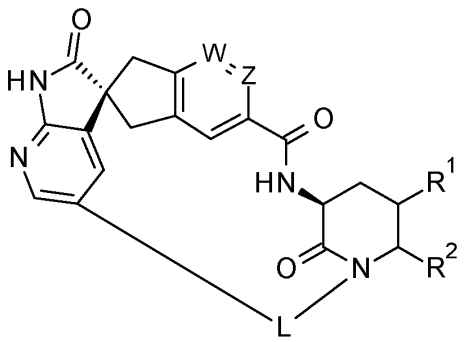
Particular compounds include compounds of Formula (2a):



(2a);

or a salt thereof wherein W, Z, L, R^1 and R^2 are as defined above.

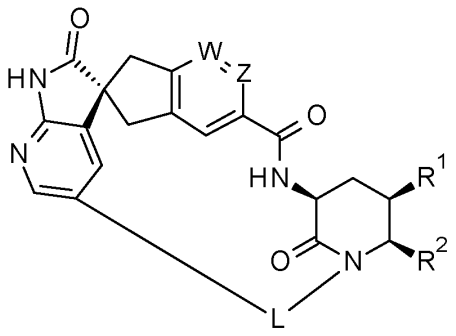
Particular compounds include compounds of Formula (3a):



(3a);

or salts thereof, wherein W, Z, L, R^1 and R^2 are as defined above.

Particular compounds include compounds of Formula (4a):

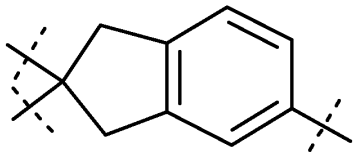
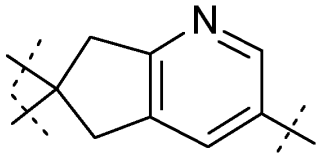
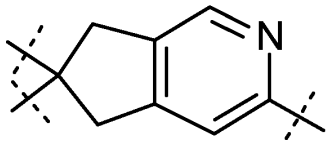
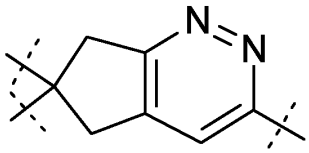


(4a);

or salts thereof, wherein W, Z, L, R^1 and R^2 are as defined above.

In the compounds herein, the ring system formed by W, Z and the atoms to which they are attached can be selected from the group consisting of an indan ring system, a pyrindan, 4-azaindan, 2,3-cyclopentenopyridine or 6,7-Dihydro-5H-cyclopenta[b]pyridine ring system, a 2-pyrindan, 5-azaindan or 6,7-Dihydro-5H-cyclopenta[c]pyridine ring system and a 4,5-diazaindan ring system.

The ring system formed by W, Z and the atoms to which they are attached can be selected from the group consisting of:

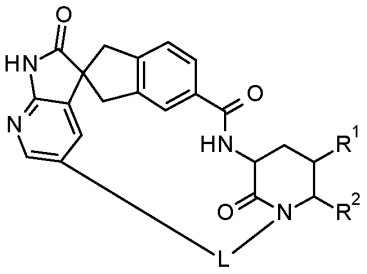
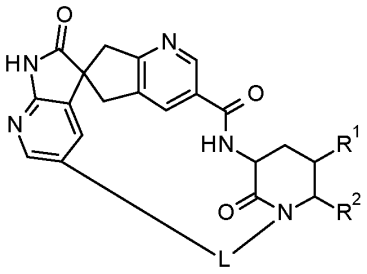
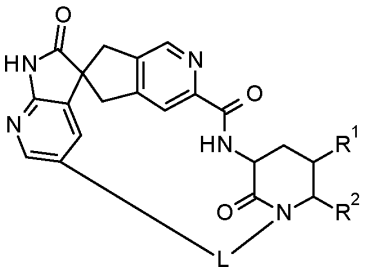
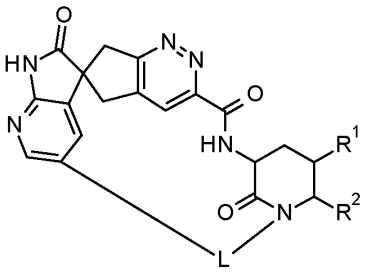

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In the compounds herein, W can be N. W can be CH.

In the compounds herein, Z can be N. Z can be CH.

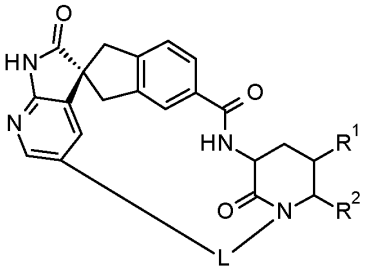
In the compounds herein, W can be N and Z can be CH. W can be CH and Z can be N. W and Z can both be CH. W and Z can both be N.

Particular compounds include compounds of Formula (1b), (1c), (1d) and (1e):

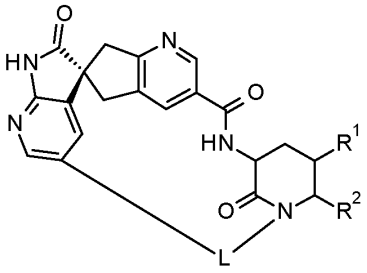

(1b);

(1c);

(1d);

(1e);

or salts thereof, wherein L, R^1 and R^2 are as defined above.

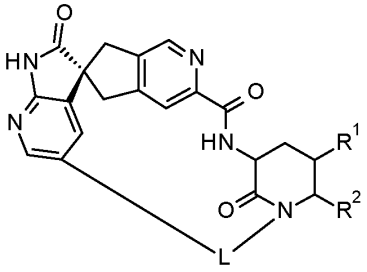
Particular compounds include compounds of Formula (2b), (2c), (2d) and (2e):



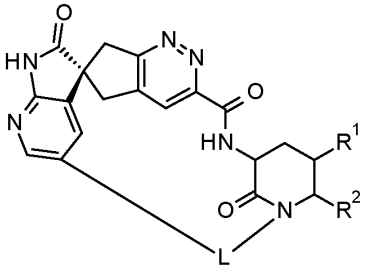
(2b);



(2c);



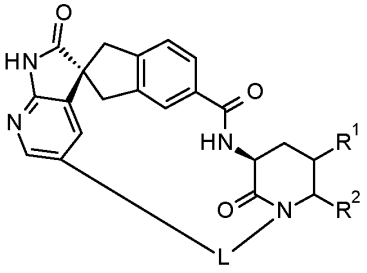
(2d);



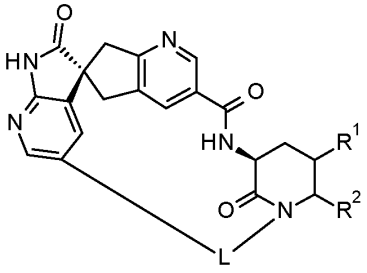
(2e);

or salts thereof, wherein L, R^1 and R^2 are as defined above.

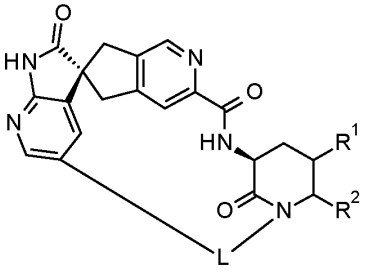
Particular compounds include compounds of Formula (3b), (3c), (3d) and (3e):



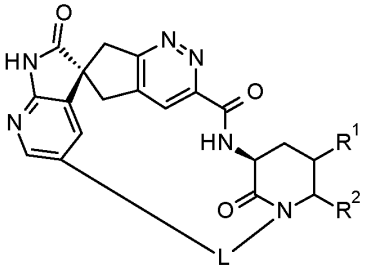
(3b);



(3c);



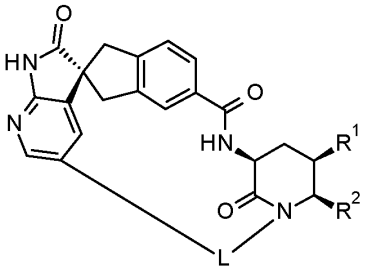
(3d);



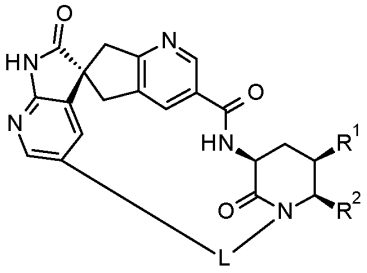
(3e);

or salts thereof, wherein L, R^1 and R^2 are as defined above.

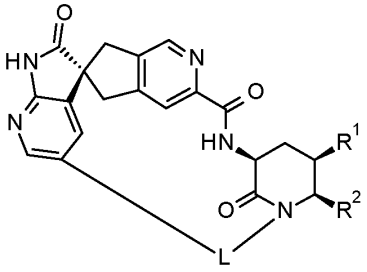
Particular compounds include compounds of Formula (4b), (4c), (4d) and (4e):



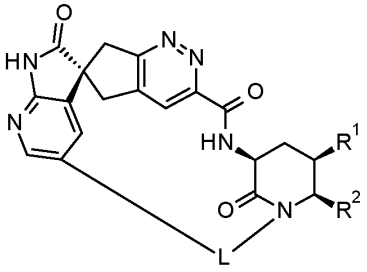
(4b);



(4c);



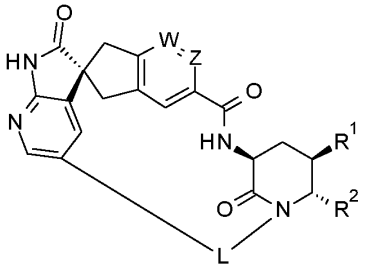
(4d);



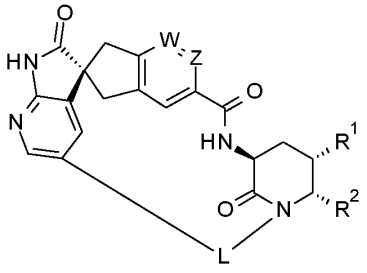
(4e);

or salts thereof, wherein L, R^1 and R^2 are as defined above.

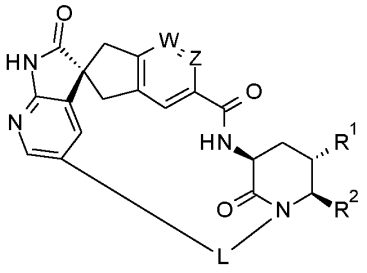
Particular compounds may also include compounds of Formula (5a) to (5g):



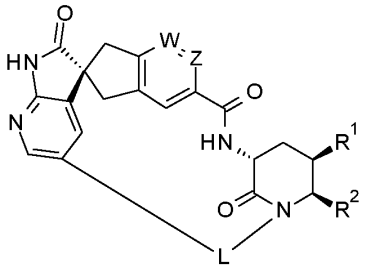
(5a);



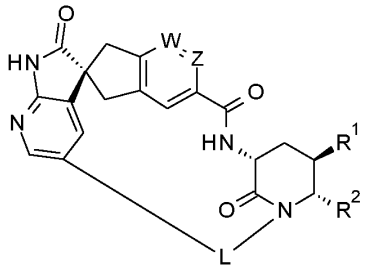
(5b);



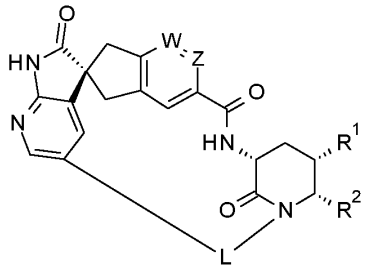
(5c);



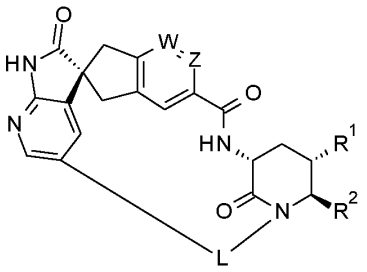
(5d);



(5e);



(5f);



(5g);

or salts thereof, wherein L, W, Z, R^1 and R^2 are as defined above.

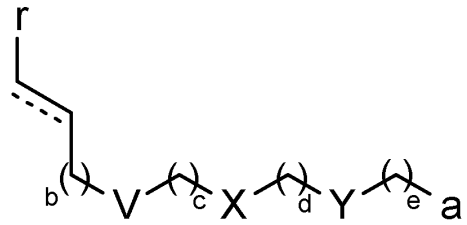
In the compounds herein, R^1 can be an aryl group optionally substituted with one or more halo groups or C_{1-3} alkyl groups which are themselves optionally substituted with one or more F atoms. R^1 can be a heteroaryl group optionally substituted with one or more halo groups or C_{1-3} alkyl groups which are themselves optionally substituted with one or more F atoms. R^1 can be a phenyl ring optionally substituted with one or more F atoms or C_{1-3} alkyl groups which are themselves optionally substituted with one or more F atoms. R^1 can be a phenyl ring optionally substituted with 1-5 F atoms. R^1 can be a phenyl ring. R^1 can be a phenyl ring substituted with 1-5 F atoms. R^1 can be a phenyl ring substituted with 1-3 F atoms.

In the compounds herein, R^2 can be H. R^2 can be alkyl optionally substituted with one or more F atoms. R^2 can be C_{1-3} alkyl. R^2 can be C_{1-3} alkyl optionally substituted with one or more F atoms. R^2 can be methyl. R^2 can be methyl optionally substituted with one or more F atoms.

In the compounds herein, L can be a C_{4-15} linker group optionally substituted with one or more F atoms. L can be a C_{4-15} linker group optionally substituted with 1-3 F atoms. L can be a C_{4-15} linker group substituted with 1-3 F atoms. L can be a C_{4-15} linker group. L can be a C_{4-15} linker group wherein one, two or three, but not all, of

the carbon atoms of the linker group is replaced by a heteroatom selected from O and N. L can be a C_{6-12} linker group, wherein one, two or three, but not all, of the carbon atoms of the linker group may be optionally replaced by a heteroatom selected from O and N. L can be a C_{4-15} linker group, wherein one, two or three, but not all, of the carbon atoms of the linker group may be optionally replaced by O. L can be a C_{6-12} linker group, wherein one, two or three, but not all, of the carbon atoms of the linker group may be optionally replaced by O. L can be partially unsaturated. L can be monounsaturated. L can be polyunsaturated. L can contain a double bond. L can be saturated. L can be substituted with one or more F atoms.

L can be a linker group of the formula:

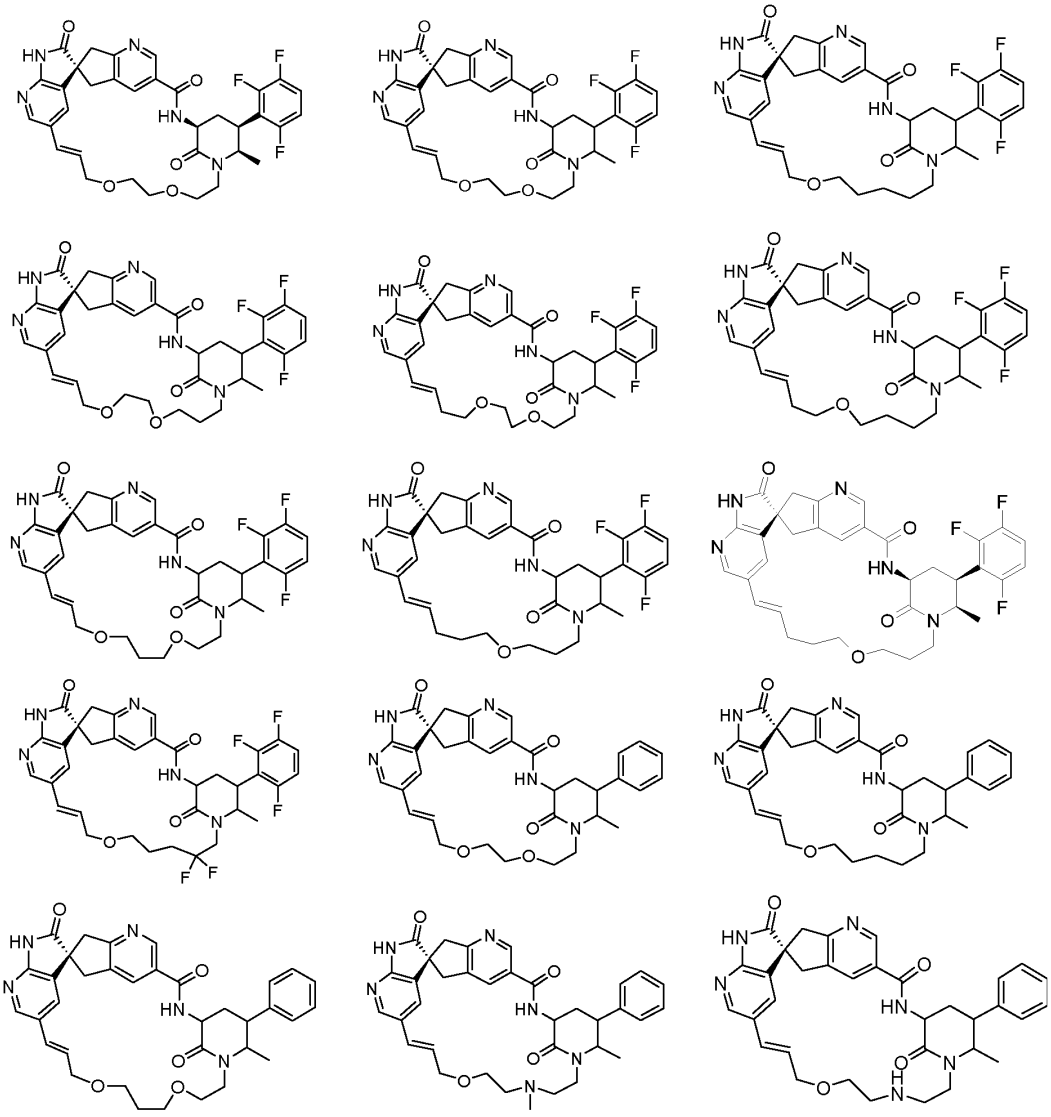


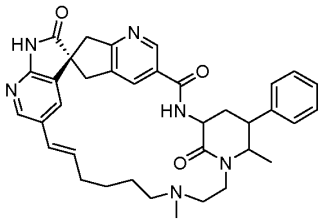
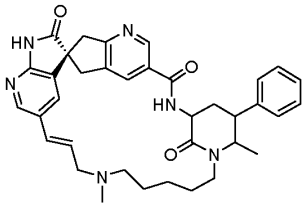
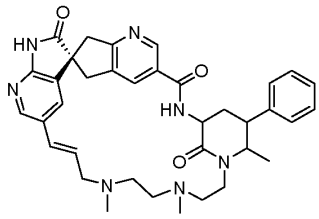
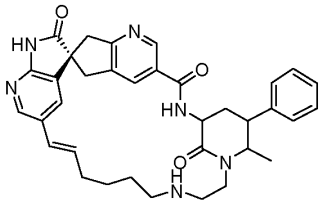
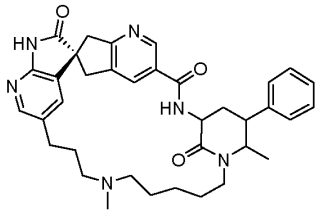
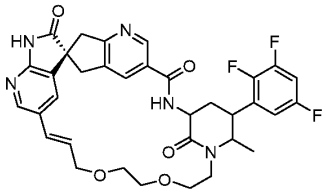
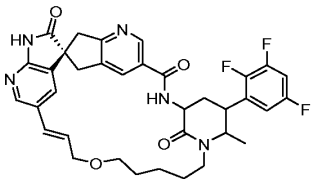
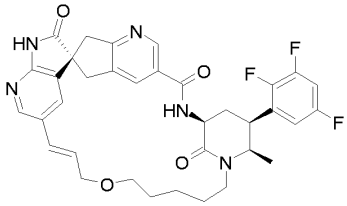
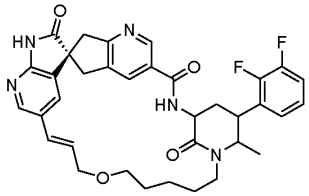
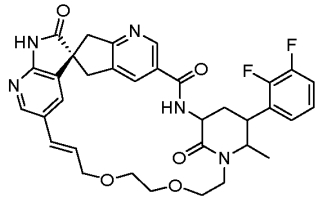
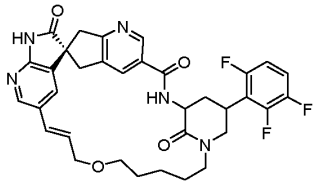
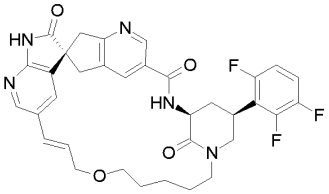
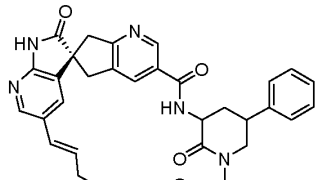
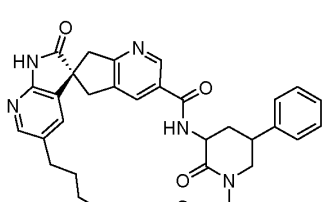
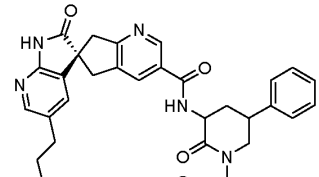
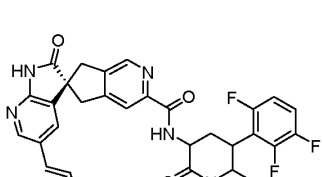
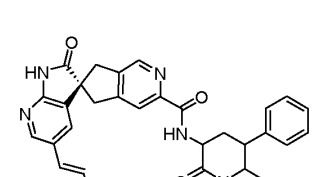
wherein "r" indicates the point of attachment to the pyridine ring and "a" indicates the point of attachment to V; X and Y can be independently selected from a bond, O, CH_2, NH and NMe; b, c, d and e are independently 1, 2 or 3 and the dotted line indicates that a single or double bond may be present.

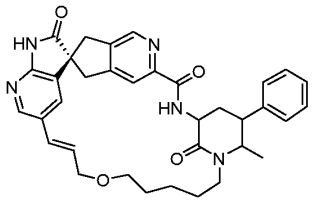
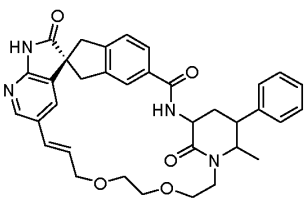
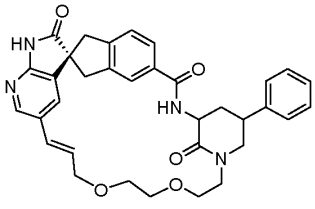
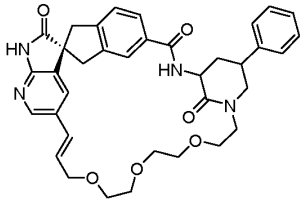
L can selected from the group consisting of:
-CHCHCH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$-;
-CHCHCH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$-;
-CH$_2$CH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$-;
-CH$_2$CH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$-;
-CHCHCH$_2$OCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$-;
-CHCHCH$_2$OCH$_2$CH$_2$N(CH$_3$)CH$_2$CH$_2$-;
-CHCHCH$_2$OCH$_2$CH$_2$NHCH$_2$CH$_2$-;
-CHCHCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_3$)CH$_2$CH$_2$-;
-CHCHCH$_2$N(CH$_3$)CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$-;
-CH$_2$CH$_2$CH$_2$N(CH$_3$)CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$-;
-CHCHCH$_2$CH$_2$CH$_2$CH$_2$NHCH$_2$CH$_2$-;

-CHCHCH$_2$N(CH$_3$)CH$_2$CH$_2$N(CH$_3$)CH$_2$CH$_2$-;
-CHCHCH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$CH$_2$-;
-CHCHCH$_2$OCH$_2$CH$_2$CH$_2$OCH$_2$CH$_2$-;
-CHCHCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$-;
-CHCHCH$_2$CH$_2$OCH$_2$CH$_2$CH$_2$CH$_2$-;
-CHCHCH$_2$CH$_2$CH$_2$OCH$_2$CH$_2$CH$_2$-
and
-CHCHCH$_2$OCH$_2$CH$_2$CH$_2$CF$_2$CH$_2$-.

The compound can be selected from the group consisting of:



and salts thereof.

The compound can be selected from the group consisting of:
(1S,22E)-13-methyl-12-(2,3,6-trifluorophenyl)-17,20-dioxa-5,9,14,26,28-pentazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;
(1S,10S,12S,13R,22E)-13-methyl-12-(2,3,6-trifluorophenyl)-17,20-dioxa-5,9,14,26,28-pentazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;
(1S,22E)-13-methyl-12-(2,3,6-trifluorophenyl)-20-oxa-5,9,14,26,28-pentazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;
(1S,23E)-13-methyl-12-(2,3,6-trifluorophenyl)-18,21-dioxa-5,9,14,27,29-pentazahexacyclo[23.5.2.11,4.13,7.110,14.028,31]pentatriaconta-3,5,7(34),23,25(32),26,28(31)-heptaene-8,30,33-trione;
(1S,23E)-13-methyl-12-(2,3,6-trifluorophenyl)-17,20-dioxa-5,9,14,27,29-pentazahexacyclo[23.5.2.11,4.13,7.110,14.028,31]pentatriaconta-3,5,7(34),23,25(32),26,28(31)-heptaene-8,30,33-trione;
(1S,22E)-13-methyl-12-(2,3,6-trifluorophenyl)-19-oxa-5,9,14,26,28-pentazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;
(1S,23E)-13-methyl-12-(2,3,6-trifluorophenyl)-17,21-dioxa-5,9,14,27,29-pentazahexacyclo[23.5.2.11,4.13,7.110,14.028,31]pentatriaconta-3,5,7(34),23,25(32),26,28(31)-heptaene-8,30,33-trione;

(1S,22E)-13-methyl-12-(2,3,6-trifluorophenyl)-18-oxa-5,9,14,26,28-pentazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;
(1S,22E)-16,16-difluoro-13-methyl-12-(2,3,6-trifluorophenyl)-20-oxa-5,9,14,26,28-pentazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;
(1S,22E)-13-methyl-12-phenyl-17,20-dioxa-5,9,14,26,28-pentazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;
(1S,22E)-13-methyl-12-phenyl-17,20-dioxa-9,14,26,28-tetrazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;
(1S,23E)-13-methyl-12-phenyl-17,21-dioxa-5,9,14,27,29-pentazahexacyclo[23.5.2.11,4.13,7.110,14.028,31]pentatriaconta-3,5,7(34),23,25(32),26,28(31)-heptaene-8,30,33-trione;
(1S,22E)-13,17-dimethyl-12-phenyl-20-oxa-5,9,14,17,26,28-hexazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;
(1S,22E)-13-methyl-12-phenyl-20-oxa-5,9,14,17,26,28-hexazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;
(1S,22E)-13,17-dimethyl-12-phenyl-5,9,14,17,26,28-hexazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;
(1S,22E)-13,20-dimethyl-12-phenyl-5,9,14,20,26,28-hexazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;
(1S,22E)-13,17,20-trimethyl-12-phenyl-5,9,14,17,20,26,28-heptazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;
(1S,22E)-13-methyl-12-phenyl-5,9,14,17,26,28-hexazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;

(1S)-13,20-dimethyl-12-phenyl-5,9,14,20,26,28-hexazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),24(31),25,27(30)-hexaene-8,29,32-trione;
(1S,22E)-13-methyl-12-(2,3,5-trifluorophenyl)-17,20-dioxa-5,9,14,26,28-pentazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;
(1S,22E)-13-methyl-12-(2,3,5-trifluorophenyl)-20-oxa-5,9,14,26,28-pentazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;
(1S,22E)-13-methyl-12-(2,3-difluorophenyl)-20-oxa-5,9,14,26,28-pentazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;
(1S,22E)-12-(2,3-difluorophenyl)-13-methyl-17,20-dioxa-5,9,14,26,28-pentazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;
(1S,22E)-12-(2,3,6-trifluorophenyl)-20-oxa-5,9,14,26,28-pentazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;
(1S,22E)-12-phenyl-17,20-dioxa-5,9,14,26,28-pentazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;
(1S,25E)-12-phenyl-17,20,23-trioxa-5,9,14,29,31-pentazahexacyclo[25.5.2.11,4.13,7.110,14.030,33]heptatriaconta-3,5,7(36),25,27(34),28,30(33)-heptaene-8,32,35-trione;
(1S)-12-phenyl-17,20-dioxa-5,9,14,26,28-pentazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),24(31),25,27(30)-hexaene-8,29,32-trione;
(1S)-12-phenyl-17,20,23-trioxa-5,9,14,29,31-pentazahexacyclo[25.5.2.11,4.13,7.110,14.030,33]heptatriaconta-3,5,7(36),27(34),28,30(33)-hexaene-8,32,35-trione;
(1S,22E)-13-methyl-12-(2,3,6-trifluorophenyl)-17,20-dioxa-6,9,14,26,28-pentazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;

(1S,22E)-13-methyl-12-phenyl-17,20-dioxa-6,9,14,26,28-pentazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;
(1S,22E)-13-methyl-12-phenyl-20-oxa-6,9,14,26,28-pentazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;
(1R,22E)-13-methyl-12-phenyl-17,20-dioxa-9,14,26,28-tetrazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;
(1R,22E)-12-phenyl-17,20-dioxa-9,14,26,28-tetrazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;
(1R,22E)-12-phenyl-17,20-dioxa-9,14,26,28-tetrazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione;
(1R,25E)-12-phenyl-17,20,23-trioxa-9,14,29,31-tetrazahexacyclo[25.5.2.11,4.13,7.110,14.030,33]heptatriaconta-3,5,7(36),25,27(34),28,30(33)-heptaene-8,32,35-trione;
(1S,10S,12S,13R,22E)-13-methyl-12-(2,3,6-trifluorophenyl)-18-oxa-5,9,14,26,28-pentaazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3(33),4,6,22,24,26,30-heptaene-8,29,32-trione;
(1S,10S,12S,13R,22E)-13-methyl-12-(2,3,5-trifluorophenyl)-20-oxa-5,9,14,26,28-pentaazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3(33),4,6,22,24,26,30-heptaene-8,29,32-trione;
(1S,10S,12S,22E)-12-(2,3,6-trifluorophenyl)-20-oxa-5,9,14,26,28-pentaazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3(33),4,6,22,24,26,30-heptaene-8,29,32-trione;
and salts thereof.

Further embodiments of the invention include methods of treatment comprising administering an effective therapeutic amount of a compound of Formula (1a) as a CGRP receptor antagonist. The treatment using a compound of Formula (1a) may be in the treatment of cerebrovascular or vascular disorders including migraine (with or

without aura), chronic migraine, pure menstrual migraine, frequent episodic migraine, menstrually-related migraine, migraine with aura, familial hemiplegic migraine, sporadic hemiplegic migraine, basilar-type migraine, cyclical vomiting, abdominal migraine, benign paroxysmal vertigo of childhood, retinal migraine, status migrainosus, cluster headache, dialysis headache, chronic headaches of unknown origin, tension/stress induced headaches, allergy induced headaches, paroxysmal hemicrania, osteoarthritis and associated osteoporotic fracture pain, hot flashes associated with menopause or medically induced menopause due to surgery or drug treatment, hemicrania continua, cyclic vomiting syndrome, opiate withdrawal syndrome, morphine tolerance, neurodegenerative disease, epilepsy, allergic rhinitis, rosacea, dental pain, earache, middle ear inflammation, sunburn, joint pain associated with osteoarthritis and rheumatoid arthritis and gout, cancer pain, neuropathic pain (including but not limited to cancer pain in all its various forms including of unexplained origin), dystonic pain, inflammatory pain, post-operative incision pain, sciatica, fibromyalgia, trigeminal neuralga, diabetic neuropathy, complex regional pain syndrome, Behçet's disease, endometriosis pain, back pain, phantom limb pain, menstrual period pain, pain associated with labour, pain resulting from burns to skin, or visceral pain associated with inflammatory bowel disease (including Crohn's disease, ileitis and ulcerative colitis), gastro-esophageal reflux disease, dyspepsia, irritable bowel syndrome, renal colic, cystitis, gout, pancreatitis and prostatitis.

The compounds of Formula (1a) may also be used in the treatment of inflammatory and immune associated disorders including chronic fatigue syndrome, skin diseases, neurogenic cutaneous redness, skin rosaceousness, erythema, bronchial hyperreactivity, asthma, mast cell activation syndrome, mastocytosis, mast cell degranulation disorder, vascular disorders, shock, sepsis, non-insulin dependent diabetes mellitus, and infectious diseases including those of a respiratory and gastrointestinal origin.

The compounds of the invention may be used alone or in combination with any other therapy or standard of care for any of the above indications.

Certain novel compounds of the invention show particularly high activities as CGRP receptor antagonists.

Definitions

In this application, the following definitions apply, unless indicated otherwise.

The term "treatment", in relation to the uses of any of the compounds described herein, including those of Formula (1a) is used to describe any form of intervention where a compound is administered to a subject suffering from, or at risk of suffering from, or potentially at risk of suffering from the disease or disorder in question. Thus, the term "treatment" covers both preventative (prophylactic) treatment and treatment where measurable or detectable symptoms of the disease or disorder are being displayed.

The term "effective therapeutic amount" (for example in relation to methods of treatment of a disease or condition) refers to an amount of the compound which is effective to produce a desired therapeutic effect. For example, if the condition is pain, then the effective therapeutic amount is an amount sufficient to provide a desired level of pain relief. The desired level of pain relief may be, for example, complete removal of the pain or a reduction in the severity of the pain.

Terms such as "alkyl" as in "C_{1-3} alkyl", "heteroaryl", "aryl" and "halo" are all used in their conventional sense (e.g. as defined in the IUPAC Gold Book), unless indicated otherwise. "Optionally substituted" as applied to any group means that the said group may if desired be substituted with one or more substituents, which may be the same or different.

To the extent that any of the compounds described have chiral centres, the present invention extends to all optical isomers of such compounds, whether in the form of racemates or resolved enantiomers. The invention described herein relates to all crystal forms, solvates and hydrates of any of the disclosed compounds however so prepared. To the extent that any of the compounds disclosed herein have acid or basic centres such as carboxylates or amino groups, then all salt forms of said

compounds are included herein. In the case of pharmaceutical uses, the salt should be seen as being a pharmaceutically acceptable salt.

Salts or pharmaceutically acceptable salts that may be mentioned include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. in vacuo, by freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of a compound in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

Examples of pharmaceutically acceptable salts include acid addition salts derived from mineral acids and organic acids, and salts derived from metals such as sodium, magnesium, potassium and calcium.

Examples of acid addition salts include acid addition salts formed with acetic, 2,2-dichloroacetic, adipic, alginic, aryl sulfonic acids (e.g. benzenesulfonic, naphthalene-2-sulfonic, naphthalene-1,5-disulfonic and p-toluenesulfonic), ascorbic (e.g. L-ascorbic), L-aspartic, benzoic, 4-acetamidobenzoic, butanoic, (+) camphoric, camphor-sulfonic, (+)-(1S)-camphor-10-sulfonic, capric, caproic, caprylic, cinnamic, citric, cyclamic, dodecylsulfuric, ethane-1,2-disulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, formic, fumaric, galactaric, gentisic, glucoheptonic, gluconic (e.g. D-gluconic), glucuronic (e.g. D-glucuronic), glutamic (e.g. L-glutamic), α-oxoglutaric, glycolic, hippuric, hydrobromic, hydrochloric, hydriodic, isethionic, lactic (e.g. (+)-L-lactic and (±)-DL-lactic), lactobionic, maleic, malic (e.g. (-)-L-malic), malonic, (±)-DL-mandelic, metaphosphoric, methanesulfonic, 1-hydroxy-2-naphthoic, nicotinic, nitric, oleic, orotic, oxalic, palmitic, pamoic, phosphoric, propionic, L-pyroglutamic, salicylic, 4-amino-salicylic, sebacic, stearic, succinic, sulfuric, tannic, tartaric (e.g.(+)-L-tartaric), thiocyanic, undecylenic and valeric acids.

Also encompassed are any solvates of the compounds and their salts. Preferred solvates are solvates formed by the incorporation into the solid state structure (e.g. crystal structure) of the compounds of the invention of molecules of a non-toxic

pharmaceutically acceptable solvent (referred to below as the solvating solvent). Examples of such solvents include water, alcohols (such as ethanol, isopropanol and butanol) and dimethylsulfoxide. Solvates can be prepared by recrystallising the compounds of the invention with a solvent or mixture of solvents containing the solvating solvent. Whether or not a solvate has been formed in any given instance can be determined by subjecting crystals of the compound to analysis using well known and standard techniques such as thermogravimetric analysis (TGA), differential scanning calorimetry (DSC) and X-ray crystallography.

The solvates can be stoichiometric or non-stoichiometric solvates. Particular solvates may be hydrates, and examples of hydrates include hemihydrates, monohydrates and dihydrates. For a more detailed discussion of solvates and the methods used to make and characterise them, see Bryn *et al*, Solid-State Chemistry of Drugs, Second Edition, published by SSCI, Inc of West Lafayette, IN, USA, 1999, ISBN 0-967-06710-3.

The term “pharmaceutical composition” in the context of this invention means a composition comprising an active agent and comprising additionally one or more pharmaceutically acceptable carriers. The composition may further contain ingredients selected from, for example, diluents, adjuvants, excipients, vehicles, preserving agents, fillers, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavouring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and dispersing agents, depending on the nature of the mode of administration and dosage forms. The compositions may take the form, for example, of tablets, dragees, powders, elixirs, syrups, liquid preparations including suspensions, sprays, inhalants, tablets, lozenges, emulsions, solutions, cachets, granules, capsules and suppositories, as well as liquid preparations for injections, including liposome preparations.

The compounds of the invention may contain one or more isotopic substitutions, and a reference to a particular element includes within its scope all isotopes of the element. For example, a reference to hydrogen includes within its scope ^{1}H, ^{2}H (D), and ^{3}H (T). Similarly, references to carbon and oxygen include within their scope respectively ^{12}C, ^{13}C and ^{14}C and ^{16}O and ^{18}O. In an analogous manner, a reference

to a particular functional group also includes within its scope isotopic variations, unless the context indicates otherwise. For example, a reference to an alkyl group such as an ethyl group or an alkoxy group such as a methoxy group also covers variations in which one or more of the hydrogen atoms in the group is in the form of a deuterium or tritium isotope, e.g. as in an ethyl group in which all five hydrogen atoms are in the deuterium isotopic form (a perdeuteroethyl group) or a methoxy group in which all three hydrogen atoms are in the deuterium isotopic form (a trideuteromethoxy group). The isotopes may be radioactive or non-radioactive.

Therapeutic dosages may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with the smaller dosages which are less than the optimum dose of the compound. Thereafter the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The magnitude of an effective dose of a compound will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound and its route of administration. The selection of appropriate dosages is within the ability of one of ordinary skill in this art, without undue burden. In general, the daily dose range may be from about 10 µg to about 30 mg per kg body weight of a human and non-human animal, preferably from about 50 µg to about 30 mg per kg of body weight of a human and non-human animal, for example from about 50 µg to about 10 mg per kg of body weight of a human and non-human animal, for example from about 100 µg to about 30 mg per kg of body weight of a human and non-human animal, for example from about 100 µg to about 10 mg per kg of body weight of a human and non-human animal and most preferably from about 100 µg to about 1 mg per kg of body weight of a human and non-human animal.

Pharmaceutical formulations

While it is possible for the active compound to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g. formulation).

Accordingly, in another embodiment of the invention, there is provided a pharmaceutical composition comprising at least one compound of Formula (1a) as defined above together with at least one pharmaceutically acceptable excipient.

The composition may be a tablet composition.

The composition may be a capsule composition.

The pharmaceutically acceptable excipient(s) can be selected from, for example, carriers (e.g. a solid, liquid or semi-solid carrier), adjuvants, diluents (e.g. solid diluents such as fillers or bulking agents; and liquid diluents such as solvents and co-solvents), granulating agents, binders, flow aids, coating agents, release-controlling agents (e.g. release retarding or delaying polymers or waxes), binding agents, disintegrants, buffering agents, lubricants, preservatives, anti-fungal and antibacterial agents, antioxidants, buffering agents, tonicity-adjusting agents, thickening agents, flavouring agents, sweeteners, pigments, plasticizers, taste masking agents, stabilisers or any other excipients conventionally used in pharmaceutical compositions.

The term "pharmaceutically acceptable" as used herein means compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of a subject (e.g. a human subject) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each excipient must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

Pharmaceutical compositions containing compounds of the Formula (1a) can be formulated in accordance with known techniques, see for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, USA.

The pharmaceutical compositions can be in any form suitable for oral, parenteral, topical, intranasal, intrabronchial, sublingual, ophthalmic, otic, rectal, intra-vaginal, or transdermal administration.

Pharmaceutical dosage forms suitable for oral administration include tablets (coated or uncoated), capsules (hard or soft shell), caplets, pills, lozenges, syrups, solutions, powders, granules, elixirs and suspensions, sublingual tablets, wafers or patches such as buccal patches.

Tablet compositions can contain a unit dosage of active compound together with an inert diluent or carrier such as a sugar or sugar alcohol, eg; lactose, sucrose, sorbitol or mannitol; and/or a non-sugar derived diluent such as sodium carbonate, calcium phosphate, calcium carbonate, or a cellulose or derivative thereof such as microcrystalline cellulose (MCC), methyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, and starches such as corn starch. Tablets may also contain such standard ingredients as binding and granulating agents such as polyvinylpyrrolidone, disintegrants (e.g. swellable crosslinked polymers such as crosslinked carboxymethylcellulose), lubricating agents (e.g. stearates), preservatives (e.g. parabens), antioxidants (e.g. BHT), buffering agents (for example phosphate or citrate buffers), and effervescent agents such as citrate/bicarbonate mixtures. Such excipients are well known and do not need to be discussed in detail here.

Tablets may be designed to release the drug either upon contact with stomach fluids (immediate release tablets) or to release in a controlled manner (controlled release tablets) over a prolonged period of time or with a specific region of the GI tract.

The pharmaceutical compositions typically comprise from approximately 1% (w/w) to approximately 95%, preferably% (w/w) active ingredient and from 99% (w/w) to 5% (w/w) of a pharmaceutically acceptable excipient (for example as defined above) or combination of such excipients. Preferably, the compositions comprise from approximately 20% (w/w) to approximately 90% (w/w) active ingredient and from 80% (w/w) to 10% of a pharmaceutically excipient or combination of excipients. The pharmaceutical compositions comprise from approximately 1% to approximately 95%, preferably from approximately 20% to approximately 90%, active ingredient.

Pharmaceutical compositions according to the invention may be, for example, in unit dose form, such as in the form of ampoules, vials, suppositories, pre-filled syringes, dragées, powders, tablets or capsules.

Tablets and capsules may contain, for example, 0-20% disintegrants, 0-5% lubricants, 0-5% flow aids and/or 0-99% (w/w) fillers/ or bulking agents (depending on drug dose). They may also contain 0-10% (w/w) polymer binders, 0-5% (w/w) antioxidants, 0-5% (w/w) pigments. Slow release tablets would in addition typically contain 0-99% (w/w) release-controlling (e.g. delaying) polymers (depending on dose). The film coats of the tablet or capsule typically contain 0-10% (w/w) polymers, 0-3% (w/w) pigments, and/or 0-2% (w/w) plasticizers.

Parenteral formulations typically contain 0-20% (w/w) buffers, 0-50% (w/w) cosolvents, and/or 0-99% (w/w) Water for Injection (WFI) (depending on dose and if freeze dried). Formulations for intramuscular depots may also contain 0-99% (w/w) oils.

The pharmaceutical formulations may be presented to a patient in “patient packs” containing an entire course of treatment in a single package, usually a blister pack.

The compounds of the Formula (1a) will generally be presented in unit dosage form and, as such, will typically contain sufficient compound to provide a desired level of biological activity. For example, a formulation may contain from 1 nanogram to 2 grams of active ingredient, e.g. from 1 nanogram to 2 milligrams of active ingredient. Within these ranges, particular sub-ranges of compound are 0.1 milligrams to 2 grams of active ingredient (more usually from 10 milligrams to 1 gram, e.g. 50 milligrams to 500 milligrams), or 1 microgram to 20 milligrams (for example 1 microgram to 10 milligrams, e.g. 0.1 milligrams to 2 milligrams of active ingredient).

For oral compositions, a unit dosage form may contain from 1 milligram to 2 grams, more typically 10 milligrams to 1 gram, for example 50 milligrams to 1 gram, e.g. 100 milligrams to 1 gram, of active compound.

The active compound will be administered to a patient in need thereof (for example a human or animal patient) in an amount sufficient to achieve the desired therapeutic effect (effective amount). The precise amounts of compound administered may be determined by a supervising physician in accordance with standard procedures.

Methods for the Preparation of Compounds of the Formula (1a)

Compounds of Formula (1a) can be prepared in accordance with synthetic methods well known to the skilled person and as described herein. The invention provides a process for the preparation of a compound as defined in Formula (1a) above.

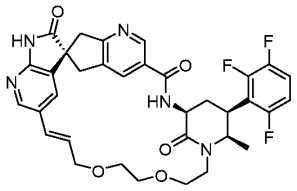
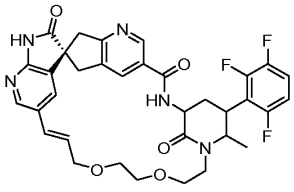
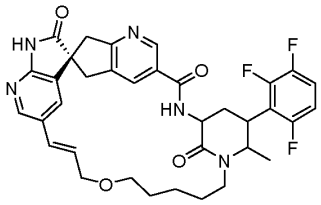
EXAMPLES

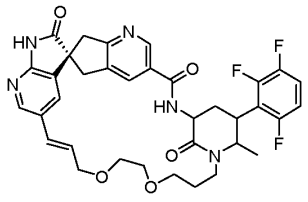
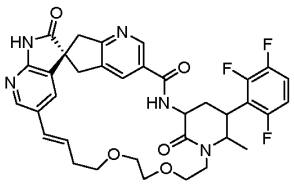
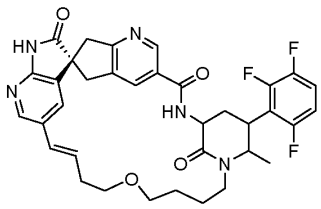
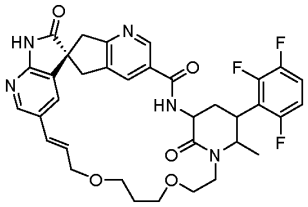
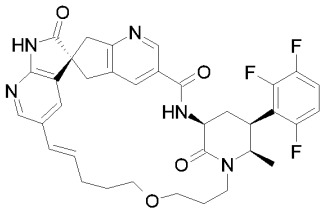
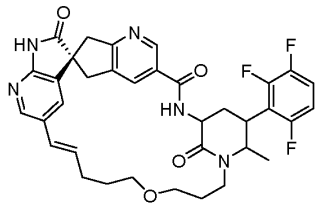
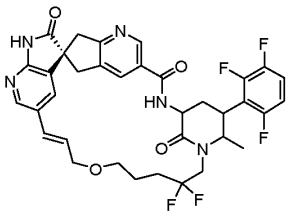
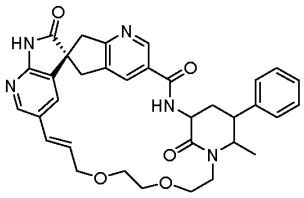
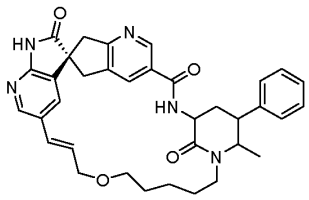
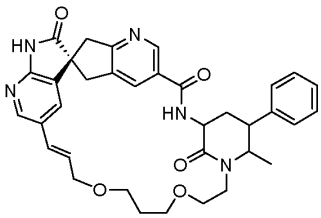
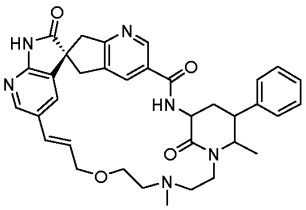
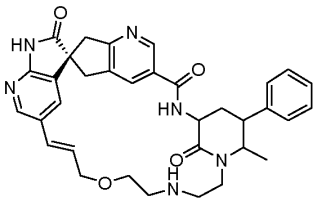
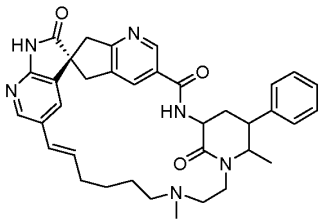
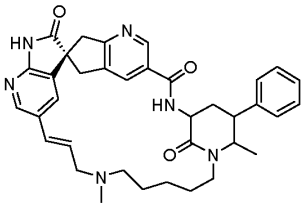
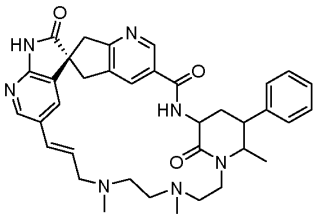
The invention will now be illustrated, but not limited, by reference to the following examples.

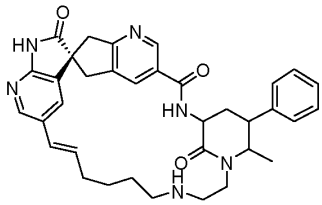
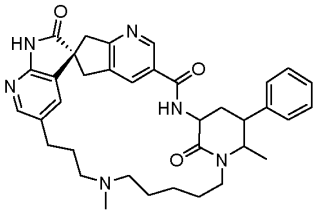
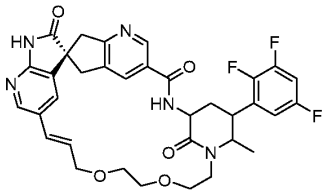
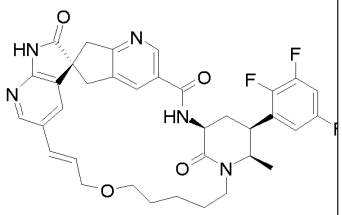
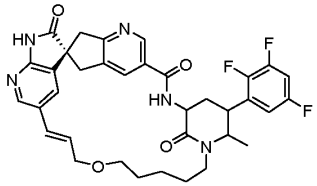
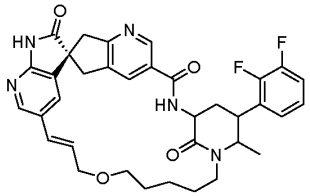
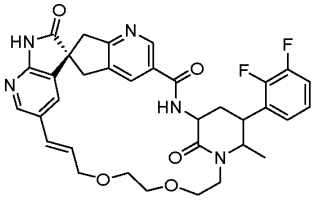
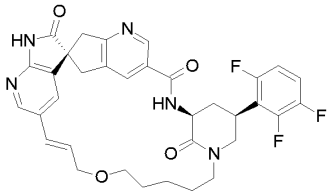
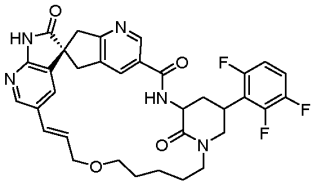
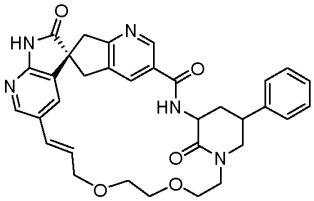
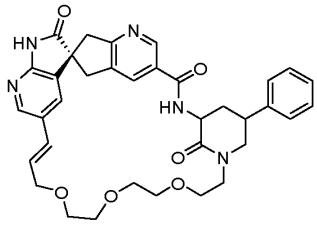
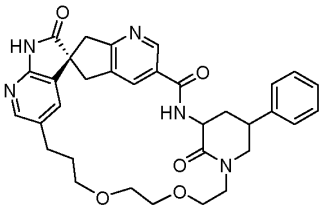
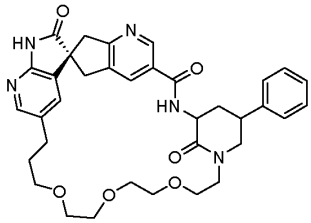
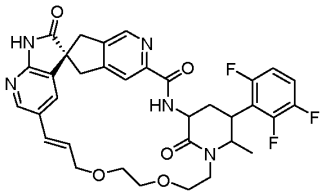
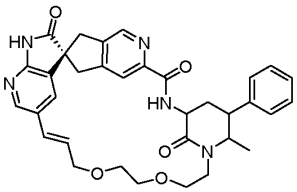
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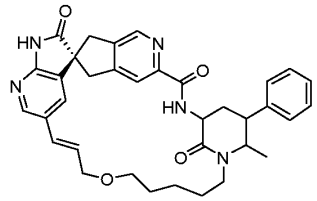
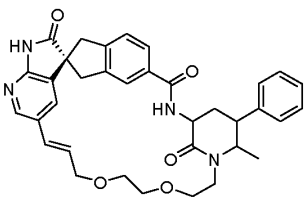
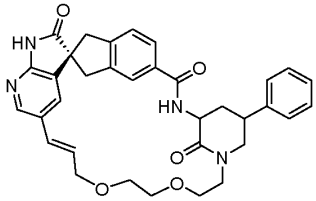
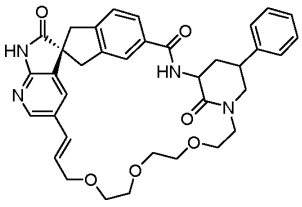
The compounds of Examples 1-1 to 10-2 shown in **Table 1** below have been prepared. The compounds were either obtained as mixtures of stereoisomers or as individual isomers. Stereochemistry of Example 1-1, 1-7, 3-2 and 5-1 Isomer 1 were confirmed by X-ray crystallography. Full stereochemical configuration of remaining examples and isomers have not been confirmed.

Table 1 – Example compounds

 Example 1-1 Isomer 1	 Example 1-1 Isomer 2/3	 Example 1-2

 Example 1-3	 Example 1-4	 Example 1-5
 Example 1-6	 Example 1-7 Isomer 1	 Example 1-7 Isomer 2/3
 Example 1-8	 Example 2-1	 Example 2-2
 Example 2-3	 Example 2-4	 Example 2-5
 Example 2-6	 Example 2-7	 Example 2-8

 Example 2-9	 Example 2-10	 Example 3-1
 Example 3-2 Isomer 1	 Example 3-2 Isomer 2/3	 Example 4-1
 Example 4-2	 Example 5-1 Isomer 1	 Example 5-1 Isomer 2/3
 Example 6-1	 Example 6-2	 Example 6-3
 Example 6-4	 Example 7-1	 Example 8-1

 Example 8-2	 Example 9-1	 Example 10-1
 Example 10-2		

General information:

NMR

NMR spectra were recorded on Bruker DPX 300 MHz equipped with a 5 mm BBI probe, Bruker AV400 MHz equipped with a 5 mm PABBO probe, Bruker DRX 500 MHz equipped with a 5 mm PABBI probe or Bruker Avance III 600 spectrometer equipped with a 5 mm RT BBI probe. The samples were recorded at 25 °C using DMSO-*d*, $CDCl_3$ or MeOD-d4 as a solvent and TMS as the internal standard.

HPLC

LC/MS System: Waters Acquity UPLC coupled with SQD mass spectrometer system

Software used: FractionLynx and MassLynx v4.1

Method 1. Ammonium Bicarbonate Generic Analytical UPLC Open Access LC/MS 12 Minute Method

LC Conditions

Column: Acquity UPLC BEH C18 (50mm x 2.1mm i.d., 1.7µm packing diameter)

Column temperature: 40 °C

Solvents: A = 10 mM aqueous solution of NH_4HCO_3 (adjusted to pH 10 with ammonia)

B = Acetonitrile

Injection Volume: 2 µl

The gradient table:

Time (min)	Flow Rate (mL/min)	%A	%B
0.0	0.9	97	3
10.0	0.9	0	100
11.5	0.9	0	100
12.00	0.05	97	3

Stop time: 12 min

UV Conditions

PDA Range: 210nm - 450nm

The UV detection was a summed signal from wavelength of 210 nm to 450 nm

Acquisition Rate: 40Hz

MS Conditions

Ionization Mode: Alternate – scan Positive and Negative Electrospray (ES^+/ES^-)

Scan Range: 100 to 1500 AMU

Scan Time: 0.15 seconds

Inter scan delays:

MS inter-scan: 0.02 seconds

Polarity/Mode switch inter-scan: 0.02 seconds

Method 2. Generic Basic Analytical UPLC Open Access

LC/MS 8 minute Method – MS range 100-1500, ES+/ES- mode

LC Conditions

Column: Acquity UPLC BEH C18 (2.1 mm x 100 mm, 1.7 µm)

Column temperature: 40 °C

Solvents: A – Water + 0.05% of Ammonia

B – Acetonitrile + 0.05% of Ammonia

Injection volume: 2 µl

Equilibration time: 1 min

Gradient table:

Time (min)	Flow Rate (mL/min)	%A	%B
0.00	0.6	97	3
0.50	0.6	97	3
7.00	0.6	3	97
7.50	0.6	3	97
7.60	0.6	97	3
8.00	0.6	97	3

Stop time: 8 min

UV Conditions

PDA Range: 210 nm – 400 nm

Resolution: 1.2 nm

Acquisition Rate: 40 Hz

MS Conditions

Ionization Mode: Electrospray Positive and Negative (ES^+/ES^-)

Scan Range: 100 to 1500 Da

Scan Time: 0.15 seconds

Method 3. Generic Basic Analytical UPLC Open Access

LC/MS 4 minute Method – MS range 100-1500, ES+/ES- mode

LC Conditions

Column: Acquity UPLC BEH C18 (2.1 mm x 50 mm, 1.7 µm)

Column temperature: 40 °C

Solvents: A – Water + 0.05% of Ammonia

B – Acetonitrile + 0.05% of Ammonia

Injection volume: 2 µl

Equilibration time: 1 min

Gradient table:

Time (min)	Flow Rate (mL/min)	%A	%B
0.00	0.9	97	3
3.50	0.9	3	97
3.90	0.9	3	97
3.91	0.9	97	3
4.00	0.9	97	3

Stop time: 4 min

UV Conditions

PDA Range: 210 nm – 400 nm

Resolution: 1.2 nm

Acquisition Rate: 40 Hz

MS Conditions

Ionization Mode: Electrospray Positive and Negative (ES^+/ES^-)

Scan Range: 100 to 1500 Da

Scan Time: 0.15 s

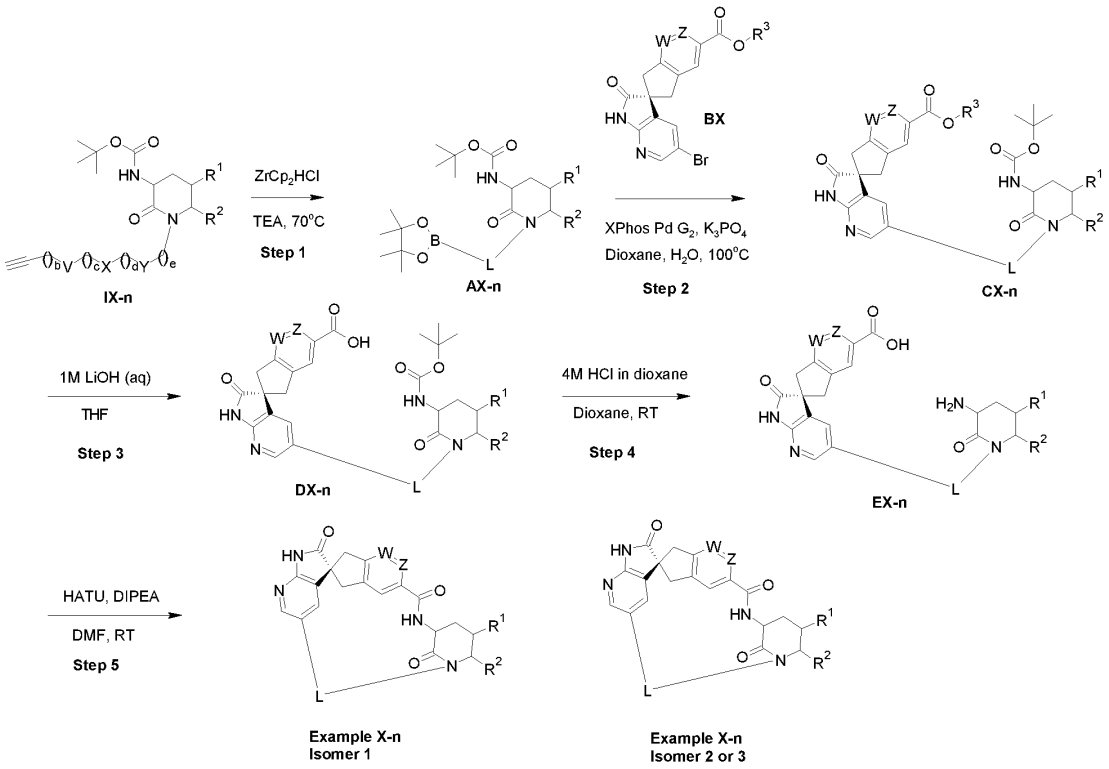
For preparative purification HPLC Waters Mass Directed Autopurification System was used. The system is composed of Waters Sample Manager 2767, Waters System Fluid Organizer, Waters Binary Gradient Module 2545, Waters 515 HPLC Pump, Waters Photodiode Array Detector 2998 and Waters Micromass ZQ MS detector. Software used: FractionLynx and MassLynx v4.1.

General HPLC method parameters: gradient mobile phase of 0.1% formic acid in H_2O and CH_3CN or 10 mM aqueous solution of NH_4HCO_3 (adjusted to pH 10 with ammonia) and CH_3CN. Column XBridge 30×150 mm, 5 µm.

PDA detector settings: wavelength: 210-400 nm, resolution: 1.2 nm, sampling rate: 1.0 points/sec, filter response: 1.

MS detector settings: MS scan: centroid, ionization mode: ES+ and ES-, mass range: 105-1500, scan time: 1.0 s, inter-scan delay: 0.1 s, capillary: 3.00 kV, cone: 30 V, extractor: 3.00 V, RF Lens: 0.2 V, source temp.: 150 °C, desolvation temp.: 350 °C, cone gas flow: 50 L/h, desolvation gas flow: 700 L/h, LM 1 resolution: 15.0, HM 1 resolution: 15.0, ion energy 1: 1.0 and multiplier: 650 V.

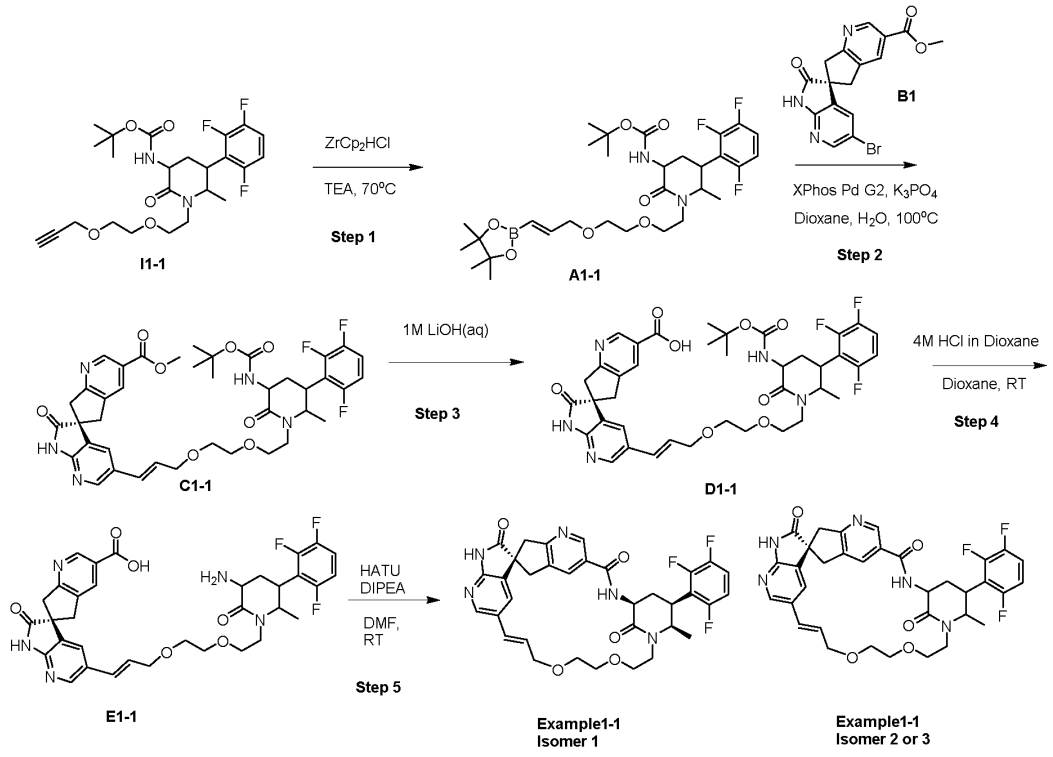
Scheme 1. General Synthesis of Examples



In Scheme 1, b, c, d, e, L, V, W, X, Y, Z, R^1 and R^2 are as defined above and R^3 is selected from methyl, ethyl and isopropyl. An alkynyl N-Boc aminopiperidinone of type IX-n or IX-n*, (IX-n indicates enriched single enantiomer all cis piperidone IX-n* indicates all cis enriched racemic piperidone) is converted to 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl-N-Boc aminopiperidinones of type AX-n by reaction for example with pinacolborane, TEA and $ZrCp_2HCl$ for 3h at 70°C, and for a further 1h after a second addition of pinacolborane (step 1). The resulting boronate can be coupled to a bromopyridyl-arylester of type BX, which is a single enantiomer, using a catalyst such as XPhos-Pd-G2 in, for example, water and dioxane at 100°C for 2h with K_3PO_4, (step 2) to afford an arylester-N-Boc-amino piperidinone intermediate of type CX-n. Hydrolysis of intermediate type CX-n with, for example, lithium hydroxide aq. in THF at room temperature, (step 3) affords an arylcarboxylic acid-N-Boc-amino piperidinone of type DX-n, Boc de-protection of which, with for example, 4M HCl in dioxane water at room temperature, (step 4) affords an aminopiperidone-arylcarboxylic acid of type EX-n. Macro lactamisation of aminopiperidinone-

arylcarboxylic acid EX-n, with for example, HATU and DIPEA in DMF at room temperature, (step 5) affords examples of this invention (Example X-n) as one or more isomers.

Scheme 2 Synthesis of Example 1-1



Experimental procedure for synthesis of Example 1-1 Isomers 1 and 2

Step 1. Synthesis of *tert*-butyl N-[6-methyl-2-oxo-1-[2-[2-[(E)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyloxy]ethoxy]ethyl]-5-(2,3,6-trifluorophenyl)-3-piperidyl]carbamate (A1-1*)

Into a vial containing compound **I1-1*** (435 mg, 0.898 mmol), pinacolborane (146 µL, 1.0 mmol), TEA (15.2 µL, 0.109 mmol), and $ZrCp_2HCl$ (29.4 mg, 0.988 mmol) were added. The vial was sealed and the suspension stirred at 70°C. After 3 hours additional pinacolborane (146 µL, 1.0 mmol) was added and stirring continued for 1 hour. The reaction mixture was quenched with *sat.* NH_4Cl (20 mL) and extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford desired crude

product **A1-1*** (776 mg) which was used as is in the next reaction step. **LC-MS (ES+):** 613.3 $[M+H]^+$.

Step 2. Synthesis of Methyl (3S)-5-[(E)-3-[2-[2-[5-(*tert*-butoxycarbonylamino)-2-methyl-6-oxo-3-(2,3,6-trifluorophenyl)-1-piperidyl]ethoxy]ethoxy]prop-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylate (Intermediate C1-1)

To a suspension of compound **B-1** (183 mg, 0.49 mmol) and compound **A1-1*** (776 mg, crude material) in degassed dioxane (1.90 mL), a solution of K_3PO_4 (312 mg, 0.098 mmol) in degassed water (520 µL) was added. Then XPhos Pd G2 (77.1 mg, 0.098 mmol) was added and the reaction mixture degassed for an additional 5 minutes, sealed and heated at 100 °C for 2 hours. The reaction mixture was diluted with DCM (30 mL) washed with *sat.* $NaHCO_3$ (4×10 mL) and *sat.* NaCl (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product (676 mg) as a brown oil. The crude material was loaded and purified on a silica column (Interchim 25 g, 15 µm, SiO_2) using Interchim PuriFlash 450 instrument with a flowrate of 20 mL/min starting with DCM (100%) and going to 100% [DCM/MeOH (20:1)] in 20 CVs. Hold 100% for 10 CVs. The appropriate fractions were collected, the solvent removed to yield the desired product **C1-1** (159 mg, 42%).

LC-MS (ES+): 780.4 $[M+H]^+$.

Step 3. Synthesis of (3S)-5-[(E)-3-[2-[2-[5-(*tert*-butoxycarbonylamino)-2-methyl-6-oxo-3-(2,3,6-trifluorophenyl)-1-piperidyl]ethoxy]ethoxy]prop-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylic acid (Intermediate D1-1)

To a solution of compound **C1-1** (159 mg, 0.204 mmol) in THF (3.0 mL), LiOH (1.0 *N* in H_2O, 815 µL, 0.815 mmol) was added. The reaction mixture was stirred at room temperature for 25 minutes. The reaction mixture was concentrated under reduced pressure and dissolved in water (15 mL). The solution was carefully washed with diethylether (2 × 10 mL). The pH value of the aq. layer was adjusted to 3.5 using 1 *N* HCl and extracted with DCM (4 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford the desired product **D1-1** (130 mg, 83%).

LC-MS (ES+): 766.3 $[M+H]^+$.

Step 4. Synthesis of (3S)-5-[(E)-3-[2-[2-[5-amino-2-methyl-6-oxo-3-(2,3,6-trifluorophenyl)-1-piperidyl]ethoxy]ethoxy]prop-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylic acid (compound E1-1)

To the solution of compound **D1-1** (130 mg, 0.169 mmol) in dioxane (3.38 mL), HCl (4.0 M in dioxane, 1.69 mL, 6.79 mmol) was added. The reaction mixture was stirred at room temperature for 1.5 hours. The reaction mixture was concentrated to yield the desired product **E1-1** (145.2 mg) which was used as is in the next reaction step.

LC-MS (ES+): 666.3 $[M+H]^+$.

Step 5. Synthesis of (1S,10S,12S,13R, 22E)-13-methyl-12-(2,3,6-trifluorophenyl)-17,20-dioxa-5,9,14,26,28-pentazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione (Example 1-1 Isomer 1) and (1S,22E)-13-methyl-12-(2,3,6-trifluorophenyl)-17,20-dioxa-5,9,14,26,28-pentazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione (Example 1-1 Isomer 2)

To a solution of DIPEA (60 µL, 0.34 mmol) and HATU (96.4 mg, 0.25 mmol) in dry DMF (28 mL) a solution of compound **E1-1** (145 mg, 0.169 mmol) and DIPEA (120 µL, 0.68 mmol) in dry DMF (14 mL) was added dropwise over period of 2 minutes. The reaction was quenched by adding DCM (50 mL) and a mixture of *sat.* $NaHCO_3/H_2O$ 1:1 (100 mL), layers were separated, and the aqueous layer extracted with DCM (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product (145 mg). The crude material was dissolved in EtOAc (70 mL). This solution was washed with sat. $NaHCO_3$ (3×15 mL). The organic layer was dried under Na_2SO_4 and concentrated under reduced pressure to afford 82.6 mg of the crude product as a yellow solid. The crude material was loaded and purified on a silica column (Interchim 4 g, 15 µm, SiO_2) using Interchim PuriFlash 450 instrument with a flowrate of 7 mL/min starting with DCM (100%). Hold DCM (100%) for 5 CV and going to 60% [DCM/MeOH (10:1)] in 10 CVs. Increasing to 75% [DCM/MeOH (10:1)] in 20 CVs and after that to 100% [DCM/MeOH (10:1)] in 10 CVs. The appropriate fractions were collected, the solvent

removed to yield the desired products **Example 1-1 Isomer 1** (29.9 mg, 27%) and **Example 1-1 Isomer 2** (32.4 mg, 30%).

Data for Isomer 1:

LC-MS (ES+): 648.1 $[M+H]^+$, R_t = 4.65 min (Method 1)

^{1}H NMR (600 MHz, DMSO-d_6): δ =1.14 (d, *J*=6.4 Hz, 3 H), 2.17 (dd, *J*=11.7, 7.3 Hz, 1 H), 2.84 (ddd, *J*=13,6, 8.0, 5.8 Hz, 1H), 2.89-2.98 (m, *J*=13.3, 11.7, 11.7, 3.5, 3.5 Hz, 1 H), 3.00 (d, *J*=16.0 Hz, 1H), 3.15 (d, *J*=15.6, 1H), 3.41-3.53 (m, 5 H), 3.59-3.65 (m, 2H), 3.62-3.67 (m, *J*=16.3 Hz, 1 H), 3.77-3.84 (m, 1H) 3.84-3.92 (m, 2H), 3.98 (t, *J*=5,5 Hz, 2 H), 4.67 (ddd, *J*=11.4, 9.2, 7.0 Hz, 1 H), 5.65 (dt, *J*=16.1, 6.1 Hz, 1 H), 6.43 (d, *J*=16.0 Hz, 1 H), 6.49 (d, *J*=2,0 Hz, 1 H), 7.17 (dddd, J =9.1, 4.0, 1.8 Hz, 1 H), 7.48 (qd, *J*=9.1, 5.4 Hz, 1 H), 8.01 (d, *J*=1.8 Hz, 1 H), 8.09 (s, 1 H), 8.66 (d, *J*=9.2 Hz, 1 H), 8.82 (s, 1H), 11.40 (s, 1 H) ppm.

^{13}C NMR (151 MHz, DMSO-d_6): δ = 15.8, 26.5, 35.6, 40.5, 44.2, 49.1, 51.1, 54.5, 58.2, 69.5, 69.7, 71.8, 71.8, 112.1, 117.1, 118.5, 123.3, 126.1, 126.6, 127.6, 130.2, 130.3, 132.4, 135.3, 147.2, 148.9, 156.0, 157.0, 165.3, 167.0, 168.4, 178.7 ppm.

Data for Isomer 2:

LC-MS (ES+): 648.1 $[M+H]^+$, R_t = 4.68 min (Method 1)

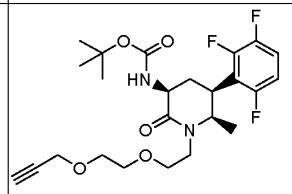
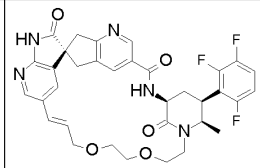
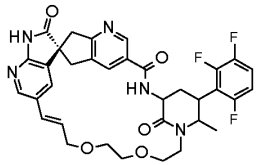
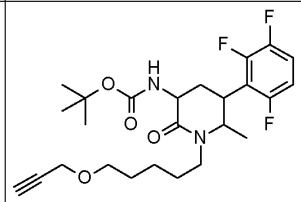
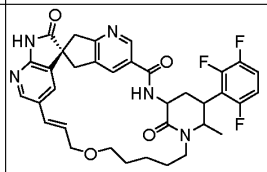
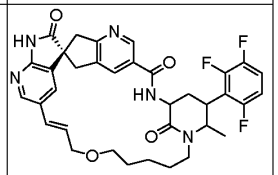
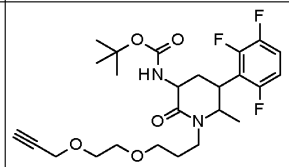
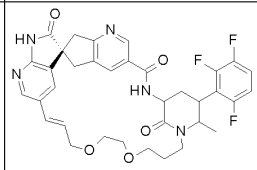
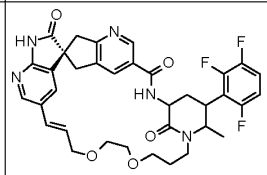
^{1}H NMR (600 MHz, DMSO-d_6): δ =1.15 (d, *J*=6.4 Hz, 3 H), 2.14 (dd, *J*=11.9, 6.8 Hz, 1 H), 2.81 (td, *J*=9.2, 3.7 Hz, 1H), 2.87-2.98 (m, *J*=13.6, 11.9, 11.5, 3.5, 3.5 Hz, 1 H), 3.05 (d, *J*=16.1 Hz, 1H), 3.06 (d, *J*=15.2 Hz, 1H), 3.32-3.36 (m, 1 H), 3.42-3.48 (m, 3H), 3.50 (d, *J*=15 Hz, 1 H), 3.62 (d, *J*=16.3,1H) 3.63 (quin, *J*=6.4, 6.0 Hz, 1H), 3.67-3.74 (m, 1 H), 3.82-3.95 (m, 4 H), 4.04 (ddd, *J*=11.6, 4.0, 1.5 Hz, 1 H), 4.65 (ddd, *J*=11.5, 8.7, 7.5 Hz, 1 H), 5.70 (ddd, *J*=16.0, 8.8, 4.1 Hz, 1 H), 6.47 (d, *J*=16.3 Hz, 1 H), 6.64 (d, *J*=1.8 Hz, 1 H), 7.12-7.20 (m, *J*=9.4, 9.4, 3.9, 1.7 Hz, 1 H), 7.47 (qd, *J*=9.4, 4.9 Hz, 1 H), 8.00 (d, *J*=2.0 Hz, 1 H), 8.12 (s, 1 H), 8.65 (d, *J*=9.2 Hz, 1 H), 8.83 (s, 1H), 11.42 (s, 1 H) ppm.

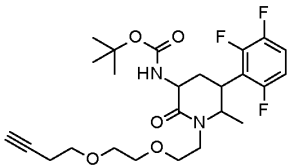
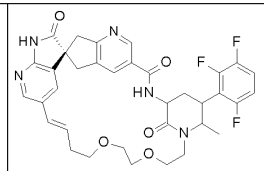
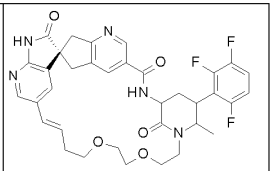
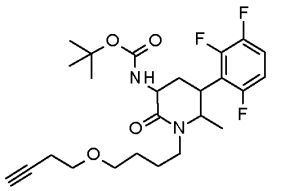
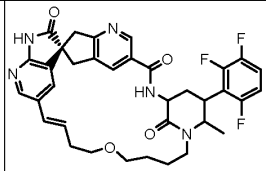
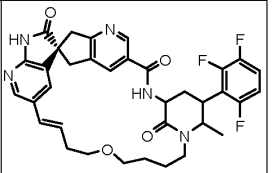
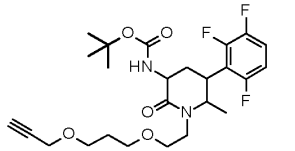
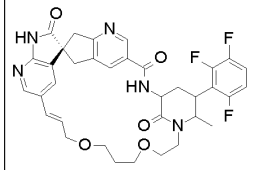
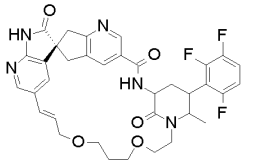
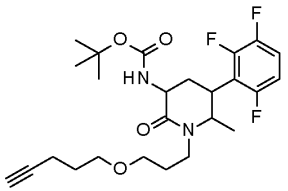
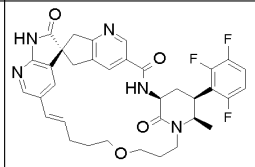
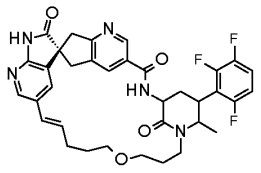
^{13}C NMR (151 MHz, DMSO-d_6): δ = 15.8, 26.6, 35.5, 41.0, 43.9, 49.1, 50.9, 54.5, 58.3, 68.7, 69.8, 72.0, 72.1, 112.1, 116.6, 118.6, 123.2, 125.9, 126.4, 128.2, 129.3, 130.3, 131.0, 134.7, 147.5, 148.6, 149.1, 156.0, 157.0, 165.5, 166.5, 168.3, 178.7 ppm.

Examples 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 2-1, 2-2, 2-3, 3-1, 3-2, 4-1, 4-2, 5-1, 7-1, 8-1, 8-2 and 9-1 were synthesized using the same experimental procedures as for the synthesis of Isomers 1 and 2 of Example 1-1 and starting from Intermediate IX-n and BX as stated in Table 2.

In **Example 2-2** where synthesis starts with intermediate **B2**, step 2 of the synthesis described in scheme 2. was not used (hydrolysis of esters).

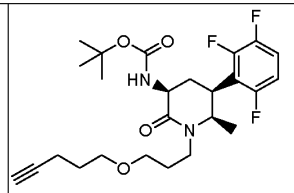
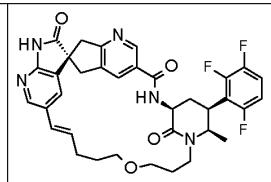
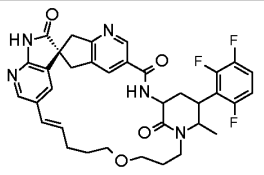
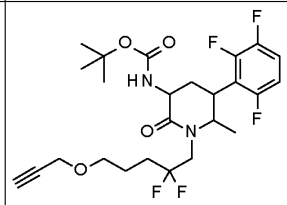
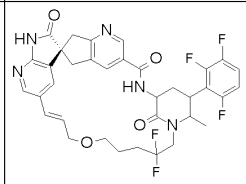
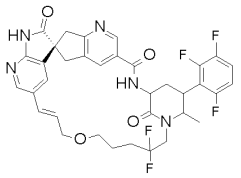
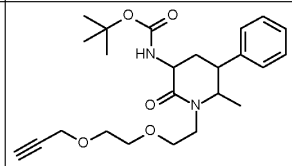
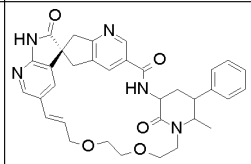
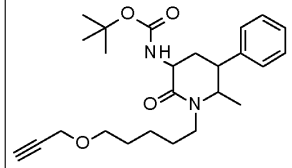
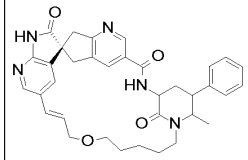
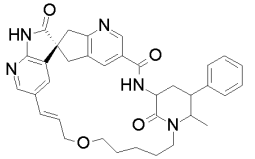
Table 2. Examples synthesis according to Scheme 2

Starting material			Final products					
Intermediate IX-n	**Structure IX-n**	**Intermediate BX**	**Example**	**Structure**	**Q**	**Example**	**Q**	**Structure**
I1-1 4.34 g,		B1 2 g,	Example 1-1 Isomer 1		517 mg,	Example 1-1 Isomer 3	50.6 mg,	
I1-2* 440 mg,		B1 160 mg	Example 1-2 Isomer 1		9.60 mg,	Example 1-2 Isomer 2	9.24 mg,	
I1-3* 300 mg,		B1 150 mg,	Example 1-3 Isomer 1		16.5 mg,	Example 1-3 Isomer 2	21.5 mg,	

I1-4* 310 mg,		B1 155 mg,	Example 1-4 Isomer 1		19 mg,	Example 1-4 Isomer 2	12.2 mg,	
I1-5* 333.0 mg,		B1 172 mg,	Example 1-5 Isomer 1		19 mg,	Example 1-5 Isomer 2	19 mg,	
I1-6* 355.2 mg,		B1 172.7 mg,	Example 1-6 Isomer 1		36.1 mg,	Example 1-6 Isomer 2	33.1 mg,	
I1-7* 400 mg,		B1 170 mg,	Example 1-7 Isomer 1		19.2 mg,	Example 1-7 Isomer 2	21.1 mg,	

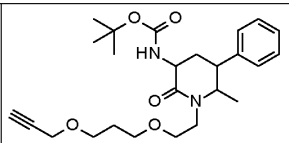
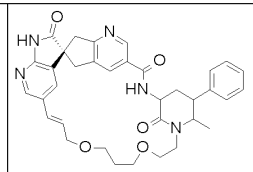
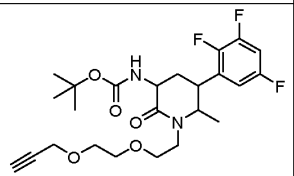
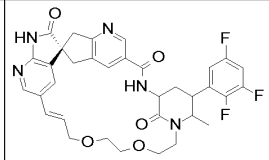
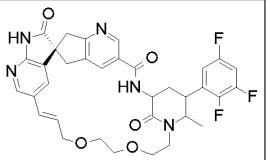
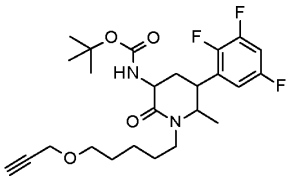
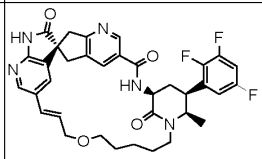
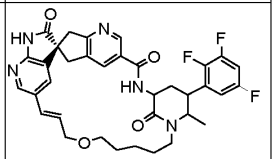
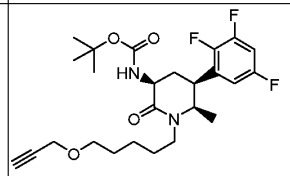
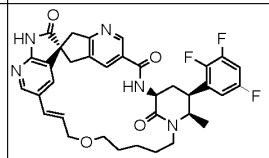
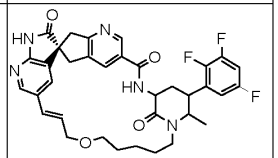
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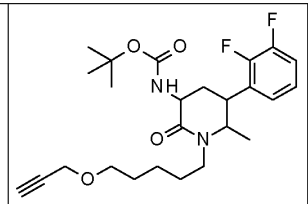
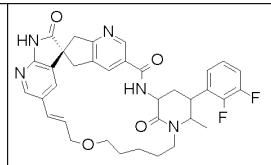
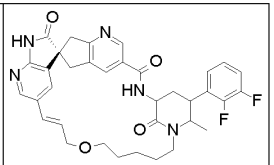
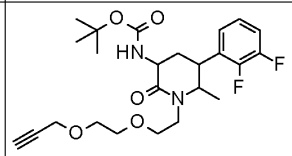
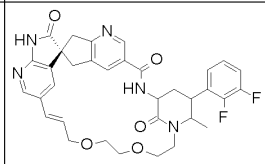
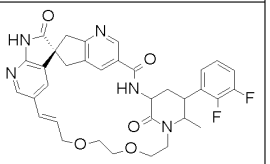
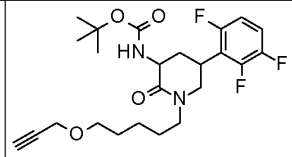
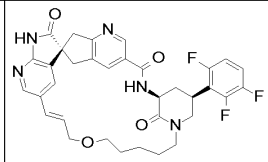
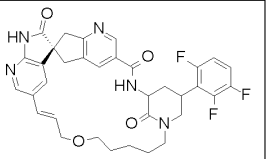
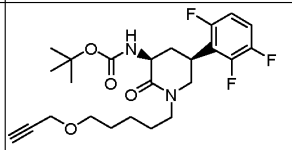
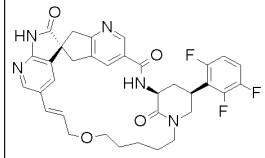
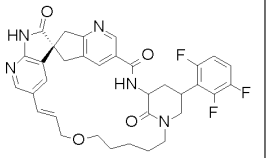
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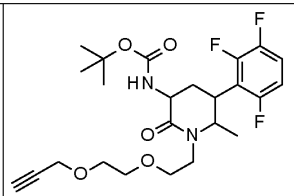
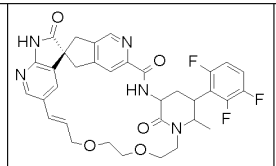
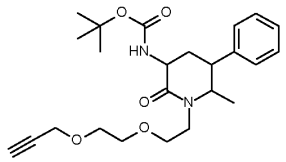
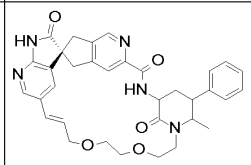
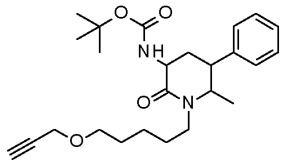
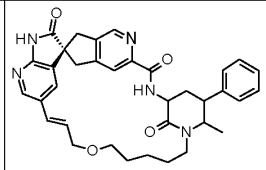
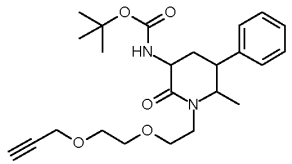
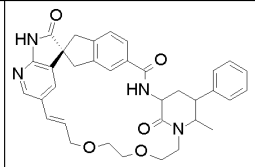
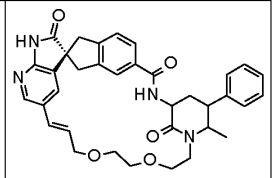
I1-7 1.93 g,		B1 1.2 g,	Example 1-7 Isomer 1		212 mg	Example 1-7 Isomer 3	17.2 mg,	
I1-8* 247 mg,		B1 130 mg,	Example 1-8 Isomer 1		9.4 mg,	Example 1-8 Isomer 2	17 mg,	
I2-1 234.1 mg,		B3 140.8 mg,	Example 2-1 Isomer 1		26.2 mg,	-	-	-
I2-2* 373 mg,		B2 207 mg,	Example 2-2 Isomer 1		12.8 mg,	Example 2-2 Isomer 2	12.2 mg,	

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I2-3 171.8 mg,		B3 100 mg,	Example 2-3 Isomer 1		40.4 mg,	-	-	-
I3-1* 400mg,		B1 200 mg,	Example 3-1 Isomer 1		68.7 mg,	Example 3-1 Isomer 2	23.3 mg,	
I3-2* 400 mg,		B1 180 mg,	Example 3-2 Isomer 1		33 mg,	Example 3-2 Isomer 2	30 mg,	
I3-2 3.32 g,		B1 1.45 g,	Example 3-2 Isomer 1		259.1 mg,	Example 3-2 Isomer 3	41.3 mg,	

I4-1* 400 mg,		B1 170 mg,	Example 4-1 Isomer 1		26.85 mg,	Example 4-1 Isomer 2	27.95 mg,	
I4-2* 400 mg,		B1 180 mg,	Example 4-2 Isomer 1		27.2 mg,	Example 4-2 Isomer 2	19.5 mg,	
I5-1* 395.0 mg,		B1 210 mg,	Example 5-1 Isomer 1		27.0 mg,	Example 5-1 Isomer 2	23.6 mg,	
I5-1 5.0 g,		B1 2.5 g,	Example 5-1 Isomer 1		727 mg,	Example 5-1 Isomer 3	57.6 mg,	

I1-1* 424.6 mg,		B5 165 mg,	Example 7-1 Mixture of 2 isomers		28.5 mg,	-	-	-
I2-1 234.1 mg,		B5 78.4 mg,	Example 8-1 Isomer 1		6.45 mg,	-	-	-
I2-2 373 mg,		B5 57.0 mg,	Example 8-2 Isomer 1		10 mg,	-	-	-
I2-1* 234.1 mg,		B6 272 mg,	Example 9-1 Isomer 1 mixture		41.8 mg,	Example 9-1 Isomer 2 mixture	34.0 mg,	

IX-n indicates enriched single enantiomer all cis piperidone. IX-n* indicates all cis enriched racemic piperidone.

Table 3. LC-MS and NMR data for Examples of Table 2

Example	Analytical Data
Example 1-1 Isomer 3	LC-MS (ES+): 648.4 $[M+H]^+$, R_t = 3.49 min (Method 2) ^{1}H NMR (600 MHz, DMSO-d_6): δ =1.08 (d, *J*=6.4 Hz, 3 H), 1.98 (br. s., *J*=13.4, 2.0, 1.0 Hz, 1 H), 2.78 (ddd, *J*=13.4, 7.5, 5.7 Hz, 1H), 3.04 (d, *J*=16.1 Hz, 1H), 3.05 (d, *J*=15.6 Hz, 1H), 3.07-3.16 (m, 13.4, 13.4, 7.2, 3.5, 3.5 Hz 1 H), 3.42-3.46 (m, 1H), 3.47-3.51 (m, 4 H), 3.59 (d, *J*=16.1 Hz, 1 H), 3.69-3.77 (m,3 H), 3.92 (dd, 12.1, 8.8 Hz, 1 H), 3.97-4.04 (m, 1 H), 4.06 (ddd, *J*=11.7, 4.0, 1.5 Hz, 1 H), 4.17 (dt, *J*=13.9, 3,8, 2.8 Hz, 1 H), 4.88 (ddd, *J*=8.6, 7.2, 1.0 Hz, 1 H), 5.84 (ddd, *J*=16.0, 9.0, 4.1 Hz, 1 H), 6.48 (d, *J*=16.3 Hz, 1 H), 6.79 (d, *J*=2.0 Hz, 1 H), 7.13-7.20 (m, *J*=9.6, 9.6, 4.0, 2.0 Hz, 1 H), 7.47 (qd, *J*=9.3, 4.8 Hz, 1 H), 8.00 (d, *J*=2.0 Hz, 1 H), 8.05 (s, 1 H), 8.71 (s, 1H), 8.89 (d, J=9.0 Hz, 1 H), 11.40 (s, 1 H) ppm
Example 1-2 Isomer 1	LC-MS (ES+): 646.5 $[M+H]^+$, R_t = 4.40 min (Method 1) ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.17 - 1.31 (m, 6 H), 1.32 - 1.40 (m, 1 H), 1.43 - 1.66 (m, 4 H), 2.16 (dd, *J*=11.9, 6.7 Hz, 1 H), 2.71 - 2.86 (m, 1 H), 2.93 - 3.09 (m, 2 H), 3.16 (d, *J*=15.9 Hz, 1 H), 3.23 - 3.30 (m, 1 H), 3.49 (d, *J*=15.3 Hz, 1 H), 3.59 - 3.67 (m, 2 H), 3.68 - 3.80 (m, 1 H), 3.87 (d, *J*=11.9 Hz, 1 H), 3.94 - 4.03 (m, 2 H), 4.60 - 4.67 (m, 1 H), 5.70 (dt, *J*=16.1, 6.0 Hz, 1 H), 6.40 (d, *J*=16.2 Hz, 1 H), 6.50 (d, *J*=1.8 Hz, 1 H), 7.13 - 7.21 (m, 1 H), 7.43 - 7.53 (m, 1 H), 8.02 (d, *J*=1.8 Hz, 1 H), 8.12 (s, 1 H), 8.75 (d, *J*=8.9 Hz, 1 H), 8.85 (s, 1 H), 11.39 (br. s., 1 H)
Example 1-2 Isomer 2	LC-MS (ES+): 646.6 $[M+H]^+$, R_t = 4.40 min (Method 1) ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.77 - 0.88 (m, 1 H), 1.20 (d, *J*=6.1 Hz, 3 H), 1.23 (br. s., 2 H), 1.27 - 1.42 (m, 4 H), 1.50 - 1.64 (m, 1 H), 1.67 - 1.79 (m, 1 H), 2.13 (dd, *J*=11.4, 7.2 Hz, 1 H), 2.64 - 2.80 (m, 1 H), 2.98 (q, *J*=12.4 Hz, 1

	H), 3.07 (d, *J*=15.9 Hz, 2 H), 3.25 - 3.31 (m, 2 H), 3.43 - 3.56 (m, 1 H), 3.57 - 3.64 (m, 2 H), 3.78 - 3.95 (m, 3 H), 3.97 - 4.06 (m, 1 H), 4.58 - 4.66 (m, 1 H), 5.72 - 5.79 (m, 1 H), 6.46 (d, *J*=16.2 Hz, 1 H), 6.69 (s, 1 H), 7.16 (t, *J*=8.2 Hz, 1 H), 7.43 - 7.51 (m, 1 H), 7.97 - 8.02 (m, 1 H), 8.14 (s, 1 H), 8.70 (d, *J*=8.9 Hz, 1 H), 8.85 (s, 1 H), 11.41 (br. s., 1 H)
Example 1-3 Isomer 1	LC-MS (ES+): 662.1 $[M+H]^+$, Rt = 3.57 min (Method 1) ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.19 (d, *J*=6.4 Hz, 3 H), 1.73 (m, *J*=13.2, 8.8, 4.3, 4.3 Hz, 1 H), 1.83 - 1.91 (m, 1 H), 2.14 - 2.18 (m, 1 H), 2.99 (d, *J*=13.4 Hz, 1 H), 3.03 - 3.11 (m, 2 H), 3.15 - 3.19 (m, 1 H), 3.34 - 3.43 (m, 3 H), 3.43 - 3.51 (m, 5 H), 3.59 - 3.65 (m, 2 H), 3.85 - 3.89 (m, 1 H), 3.93 - 4.04 (m, 2 H), 4.56 - 4.61 (m, 1 H), 5.71 (ddd, *J*=16.1, 7.3, 4.7 Hz, 1 H), 6.41 (d, *J*=16.1 Hz, 1 H), 6.61 (d, *J*=2.0 Hz, 1 H), 7.18 (t, *J*=9.5 Hz, 1 H), 7.48 (qd, *J*=9.4, 4.8 Hz, 1 H), 8.05 (d, *J*=2.0 Hz, 1 H), 8.13 (s, 1 H), 8.80 (d, *J*=8.8 Hz, 1 H), 8.84 (s, 1 H), 11.39 (br. s., 1 H)
Example 1-3 Isomer 2	LC-MS (ES+): 662.1 $[M+H]^+$, Rt = 3.64 min (Method 1) ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.19 (d, *J*=6.4 Hz, 3 H), 1.67 - 1.77 (m, 1 H), 1.80 - 1.89 (m, 1 H), 2.14 (dd, *J*=12.0, 6.9 Hz, 1 H), 3.01 - 3.14 (m, 4 H), 3.34 - 3.44 (m, 3 H), 3.44 - 3.53 (m, 5 H), 3.58 - 3.65 (m, 2 H), 3.84 - 3.89 (m, 1 H), 3.91 - 3.96 (m, 1 H), 4.04 - 4.09 (m, 1 H), 4.50 (dt, *J*=11.4, 7.9 Hz, 1 H), 5.82 - 5.87 (m, 1 H), 6.41 (d, *J*=16.1 Hz, 1 H), 6.70 (d, *J*=2.0 Hz, 1 H), 7.17 (t, *J*=9.6 Hz, 1 H), 7.48 (qd, *J*=9.3, 4.9 Hz, 1 H), 8.07 (d, *J*=2.0 Hz, 1 H), 8.17 (s, 1 H), 8.81 (d, *J*=8.4 Hz, 1 H), 8.93 (s, 1 H), 11.39 (s, 1 H)
Example 1-4 Isomer 1	LC-MS (ES+): 662.0 $[M+H]^+$, Rt = 4.07 min (Method 1) ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.16 (d, *J*=6.4 Hz, 3 H), 2.17 (dd, *J*=11.7, 7.0 Hz, 1 H), 2.25 - 2.36 (m, 1 H), 2.99 - 3.12 (m, 3 H), 3.14 - 3.20 (m, 1 H), 3.35 - 3.41 (m, 2 H), 3.42 - 3.45 (m, 2 H), 3.46 - 3.58 (m, 3 H), 3.59 - 3.68 (m, 4 H), 3.70 - 3.79 (m, 1 H), 3.86 - 3.94 (m, 1 H), 4.55 - 4.61 (m, 1 H), 5.60 (dt, *J*=15.8, 7.2 Hz, 1 H), 6.33 - 6.37 (m, 1 H),

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	6.57 (d, *J*=2.0 Hz, 1 H), 7.18 (t, *J*=9.3 Hz, 1 H), 7.46 - 7.52 (m, 1 H), 7.94 - 7.97 (m, 1 H), 8.14 (s, 1 H), 8.80 - 8.85 (m, 1 H), 8.86 (s, 1 H), 11.36 (br. s., 1 H)
Example 1-4 Isomer 2	LC-MS (ES+): 662.0 $[M+H]^+$, Rt = 4.05 min (Method 1) ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.77 - 0.90 (m, 1 H), 1.16 (d, *J*=6.4 Hz, 3 H), 2.14 (dd, *J*=11.7, 6.9 Hz, 1 H), 2.22 - 2.38 (m, 2 H), 2.52 - 2.52 (m, 1 H), 3.01 - 3.17 (m, 4 H), 3.34 - 3.41 (m, 2 H), 3.43 - 3.51 (m, 4 H), 3.54 - 3.66 (m, 5 H), 3.69 - 3.79 (m, 1 H), 3.82 - 3.97 (m, 1 H), 4.48 (dt, *J*=11.5, 7.7 Hz, 1 H), 5.64 - 5.73 (m, 1 H), 6.34 (d, *J*=15.9 Hz, 1 H), 6.65 (d, *J*=1.8 Hz, 1 H), 7.14 - 7.21 (m, 1 H), 7.48 (qd, *J*=9.4, 4.9 Hz, 1 H), 7.96 (d, *J*=2.1 Hz, 1 H), 8.19 (s, 1 H), 8.84 (d, *J*=8.2 Hz, 1 H), 8.93 (s, 1 H), 11.35 (br. s., 1 H)
Example 1-5 Isomer 1	LC-MS (ES+): 646.7 $[M+H]^+$, Rt = 4.30 min (Method 1) ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.21 (d, *J*=6.4 Hz, 3 H), 1.44 - 1.52 (m, 3 H), 1.67 - 1.74 (m, 1 H), 2.17 (dd, *J*=12.2, 7.4 Hz, 1 H), 2.26 - 2.35 (m, 2 H), 2.81 - 2.87 (m, 1 H), 2.98 - 3.05 (m, 2 H), 3.17 (d, *J*=15.8 Hz, 1 H), 3.28 - 3.31 (m, 1 H), 3.33 - 3.43 (m, 3 H), 3.49 (d, *J*=15.6 Hz, 1 H), 3.58 - 3.65 (m, 2 H), 3.72 (dt, *J*=13.8, 6.9 Hz, 1 H), 3.82 - 3.87 (m, 1 H), 4.58 - 4.63 (m, 1 H), 5.61 (dt, *J*=15.8, 7.1 Hz, 1 H), 6.34 (d, *J*=16.0 Hz, 1 H), 6.56 (d, *J*=2.0 Hz, 1 H), 7.18 (t, *J*=9.5 Hz, 1 H), 7.48 (qd, *J*=9.3, 5.0 Hz, 1 H), 7.94 (d, *J*=2.0 Hz, 1 H), 8.10 (s, 1 H), 8.77 (d, *J*=9.0 Hz, 1 H), 8.83 (s, 1 H), 11.36 (br. s., 1 H)
Example 1-5 Isomer 2	LC-MS (ES+): 646.6 $[M+H]^+$, Rt = 4.36 min (Method 1) ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.23 (d, *J*=6.2 Hz, 3 H), 1.36 - 1.44 (m, 1 H), 1.44 - 1.51 (m, 2 H), 1.70 - 1.78 (m, 1 H), 2.10 - 2.15 (m, 1 H), 2.26 (br. s., 1 H), 2.32 - 2.41 (m, 1 H), 2.68 - 2.78 (m, 1 H), 3.05 - 3.16 (m, 3 H), 3.19 - 3.28 (m, 2 H), 3.33 - 3.37 (m, 1 H), 3.41 - 3.52 (m, 2 H), 3.53 - 3.66 (m, 2 H), 3.79 - 3.89 (m, 2 H), 4.49 - 4.55 (m, 1 H), 5.74

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	- 5.80 (m, 1 H), 6.34 (d, *J*=16.0 Hz, 1 H), 6.75 (d, *J*=1.8 Hz, 1 H), 7.17 (t, *J*=9.3 Hz, 1 H), 7.44 - 7.51 (m, 1 H), 7.95 (d, *J*=1.7 Hz, 1 H), 8.16 (s, 1 H), 8.79 (d, *J*=8.6 Hz, 1 H), 8.87 (s, 1 H), 11.37 (br. s., 1 H)
Example 1-6 Isomer 1	LC-MS (ES+): 662.7 $[M+H]^+$, Rt = 4.82 min (Method 1) ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.14 (d, *J*=6.4 Hz, 3 H), 1.64 - 1.73 (m, 2 H), 2.14 - 2.19 (m, 1 H), 2.92 - 3.03 (m, 1 H), 3.03 - 3.08 (m, 2 H), 3.17 (d, *J*=15.8 Hz, 1 H), 3.34 - 3.45 (m, 3 H), 3.47 - 3.56 (m, 3 H), 3.58 - 3.65 (m, 3 H), 3.76 (ddd, *J*=12.8, 8.8, 3.8 Hz, 1 H), 3.87 - 3.98 (m, 3 H), 4.59 - 4.65 (m, 1 H), 5.69 - 5.76 (m, 1 H), 6.40 (d, *J*=16.0 Hz, 1 H), 6.58 (d, *J*=2.0 Hz, 1 H), 7.18 (t, *J*=9.5 Hz, 1 H), 7.49 (qd, *J*=9.4, 5.0 Hz, 1 H), 8.06 (d, *J*=2.0 Hz, 1 H), 8.14 (s, 1 H), 8.77 (d, *J*=9.0 Hz, 1 H), 8.86 (s, 1 H), 11.39 (s, 1 H)
Example 1-6 Isomer 2	LC-MS (ES+): 662.6 $[M+H]^+$, Rt = 4.84 min (Method 1) ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.14 (d, *J*=6.4 Hz, 3 H), 1.63 - 1.77 (m, 2 H), 2.14 (dd, *J*=11.3, 6.9 Hz, 1 H), 2.98 - 3.14 (m, 4 H), 3.34 - 3.44 (m, 3 H), 3.46 - 3.52 (m, 3 H), 3.55 - 3.65 (m, 3 H), 3.73 (ddd, *J*=12.9, 8.6, 3.8 Hz, 1 H), 3.86 - 3.94 (m, 2 H), 3.96 - 4.02 (m, 1 H), 4.52 (dt, *J*=11.4, 7.8 Hz, 1 H), 5.78 - 5.83 (m, 1 H), 6.41 (d, *J*=16.1 Hz, 1 H), 6.67 (d, *J*=2.0 Hz, 1 H), 7.17 (t, *J*=9.5 Hz, 1 H), 7.45 - 7.51 (m, 1 H), 8.08 (d, *J*=2.0 Hz, 1 H), 8.17 (s, 1 H), 8.80 (d, *J*=8.4 Hz, 1 H), 8.92 (s, 1 H), 11.39 (s, 1 H)
Example 1-7 Isomer 1	LC-MS (ES+): 646.0 $[M+H]^+$, Rt = 5.00 min (Method 1) ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.15 - 1.27 (m, 3 H), 1.53 (dq, *J*=13.5, 6.8 Hz, 1 H), 1.58 - 1.65 (m, 1 H), 1.69 - 1.80 (m, 2 H), 2.02 - 2.10 (m, 1 H), 2.14 - 2.21 (m, 2 H), 2.94 - 3.01 (m, 1 H), 3.01 - 3.09 (m, 1 H), 3.13 (d, *J*=15.4 Hz, 1 H), 3.19 - 3.22 (m, 1 H), 3.22 - 3.31 (m, 2 H), 3.33 - 3.51 (m, 4 H), 3.60 - 3.68 (m, 2 H), 3.84 - 3.89 (m, 1 H), 4.52 - 4.57 (m, 1 H), 5.57 (ddd, *J*=15.7, 8.4, 6.1 Hz, 1 H), 6.27 (d, *J*=15.8 Hz, 1 H), 6.37 (d, *J*=2.0 Hz, 1 H), 7.18 (t, *J*=9.4 Hz, 1 H),

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	7.49 (qd, *J*=9.4, 5.0 Hz, 1 H), 7.94 (d, *J*=2.0 Hz, 1 H), 8.17 (s, 1 H), 8.76 (d, *J*=8.8 Hz, 1 H), 8.88 (s, 1 H), 11.33 (br. s., 1 H)
Example 1-7 Isomer 2	LC-MS (ES+): 646.0 $[M+H]^+$, Rt = 4.98 min (Method 1) ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.21 (d, *J*=6.6 Hz, 3 H), 1.49 - 1.56 (m, 1 H), 1.65 (ddd, *J*=12.7, 9.4, 6.4 Hz, 1 H), 1.72 - 1.81 (m, 2 H), 2.00 - 2.07 (m, 1 H), 2.12 - 2.19 (m, 2 H), 3.03 - 3.11 (m, 4 H), 3.25 - 3.32 (m, 2 H), 3.36 - 3.43 (m, 2 H), 3.49 (d, *J*=15.6 Hz, 1 H), 3.52 - 3.58 (m, 1 H), 3.58 - 3.68 (m, 2 H), 3.84 - 3.89 (m, 1 H), 4.51 - 4.56 (m, 1 H), 5.64 (ddd, *J*=15.5, 9.3, 5.7 Hz, 1 H), 6.29 (d, *J*=15.8 Hz, 1 H), 6.61 (d, *J*=2.0 Hz, 1 H), 7.15 - 7.20 (m, 1 H), 7.48 (qd, *J*=9.3, 5.0 Hz, 1 H), 7.93 (d, *J*=2.0 Hz, 1 H), 8.17 (s, 1 H), 8.74 (d, *J*=8.6 Hz, 1 H), 8.88 (s, 1 H), 11.35 (s, 1 H)
Example 1-7 Isomer 3	LC-MS(ES+): 646.4 $[M+H]^+$, Rt=3.65 min (Method 2) ^{1}H NMR (600 MHz, DMSO-d_6): δ ppm 1.07 (d, *J* = 6.2 Hz, 3 H), 1.58 - 1.63 (m, 1 H), 1.66 - 1.79 (m, 2 H), 1.94 - 2.00 (m, 1 H), 2.03 - 2.10 (m, 1 H), 2.13 - 2.21 (m, 2 H), 2.77 (dt, *J* = 13.2, 4.4 Hz, 1 H), 3.04 - 3.10 (m, 2 H), 3.10 - 3.17 (m, 1 H), 3.26 - 3.40 (m, 4 H), 3.45 (d, *J* = 16.0 Hz, 1 H), 3.56 (d, *J* = 16.7 Hz, 1 H), 3.66 - 3.72 (m, 1 H), 3.88 - 3.94 (m, 1 H), 4.21 - 4.29 (m, 1 H), 4.90 (t, *J* = 8.1 Hz, 1 H), 5.76 - 5.84 (m, 1 H), 6.31 (d, *J* = 15.4 Hz, 1 H), 6.83 (d, *J* = 1.8 Hz, 1 H), 7.15 - 7.22 (m, 1 H), 7.44 - 7.52 (m, 1 H), 7.94 (d, *J* = 2.0 Hz, 1 H), 8.05 (s, 1 H), 8.76 (s, 1 H), 8.87 (d, *J* = 9.4 Hz, 1 H), 11.35 (s, 1 H)
Example 1-8 Isomer 1	LC-MS (ES+): 682.7 $[M+H]^+$, Rt = 4.75 min (Method 1) ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.23 (d, *J*=6.4 Hz, 3 H), 1.61 - 1.73 (m, 2 H), 1.87 - 2.06 (m, 2 H), 2.21 (dd, *J*=11.5, 7.1 Hz, 1 H), 2.97 - 3.08 (m, 2 H), 3.14 (d, *J*=15.4 Hz, 1 H), 3.28 - 3.33 (m, 2 H), 3.42 - 3.53 (m, 2 H), 3.65 (d, *J*=16.0 Hz, 1 H), 3.73 (quin, *J*=5.9 Hz, 1 H), 3.90 - 4.05 (m, 3 H), 4.09 - 4.19 (m, 1 H), 4.66 - 4.72 (m, 1 H), 5.60 - 5.70

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	(m, 1 H), 6.41 - 6.47 (m, 2 H), 7.18 (t, *J*=9.6 Hz, 1 H), 7.49 (qd, *J*=9.3, 4.9 Hz, 1 H), 7.99 (d, *J*=2.0 Hz, 1 H), 8.15 (s, 1 H), 8.88 (s, 1 H), 8.96 (d, *J*=8.8 Hz, 1 H), 11.39 (s, 1 H)
Example 1-8 Isomer 2	LC-MS (ES+): 682.7 $[M+H]^+$, Rt = 1.86 min (Method 3) ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.23 (d, *J*=6.4 Hz, 3 H), 1.53 - 1.61 (m, 1 H), 1.69 (d, *J*=4.2 Hz, 1 H), 1.85 - 2.01 (m, 2 H), 2.16 - 2.20 (m, 1 H), 2.96 - 3.08 (m, 3 H), 3.20 - 3.26 (m, 1 H), 3.34 - 3.43 (m, 2 H), 3.46 - 3.53 (m, 1 H), 3.60 - 3.65 (m, 1 H), 3.69 - 3.74 (m, 1 H), 3.89 - 3.96 (m, 2 H), 4.06 (dt, *J*=10.6, 1.9 Hz, 1 H), 4.17 - 4.27 (m, 1 H), 4.69 - 4.74 (m, 1 H), 5.65 (ddd, *J*=16.1, 9.2, 3.9 Hz, 1 H), 6.46 (s, 1 H), 6.49 (s, 1 H), 6.63 (d, *J*=2.0 Hz, 1 H), 7.15 - 7.20 (m, 1 H), 7.45 - 7.51 (m, 1 H), 7.99 (d, *J*=2.2 Hz, 1 H), 8.13 (s, 1 H), 8.85 (s, 1 H), 8.92 (d, *J*=8.8 Hz, 1 H), 11.41 (br. s., 1 H)
Example 2-1 Isomer 1	LC-MS (ES+): 595.0 $[M+H]^+$, Rt = 4.54 min (Method 1) ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm = 0.91 (d, *J* = 6.4 Hz, 3 H), 2.13 (dd, *J* = 11.3, 7.6 Hz, 1 H), 2.57 (q, *J* = 12.5 Hz, 1 H), 2.84 (ddd, *J* = 13.4, 7.9, 5.8 Hz, 1 H), 3.01 (d, *J* = 16.2 Hz, 1 H), 3.15 (d, *J* = 15.6 Hz, 1 H), 3.40 - 3.50 (m, 5 H), 3.52 - 3.58 (m, 1 H), 3.60 - 3.68 (m, 1 H), 3.67 - 3.73 (m, 1 H), 3.78 - 3.85 (m, 2 H), 3.91 (ddd, *J* = 13.4, 8.2, 5.3 Hz, 1 H), 3.96 - 4.01 (m, 2 H), 4.61 - 4.72 (m, 1 H), 5.65 (dt, *J* = 16.2, 6.1 Hz, 1 H), 6.43 (d, *J* = 16.2 Hz, 1 H), 6.50 (d, *J* = 1.8 Hz, 1 H), 7.25 - 7.30 (m, 1 H), 7.27 (d, *J* = 7.9 Hz, 2 H), 7.34 - 7.42 (m, 2 H), 8.01 (d, *J* = 1.8 Hz, 1 H), 8.10 (s, 1 H), 8.70 (d, *J* = 9.2 Hz, 1 H), 8.83 (s, 1 H), 11.40 (s, 1 H)
Example 2-2 Isomer 1	LC-MS (ES+): 592.9 $[M+H]^+$, Rt = 4.83 min (Method 1) ^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 1.09 (d, *J*=6.4 Hz, 3 H), 1.36 - 1.53 (m, 3 H), 1.55 - 1.61 (m, 1 H), 1.65 (dd, *J*=11.9, 6.1 Hz, 1 H), 1.74 - 1.85 (m, 1 H), 2.21 - 2.36 (m, 1 H), 2.72 (q, *J*=12.5 Hz, 1 H), 2.80 - 2.93 (m, 1 H), 3.05 (d, *J*=16.2 Hz, 1 H), 3.15 (d, *J*=15.9 Hz, 1 H), 3.36 - 3.48 (m, 2 H), 3.52 - 3.61 (m, 1 H), 3.69 (d, *J*=15.6 Hz, 1 H), 3.75

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	(quin, *J*=6.0 Hz, 1 H), 3.81 (d, *J*=16.2 Hz, 1 H), 3.94 - 4.04 (m, 2 H), 4.04 - 4.11 (m, 1 H), 4.66 - 4.78 (m, 1 H), 5.88 (dt, *J*=15.9, 6.2 Hz, 1 H), 6.39 (d, *J*=15.9 Hz, 1 H), 6.79 (d, *J*=1.8 Hz, 1 H), 7.25 - 7.34 (m, 3 H), 7.34 - 7.39 (m, 2 H), 7.94 (d, *J*=1.8 Hz, 1 H), 8.22 (s, 1 H), 8.83 (s, 1 H)
Example 2-2 Isomer 2	LC-MS (ES+): 592.9 $[M+H]^+$, Rt = 4.93 min (Method 1) ^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 1.07 (d, *J*=6.7 Hz, 3 H), 1.36 - 1.52 (m, 4 H), 1.61 - 1.71 (m, 1 H), 1.85 - 1.98 (m, 1 H), 2.26 (dd, *J*=11.9, 7.3 Hz, 1 H), 2.67 (q, *J*=12.5 Hz, 1 H), 2.76 - 2.88 (m, 1 H), 3.11 (d, *J*=16.2 Hz, 2 H), 3.37 - 3.47 (m, 2 H), 3.51 - 3.60 (m, 1 H), 3.64 (d, *J*=15.6 Hz, 1 H), 3.71 - 3.77 (m, 1 H), 3.81 (d, *J*=16.8 Hz, 1 H), 3.92 - 4.09 (m, 3 H), 4.72 - 4.81 (m, 1 H), 5.94 (ddd, *J*=15.9, 9.2, 4.3 Hz, 1 H), 6.42 (d, *J*=16.2 Hz, 1 H), 6.95 (d, *J*=1.8 Hz, 1 H), 7.24 - 7.32 (m, 3 H), 7.32 - 7.39 (m, 2 H), 7.94 (d, *J*=1.8 Hz, 1 H), 8.16 (s, 1 H), 8.96 (s, 1 H)
Example 2-3 Isomer 1	LC-MS (ES+): 608.2 $[M+H]^+$, Rt = 4.81 min (Method 1) ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 0.90 (d, *J*=6.4 Hz, 3 H), 1.65 - 1.72 (m, 2 H), 2.12 (dd, *J*=11.6, 7.4 Hz, 1 H), 2.52 - 2.63 (m, 1 H), 3.02 - 3.08 (m, 2 H), 3.18 (d, *J*=15.8 Hz, 1 H), 3.34 - 3.41 (m, 2 H), 3.42 - 3.48 (m, 1 H), 3.48 - 3.66 (m, 6 H), 3.67 - 3.73 (m, 1 H), 3.78 (ddd, *J*=13.1, 8.8, 4.2 Hz, 1 H), 3.91 - 3.98 (m, 2 H), 4.60 - 4.65 (m, 1 H), 5.70 - 5.76 (m, 1 H), 6.40 (d, *J*=16.1 Hz, 1 H), 6.59 (d, *J*=2.0 Hz, 1 H), 7.25 - 7.30 (m, 3 H), 7.35 - 7.38 (m, 2 H), 8.06 (d, *J*=2.0 Hz, 1 H), 8.14 (s, 1 H), 8.81 (d, *J*=8.8 Hz, 1 H), 8.87 (s, 1 H), 11.40 (s, 1 H)
Example 3-1 Isomer 1	LC-MS (ES+): 648.6 $[M+H]^+$, Rt = 4.71 min (Method 1) ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.00 (d, *J*=6.6 Hz, 3 H), 2.06 - 2.13 (m, 1 H), 2.63 (q, *J*=12.5 Hz, 1 H), 2.85 (ddd, *J*=13.6, 8.1, 5.8 Hz, 1 H), 3.01 (d, *J*=16.0 Hz, 1 H), 3.15 (d, *J*=15.4 Hz, 1 H), 3.41 - 3.53 (m, 5 H), 3.62 - 3.65 (m, 1 H), 3.65 (d, *J*=16.3 Hz, 1 H), 3.71 (quin, *J*=5.7 Hz, 1 H), 3.80 (ddd, *J*=9.2, 7.9, 5.5 Hz, 1 H), 3.85 (ddd, *J*=13.6, 4.0, 2.0 Hz,

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	1 H), 3.90 (ddd, *J*=13.4, 8.1, 5.2 Hz, 1 H), 3.99 (dt, *J*=4.0, 2.1 Hz, 2 H), 4.68 (ddd, *J*=11.3, 9.1, 7.6 Hz, 1 H), 5.66 (dt, *J*=16.0, 6.2 Hz, 1 H), 6.43 (d, *J*=16.1 Hz, 1 H), 6.49 (d, *J*=1.8 Hz, 1 H), 7.00 - 7.08 (m, 1 H), 7.45 - 7.54 (m, 1 H), 8.02 (d, *J*=2.0 Hz, 1 H), 8.10 (s, 1 H), 8.74 (d, *J*=9.2 Hz, 1 H), 8.81 (s, 1 H), 11.40 (br. s., 1 H)
Example 3-1 Isomer 2	LC-MS (ES+): 648.6 $[M+H]^+$, Rt = 4.74 min (Method 1) ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.00 (d, *J*=6.6 Hz, 3 H), 2.03 - 2.08 (m, 1 H), 2.64 (q, *J*=12.8 Hz, 1 H), 2.82 (ddd, *J*=12.8, 8.3, 6.8 Hz, 1 H), 3.05 (d, *J*=13.0 Hz, 1 H), 3.08 (d, *J*=12.1 Hz, 1 H), 3.33 - 3.37 (m, 1 H), 3.39 - 3.49 (m, 3 H), 3.51 (d, *J*=15.0 Hz, 1 H), 3.62 (d, *J*=16.1 Hz, 1 H), 3.68 - 3.75 (m, 2 H), 3.83 - 3.94 (m, 4 H), 4.04 (ddd, *J*=11.6, 4.0, 1.5 Hz, 1 H), 4.64 (ddd, *J*=11.4, 8.8, 7.7 Hz, 1 H), 5.69 (ddd, *J*=16.0, 8.8, 4.2 Hz, 1 H), 6.46 (d, *J*=16.1 Hz, 1 H), 6.63 (d, *J*=2.0 Hz, 1 H), 6.99 - 7.03 (m, 1 H), 7.47 - 7.52 (m, 1 H), 8.00 (d, *J*=2.0 Hz, 1 H), 8.10 (s, 1 H), 8.72 (d, *J*=8.8 Hz, 1 H), 8.85 (s, 1 H), 11.41 (s, 1 H)
Example 3-2 Isomer 1	LC-MS (ESI+): 646.7 $[M+H]^+$, Rt = 4.54 min (Method 1) ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.05 (d, *J*=6.4 Hz, 3 H), 1.22 - 1.30 (m, 1 H), 1.36 (td, *J*=13.2, 7.2 Hz, 1 H), 1.40 - 1.51 (m, 2 H), 1.52 - 1.59 (m, 1 H), 1.59 - 1.67 (m, 1 H), 2.08 (dd, *J*=11.1, 7.2 Hz, 1 H), 2.68 (q, *J*=12.5 Hz, 1 H), 2.80 (dt, *J*=12.8, 6.1 Hz, 1 H), 3.02 (d, *J*=16.2 Hz, 1 H), 3.16 (d, *J*=15.6 Hz, 1 H), 3.25 - 3.30 (m, 1 H), 3.33 - 3.40 (m, 1 H), 3.50 (d, *J*=15.3 Hz, 1 H), 3.64 (d, *J*=15.9 Hz, 1 H), 3.70 (quin, *J*=6.4 Hz, 1 H), 3.78 (dt, *J*=13.4, 6.6 Hz, 1 H), 3.84 (d, *J*=13.4 Hz, 1 H), 3.94 - 4.00 (m, 2 H), 4.65 (ddd, *J*=11.6, 8.9, 7.6 Hz, 1 H), 5.70 (dt, *J*=16.0, 6.2 Hz, 1 H), 6.40 (d, *J*=16.2 Hz, 1 H), 6.50 (d, *J*=1.8 Hz, 1 H), 6.99 - 7.09 (m, 1 H), 7.45 - 7.52 (m, 1 H), 8.01 (d, *J*=2.1 Hz, 1 H), 8.12 (s, 1 H), 8.82 (d, *J*=8.9 Hz, 1 H), 8.84 (s, 1 H), 11.39 (br. s., 1 H)
Example 3-2	LC-MS (ESI+): 646.6 $[M+H]^+$, Rt = 4.55 min (Method 1)

Isomer 2	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.06 (d, J=6.4 Hz, 3 H), 1.25 - 1.32 (m, 2 H), 1.32 - 1.41 (m, 2 H), 1.58 (dt, J=12.4, 6.1 Hz, 1 H), 1.73 (dd, J=15.0, 7.6 Hz, 1 H), 2.05 (dd, J=11.3, 7.3 Hz, 1 H), 2.68 (q, J=12.8 Hz, 1 H), 2.75 (ddd, J=12.2, 7.1, 5.6 Hz, 1 H), 3.07 (d, J=8.2 Hz, 1 H), 3.10 (d, J=7.6 Hz, 1 H), 3.27 - 3.31 (m, 2 H), 3.50 (d, J=15.3 Hz, 1 H), 3.61 (d, J=16.5 Hz, 1 H), 3.70 (quin, J=5.9 Hz, 1 H), 3.79 - 3.86 (m, 2 H), 3.92 (dd, J=12.8, 9.2 Hz, 1 H), 4.01 (d, J=12.8 Hz, 1 H), 4.62 (ddd, J=11.3, 8.5, 7.0 Hz, 1 H), 5.75 (ddd, J=15.9, 9.1, 4.0 Hz, 1 H), 6.45 (d, J=16.2 Hz, 1 H), 6.69 (d, J=2.1 Hz, 1 H), 6.98 - 7.03 (m, 1 H), 7.49 (m, J=9.5, 9.5, 6.7, 3.1 Hz, 1 H), 7.99 (d, J=1.8 Hz, 1 H), 8.12 (s, 1 H), 8.77 (d, J=8.9 Hz, 1 H), 8.86 (s, 1 H), 11.40 (br. s., 1 H)
Example 3-2 Isomer 3	LC-MS(ES+): 646.4 $[M+H]^+$, Rt=3.88 min (Method 2) ^{1}H NMR (600 MHz, DMSO-d_6): δ ppm 0.91 (d, J = 6.6 Hz, 3 H), 1.29 - 1.62 (m, 6 H), 1.82 (d, J = 15.8 Hz, 1 H), 2.66 - 2.72 (m, 1 H), 2.86 - 2.94 (m, 1 H), 3.01 - 3.10 (m, 2 H), 3.27 - 3.31 (m, 2 H), 3.45 (d, J = 15.8 Hz, 1 H), 3.58 (d, J = 16.1 Hz, 1 H), 3.74 - 3.79 (m, 1 H), 3.90 - 3.97 (m, 2 H), 3.99 - 4.02 (m, 1 H), 4.09 - 4.16 (m, 1 H), 4.87 - 4.94 (m, 1 H), 5.81 - 5.89 (m, 1 H), 6.48 (d, J = 16.7 Hz, 1 H), 6.80 (d, J = 2.0 Hz, 1 H), 7.06 (br. s., 1 H), 7.47 - 7.52 (m, 1 H), 8.00 (d, J = 2.0 Hz, 1 H), 8.05 (s, 1 H), 8.74 (s, 1 H), 8.83 (d, J = 9.4 Hz, 1 H), 11.40 (s, 1 H)
Example 4-1 Isomer 1	LC-MS (ES+): 628.25 $[M+H]^+$, Rt = 4.47 min (Method 1) ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.03 (d, J=6.7 Hz, 3 H), 1.22 - 1.28 (m, 1 H), 1.36 (dt, J=13.4, 6.6 Hz, 1 H), 1.40 - 1.51 (m, 2 H), 1.52 - 1.60 (m, 1 H), 1.60 - 1.69 (m, 1 H), 2.04 - 2.11 (m, 1 H), 2.71 (q, J=12.6 Hz, 1 H), 2.80 (dt, J=13.1, 5.8 Hz, 1 H), 3.02 (d, J=16.2 Hz, 1 H), 3.16 (d, J=15.6 Hz, 1 H), 3.25 - 3.30 (m, 1 H), 3.34 - 3.41 (m, 1 H), 3.50 (d, J=15.6 Hz, 1 H), 3.64 (d, J=16.2 Hz, 1 H), 3.70 (quin, J=5.8 Hz, 1 H), 3.78 (q, J=6.7 Hz, 1 H), 3.83 (d, J=15.6 Hz, 1 H), 3.93 - 4.04 (m, 2 H), 4.66 (ddd, J=11.6, 8.9, 7.0 Hz, 1 H), 5.70 (dt, J=16.1, 6.0 Hz, 1 H), 6.40 (d, J=16.2 Hz, 1 H), 6.50 (d, J=2.1 Hz, 1 H), 7.12 (t, J=6.9 Hz, 1 H), 7.25 (td, J=7.9, 6.5 Hz, 1 H), 7.38 (q, J=8.5 Hz, 1 H), 8.02 (d, J=1.8 Hz, 1 H),

	8.13 (s, 1 H), 8.81 (d, *J*=9.2 Hz, 1 H), 8.85 (s, 1 H), 11.39 (s, 1 H)
Example 4-1 Isomer 2	LC-MS (ES+): 628.19 $[M+H]^+$, Rt = 4.42 min (Method 1) ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.04 (d, *J*=6.4 Hz, 3 H), 1.25 - 1.32 (m, 2 H), 1.32 - 1.40 (m, 2 H), 1.57 (dt, *J*=12.4, 6.1 Hz, 1 H), 1.75 (dt, *J*=15.6, 7.9 Hz, 1 H), 2.04 (dd, *J*=11.3, 7.6 Hz, 1 H), 2.67 - 2.73 (m, 1 H), 2.73 - 2.79 (m, 1 H), 3.07 (d, *J*=5.8 Hz, 1 H), 3.10 (d, *J*=4.9 Hz, 1 H), 3.27 - 3.31 (m, 2 H), 3.50 (d, *J*=15.3 Hz, 1 H), 3.61 (d, *J*=16.2 Hz, 1 H), 3.69 (quin, *J*=5.9 Hz, 1 H), 3.78 - 3.88 (m, 2 H), 3.92 (dd, *J*=12.8, 9.5 Hz, 1 H), 4.01 (ddd, *J*=13.0, 3.8, 1.0 Hz, 1 H), 4.63 (ddd, *J*=11.3, 8.5, 7.0 Hz, 1 H), 5.75 (ddd, *J*=15.9, 9.2, 4.3 Hz, 1 H), 6.46 (d, *J*=15.9 Hz, 1 H), 6.69 (d, *J*=1.8 Hz, 1 H), 7.09 (t, *J*=7.1 Hz, 1 H), 7.24 (td, *J*=7.6, 6.5 Hz, 1 H), 7.37 (q, *J*=8.5 Hz, 1 H), 7.99 (d, *J*=1.8 Hz, 1 H), 8.13 (s, 1 H), 8.76 (d, *J*=8.9 Hz, 1 H), 8.87 (s, 1 H), 11.41 (br. s., 1 H)
Example 4-2 Isomer 1	LC-MS (ES+): 630.63 $[M+H]^+$, Rt = 3.76 min (Method 1) ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 0.98 (d, *J*=6.4 Hz, 3 H), 2.09 (dd, *J*=10.0, 9.7 Hz, 1 H), 2.67 (q, *J*=12.6 Hz, 1 H), 2.85 (ddd, *J*=14.3, 8.6, 5.2 Hz, 1 H), 3.01 (d, *J*=16.0 Hz, 1 H), 3.16 (d, *J*=15.4 Hz, 1 H), 3.41 - 3.54 (m, 5 H), 3.62 - 3.68 (m, 2 H), 3.71 (quin, *J*=5.5 Hz, 1 H), 3.79 - 3.83 (m, 1 H), 3.82 - 3.88 (m, 1 H), 3.90 (s, 1 H), 3.96 - 4.03 (m, 2 H), 4.70 (dt, *J*=11.2, 8.8 Hz, 1 H), 5.65 (dt, *J*=16.2, 6.0 Hz, 1 H), 6.43 (d, *J*=16.3 Hz, 1 H), 6.49 (d, *J*=1.7 Hz, 1 H), 7.13 (t, *J*=6.8 Hz, 1 H), 7.25 (q, *J*=7.1 Hz, 1 H), 7.38 (q, *J*=8.3 Hz, 1 H), 8.02 (d, *J*=1.8 Hz, 1 H), 8.10 (s, 1 H), 8.72 (d, *J*=9.2 Hz, 1 H), 8.83 (s, 1 H), 11.40 (s, 1 H)
Example 4-2 Isomer 2	LC-MS (ES+): 630.62 $[M+H]^+$, Rt = 3.81 min (Method 1) ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 0.98 (d, *J*=6.6 Hz, 3 H), 2.05 (dd, *J*=11.6, 7.4 Hz, 1 H), 2.68 (q, *J*=12.6 Hz, 1 H), 2.82 (ddd, *J*=12.7, 8.4, 5.8 Hz, 1 H), 3.05 (d, *J*=10.1 Hz, 1 H), 3.08 (d, *J*=9.4 Hz, 1 H), 3.34 - 3.36 (m, 1 H), 3.40 - 3.48

	(m, 3 H), 3.51 (d, *J*=15.2 Hz, 1 H), 3.63 (d, *J*=16.1 Hz, 1 H), 3.68 - 3.74 (m, 2 H), 3.84 (ddd, *J*=14.5, 4.6, 2.2 Hz, 1 H), 3.86 - 3.95 (m, 3 H), 4.04 (ddd, *J*=11.7, 4.0, 1.7 Hz, 1 H), 4.66 (dt, *J*=11.4, 8.1 Hz, 1 H), 5.68 (ddd, *J*=16.0, 8.9, 4.2 Hz, 1 H), 6.46 (d, *J*=16.1 Hz, 1 H), 6.63 (d, *J*=1.8 Hz, 1 H), 7.09 (t, *J*=7.2 Hz, 1 H), 7.24 (td, *J*=7.6, 6.0 Hz, 1 H), 7.38 (q, *J*=8.4 Hz, 1 H), 8.00 (d, *J*=2.0 Hz, 1 H), 8.11 (s, 1 H), 8.71 (d, *J*=9.0 Hz, 1 H), 8.85 (s, 1 H), 11.41 (s, 1 H)
Example 5-1 Isomer 1	LC-MS (ES+): 632.21 $[M+H]^+$, Rt = 5.01 min (Method 1) ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 1.19 - 1.38 (m, 4 H), 1.59 - 1.70 (m, 2 H), 2.16 - 2.26 (m, 1 H), 2.61 - 2.68 (m, 1 H), 2.75 (q, *J* = 13.1 Hz, 1 H), 2.99 (d, *J* = 15.9 Hz, 1 H), 3.13 (d, *J* = 15.6 Hz, 1 H), 3.18 - 3.25 (m, 1 H), 3.25 - 3.30 (m, 1 H), 3.33 - 3.37 (m, 1 H), 3.49 (d, *J* = 15.6 Hz, 1 H), 3.63 (d, *J* = 15.9 Hz, 1 H), 3.68 (t, *J* = 11.6 Hz, 1 H), 3.75 - 3.84 (m, 1 H), 3.95 (ddd, *J* = 13.1, 4.3, 1.5 Hz, 1 H), 4.03 (dd, *J* = 13.7, 7.9 Hz, 1 H), 4.16 (td, *J* = 11.6, 3.7 Hz, 1 H), 4.55 - 4.67 (m, 1 H), 5.71 (ddd, *J* = 15.9, 7.9, 4.6 Hz, 1 H), 6.41 (d, *J* = 15.9 Hz, 1 H), 6.47 (d, *J* = 1.8 Hz, 1 H), 7.12 - 7.24 (m, 1 H), 7.41 - 7.53 (m, 1 H), 7.99 (d, *J* = 1.8 Hz, 1 H), 8.03 (s, 1 H), 8.75 (d, *J* = 7.9 Hz, 1 H), 8.76 (s, 1 H), 11.39 (s, 1 H)
Example 5-1 Isomer 2	LC-MS (ES+): 632.26 $[M+H]^+$, Rt = 5.05 min (Method 1) ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.14 - 1.24 (m, 1 H), 1.27 - 1.40 (m, 3 H), 1.52 - 1.62 (m, 2 H), 2.21 (m, *J*=9.6, 6.9, 2.2, 2.2 Hz, 1 H), 2.61 - 2.67 (m, 2 H), 3.01 (d, *J*=15.4 Hz, 1 H), 3.05 (d, *J*=16.3 Hz, 1 H), 3.18 (q, *J*=7.3 Hz, 1 H), 3.26 (ddd, *J*=11.6, 4.8, 1.7 Hz, 1 H), 3.35 (dt, *J*=8.4, 5.5 Hz, 1 H), 3.46 (d, *J*=15.2 Hz, 1 H), 3.59 (d, *J*=16.1 Hz, 1 H), 3.68 (t, *J*=11.6 Hz, 1 H), 3.78 (m, *J*=12.3, 12.3, 4.4, 3.0 Hz, 1 H), 3.91 (dd, *J*=13.5, 8.7 Hz, 1 H), 4.07 (ddd, *J*=12.8, 4.0, 2.0 Hz, 1 H), 4.14 (ddd, *J*=13.9, 10.8, 2.9 Hz, 1 H), 4.71 (ddd, *J*=11.7, 9.2, 7.2 Hz, 1 H), 5.78 (ddd, *J*=16.1, 8.8, 3.9 Hz, 1 H), 6.45 (d, *J*=16.5 Hz, 1 H), 6.72 (d, *J*=2.0 Hz, 1 H), 7.16 (m, *J*=9.7, 9.7, 3.7, 1.8 Hz, 1 H), 7.45 (qd, *J*=9.4, 4.9 Hz, 1 H), 7.98 (d, *J*=1.8 Hz, 2 H), 8.62 (d, *J*=9.2 Hz, 1 H), 8.71 (t, *J*=1.0 Hz, 1 H), 11.38 (s, 1 H)

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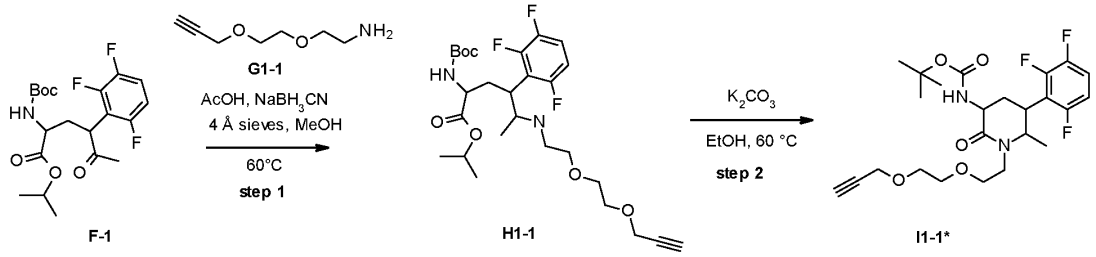
Example 5-1 Isomer 3	LC-MS(ES+): 632.40 $[M+H]^+$, Rt=3.67 min (Method 2) ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 1.15 - 1.21 (m, 1 H), 1.30 - 1.38 (m, 2 H), 1.39 - 1.45 (m, 1 H), 1.50 - 1.60 (m, 2 H), 1.99 (d, J = 13.7 Hz, 1 H), 2.59 - 2.67 (m, 2 H), 3.08 (d, J = 16.2 Hz, 2 H), 3.22 - 3.29 (m, 1 H), 3.34 - 3.39 (m, 1 H), 3.48 - 3.55 (m, 3 H), 3.59 (d, J = 16.5 Hz, 1 H), 3.87 - 3.94 (m, 1 H), 3.95 - 4.10 (m, 3 H), 4.83 - 4.94 (m, 1 H), 5.80 - 5.88 (m, 1 H), 6.46 (d, J = 16.2 Hz, 1 H), 6.82 (d, J = 1.8 Hz, 1 H), 7.14 - 7.21 (m, 1 H), 7.42 - 7.51 (m, 1 H), 8.00 (d, J = 1.8 Hz, 1 H), 8.06 (s, 1 H), 8.75 (s, 1 H), 8.92 (d, J = 9.2 Hz, 1 H), 11.41 (s, 1 H)
Example 7-1 Mixture of isomers	LC-MS (ES+): 648.24 $[M+H]^+$, Rt = 4.93, 5.10 min (Method 1) ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.12 (d, J=6.4 Hz, 3 H), 1.24 (d, J=6.1 Hz, 3 H), 2.09 - 2.15 (m, 2 H), 2.86 - 2.95 (m, 2 H), 3.04 (q, J=13.0 Hz, 1 H), 3.11 - 3.20 (m, 4 H), 3.36 - 3.41 (m, 1 H), 3.42 - 3.57 (m, 12 H), 3.59 - 3.68 (m, 4 H), 3.76 - 3.82 (m, 4 H), 3.82 - 3.94 (m, 3 H), 3.95 - 4.01 (m, 2 H), 4.01 - 4.08 (m, 2 H), 4.80 (td, J=11.2, 6.1 Hz, 1 H), 5.53 - 5.63 (m, 2 H), 6.42 (t, J=17.1 Hz, 2 H), 6.43 (d, J=1.8 Hz, 1 H), 6.47 (d, J=1.8 Hz, 1 H), 7.17 (t, J=9.1 Hz, 2 H), 7.48 (m, J=9.0, 9.0, 4.8, 4.8, 4.8, 4.8 Hz, 2 H), 7.98 (d, J=1.8 Hz, 1 H), 8.01 (d, J=1.8 Hz, 1 H), 8.05 (s, 1 H), 8.07 (s, 1 H), 8.61 (s, 1 H), 8.67 (s, 1 H), 8.81 (d, J=10.3 Hz, 1 H), 9.14 (d, J=7.2 Hz, 1 H), 11.33 - 11.44 (m, 2 H)
Example 8-1 Single isomer	LC-MS (ES+): 594.48 $[M+H]^+$, Rt = 5.05 min (Method 1) ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.88 (d, J=6.4 Hz, 3 H), 2.06 (dd, J=11.4, 6.9 Hz, 1 H), 2.69 (q, J=12.2 Hz, 1 H), 2.90 (ddd, J=13.6, 7.9, 6.0 Hz, 1 H), 3.14 (d, J=15.9 Hz, 1 H), 3.18 (d, J=16.5 Hz, 1 H), 3.41 - 3.50 (m, 4 H), 3.54 (d, J=15.3 Hz, 2 H), 3.58 (dd, J=14.0, 3.7 Hz, 1 H), 3.61 - 3.72 (m, 2 H), 3.79 (ddd, J=13.1, 8.2, 5.2 Hz, 1 H), 3.86 (td, J=8.6, 5.0 Hz, 1 H), 3.92 - 4.03 (m, 2 H), 4.81 (ddd, J=11.4, 10.7, 7.0 Hz, 1 H), 5.60 (dt, J=16.2, 6.0 Hz, 1 H), 6.41 (d, J=16.4 Hz, 1 H), 6.43 (d, J=2.1 Hz, 1 H), 7.24 - 7.29 (m, 3 H), 7.37 (t, J=7.6 Hz, 2 H), 8.01 (d, J=1.8 Hz, 1 H), 8.06 (s, 1

	H), 8.67 (s, 1 H), 8.81 (d, *J*=10.4 Hz, 1 H), 11.38 - 11.41 (m, 1 H)
Example 8-2 Single isomer	LC-MS (ESI+): 592.24 $[M+H]^+$, Rt = 5.02 min (Method 1) ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 0.92 (d, *J*=6.6 Hz, 3 H), 1.18 - 1.31 (m, 1 H), 1.37 (s, 1 H), 1.48 - 1.58 (m, 3 H), 1.58 - 1.63 (m, 1 H), 2.06 (dd, *J*=11.0, 7.0 Hz, 1 H), 2.72 (q, *J*=12.1 Hz, 1 H), 2.87 (dt, *J*=13.2, 6.8 Hz, 1 H), 3.16 (d, *J*=16.0 Hz, 1 H), 3.19 (d, *J*=16.5 Hz, 1 H), 3.28 (td, *J*=8.6, 4.8 Hz, 1 H), 3.35 - 3.38 (m, 1 H), 3.53 (d, *J*=16.0 Hz, 2 H), 3.57 (ddd, *J*=14.3, 4.4, 2.2 Hz, 1 H), 3.61 (q, *J*=6.2 Hz, 1 H), 3.68 (quin, *J*=6.1 Hz, 1 H), 3.95 (ddd, *J*=12.8, 5.5, 1.3 Hz, 1 H), 3.99 (ddd, *J*=13.6, 6.2, 1.8 Hz, 1 H), 4.81 (ddd, *J*=12.1, 10.2, 6.7 Hz, 1 H), 5.66 (dt, *J*=16.1, 5.9 Hz, 1 H), 6.37 (dt, *J*=16.1, 1.0 Hz, 1 H), 6.46 (d, *J*=2.0 Hz, 1 H), 7.26 (t, *J*=7.3 Hz, 1 H), 7.27 (d, *J*=7.3 Hz, 2 H), 7.37 (t, *J*=7.4 Hz, 2 H), 8.02 (d, *J*=2.0 Hz, 1 H), 8.06 (s, 1 H), 8.68 (s, 1 H), 8.88 (d, *J*=10.1 Hz, 1 H), 11.33 - 11.44 (m, 1 H)
Example 9-1 Mixture of diastereomers	LC-MS (ESI+): 594.04 $[M+H]^+$, Rt = 5.04, 5.08 min (Method 1) ^{1}H NMR (500 MHz, DMSO-d$_6$): δ ppm 0.90 (d, *J*=6.4 Hz, 3 H), 2.01 - 2.07 (m, 1 H), 2.55 - 2.64 (m, 1 H), 2.77 - 2.84 (m, 1 H), 2.98 (d, *J*=15.0 Hz, 1 H), 3.05 (d, *J*=15.6 Hz, 1 H), 3.30 (br. s., 1 H), 3.39 - 3.56 (m, 6 H), 3.65 - 3.75 (m, 2 H), 3.83 - 3.92 (m, 3 H), 4.00 - 4.05 (m, 1 H), 4.60 - 4.69 (m, 1 H), 5.58 - 5.66 (m, 1 H), 6.45 (d, J = 16.2 Hz, 1 H), 6.65 (d, *J*=2.1 Hz, 1 H), 7.23 - 7.27 (m, 3 H), 7.34 - 7.36 (m, 2 H), 7.45 (d, *J*=7.9 Hz, 1 H), 7.78 (d, *J*=7.9 Hz, 1 H), 7.80 (s, 1 H), 7.98 (d, *J*=1.8 Hz, 1 H), 8.48 (d, *J*=8.9 Hz, 1 H), 11.35 (br. s., 1 H)

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Scheme 3. Synthesis of Intermediate I1-1*



Experimental procedure of synthesis of Intermediate I1-1*

Step 1. Synthesis of isopropyl 2-(*tert*-butoxycarbonylamino)-5-[2-(2-prop-2-ynoxyethoxy)ethylamino]-4-(2,3,6-trifluorophenyl)hexanoate (H1-1)

To compound **F-1 (**CAS 1488326-89-1) (1.75 g, 4.19 mmol), a solution of compound **G1-1** (1.98 g, 9.16 mmol) in dry MeOH (17.8 mL), activated 4Å molecular powdered sieves (3.6 g), glacial acetic acid (240 µL, 4.19 mmol), and $NaCNBH_3$ (144 mg, 9.17 mmol) were added. The mixture was heated at 60°C overnight. The reaction mixture was filtered through a pad of Celite and the filtrate concentrated to yield m=4.42 g of the crude material. This crude product was dissolved in EtOAc (20 mL) and sat. $NaHCO_3$ (80 mL). The organic layer was separated, and the aq. layer extracted with EtOAc (3×15 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated to yield the desired product **H1-1** (m=2.317 g) as a yellowish oil.

LC-MS (ES+): 545.3 $[M+H]^+$.

Step 2. Synthesis of *tert*-butyl N-[6-methyl-2-oxo-1-[2-(2-prop-2-ynoxyethoxy)ethyl]-5-(2,3,6-trifluorophenyl)-3-piperidyl]carbamate (I1-1*)

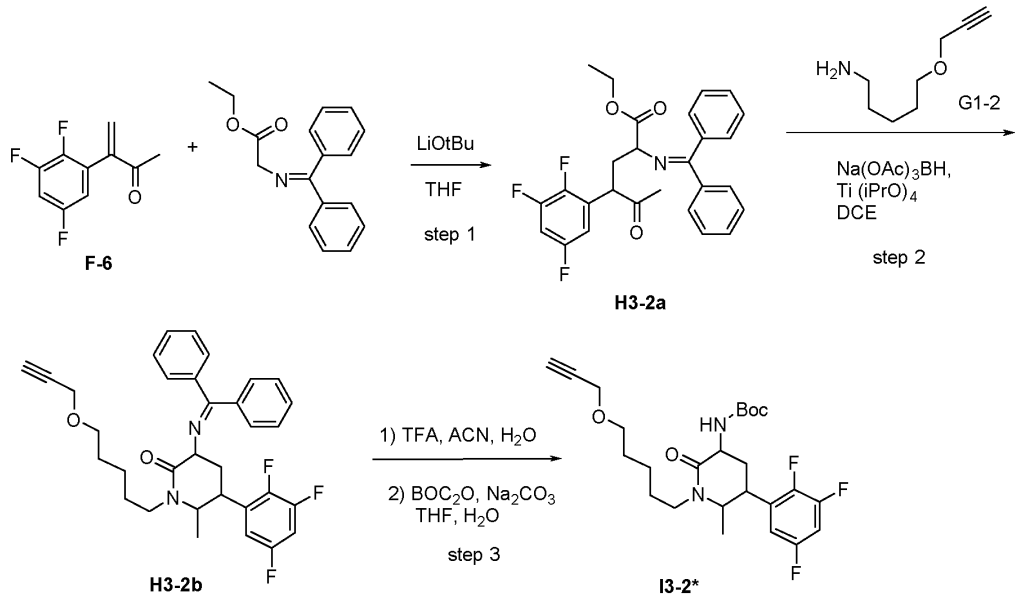
Into a solution of compound **H1-1** (2.317 g, 4.25 mmol) in EtOH (65 mL), K_2CO_3 (1.94 g, 14 mmol) was added and the reaction mixture heated at 60°C overnight. The mixture was concentrated and the residue dissolved in DCM (40 mL) and water (200 mL). The layers were separated, and the aqueous layer extracted with DCM (3 × 15 mL). The combined organic layer was dried and concentrated to give crude product (1.798 g). The crude material was loaded and purified on a silica column (Interchim 80 g, 15 µm, SiO_2) using Interchim PuriFlash 450 instrument with a flowrate of 30 mL/min starting with DCM (100%) and going to 40% DCM/MeOH (40/1) in 15 CVs.

Hold 40% DCM/MeOH (40/1) for 15 CVs and increasing to 60% DCM/MeOH (40/1) in 10 CVs. The relevant fractions were collected, the solvent removed as appropriate to yield **I1-1*** (445 mg, 22.3%).

LC-MS (ES+): 485.2 $[M+H]^+$.

Intermediates I1-1, I1-2*, I1-3*, I1-4*, I1-5*, I1-6*, I1-7*, I1-7, I2-2, I3-1* were synthesized using the same experimental procedures as for the synthesis of Intermediate I1-1* and starting from Intermediates GX-n and F-X as stated in Table 4.

Scheme 4. Synthesis of Intermediate I3-2*



Experimental procedure of synthesis of Intermediate I3-2*

Step 1. Synthesis of ethyl 2-(benzhydrylideneamino)-5-oxo-4-(2,3,5-trifluorophenyl)hexanoate (H3-2a)

3-(2,3,5-trifluorophenyl)but-3-en-2-one **F-6** (2.00 g, 9.99 mmol) was dissolved in THF (12 mL), ethyl N-(diphenylmethylene)glycinate (2671 mg, 9.99 mmol) was added, the reaction mixture was purged with nitrogen and cooled down to 0°C. Then LiOtBu (881 mg, 11.0 mmol) was added portionwise and the reaction mixture was stirred at 0-10°C for 3 hours. Reaction was quenched with cold water (10 mL) and extracted

with MTBE (2x 40 mL). Organics collected and washed with brine, dried and concentrated to give crude (4.7 g) that was purified by chromatography on an Interchim cartridge 40 g using EtOAc in cyclohexane 0-30% 20CV to give ethyl 2-(benzhydrylideneamino)-5-oxo-4-(2,3,5-trifluorophenyl)hexanoate **H3-2a** (3.2 g, 57%) that was used in the next step as is.

LC-MS (ESI+): 468.5 $[M+H]^+$.

Step 2. Synthesis of 3-(benzhydrylideneamino)-6-methyl-1-(5-prop-2-ynoxypentyl)-5-(2,3,5-trifluorophenyl)piperidin-2-one, (H3-2b)

H3-2a (2.780 g, 5.947 mmol) was dissolved in DCE (50 mL). The reaction mixture was cooled down to 0°C and **G1-2** (1602 mg, 9.019 mmol) was added followed by triethylamine (994.6 µL, 7.136 mmol) and titanium(IV) isopropoxide (2289 µL, 7.731 mmol). The reaction mixture was heated at 45°C for 3 hours the reaction mixture was cooled down to 0°C and $Na(OAc)_3BH$ (4149 mg, 19.58 mmol) was added. The reaction mixture was heated at 40°C for 3 hours then an additional amount of DCE (15 mL) and the reaction mixture was heated at 40°C overnight. Reaction was quenched with brine (40 mL), the reaction mixture was filtered then filtrate was extracted with DCM (4x 35 mL), organic layers were collected, washed with sat. $NaHCO_3$ (1x30mL) dried and concentrated to give crude 3-(benzhydrylideneamino)-6-methyl-1-(5-prop-2-ynoxypentyl)-5-(2,3,5-trifluorophenyl)piperidin-2-one **H3-2b** (3.67 g, 100%) used as is.

LC-MS (ESI+): 547.7 $[M+H]^+$.

Step 3. Synthesis of *tert*-butyl N-[6-methyl-2-oxo-1-(5-prop-2-ynoxypentyl)-5-(2,3,5-trifluorophenyl)-3-piperidyl]carbamate (I3-2*)

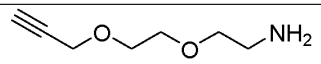
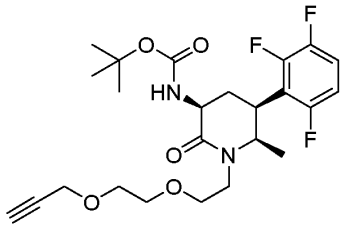
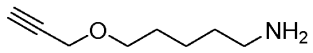
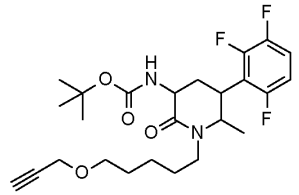
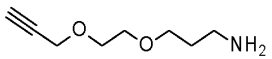
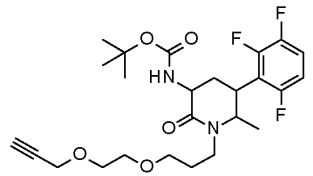
H3-2b (3.67 g, 6.71 mmol) was dissolved in ACN/water (24.5/ 12.2 mL). After that TFA (1028 µL, 13.4 mmol) was added and the reaction mixture was stirred at rt until full deprotection, then THF (10.2 mL) and water (5.45 mL) were added into the reaction mixture, followed by Na_2CO_3 (2137 mg, 20.2 mmol) and Boc_2O (2200 mg, 10.1 mmol) and the reaction mixture was stirred for 2 hours then stored in the fridge. The reaction mixture was filtered through a pad of Celite, filtrate was diluted with DCM and water, layers were separated, aq. layer was extracted with DCM (2x30 mL). Organics collected, dried and concentrated to give crude (6.0 g) that was

divided on two Interchim columns 40 g 25 µm, and purified using EtOAc in cyclohexane 0% 3CV, 0-50 % 30CV to give *tert*-butyl N-[6-methyl-2-oxo-1-(5-prop-2-ynoxypentyl)-5-(2,3,5-trifluorophenyl)-3-piperidyl]carbamate **I3-2*** (520 mg, 16%).

LC-MS (ESI+): 483.6 $[M+H]^+$.

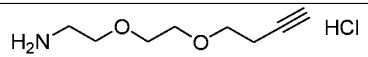
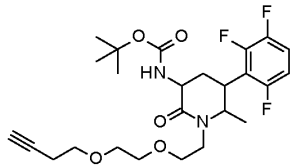
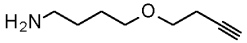
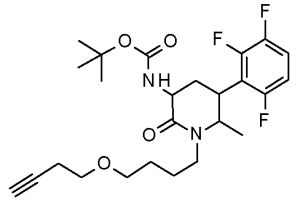
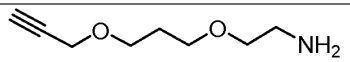
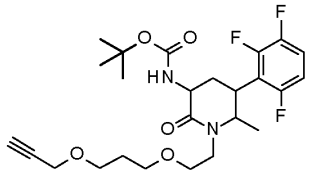
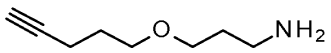
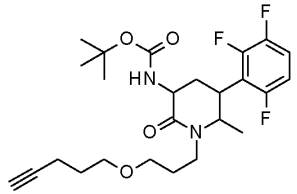
Intermediates I4-1*, I4-2* and I3-1* were synthesized using the same experimental procedures as for the synthesis of Intermediate I3-2* with building blocks as detailed in table 4.

Table 4. Structures and quantities of Intermediates for Scheme 3 and 4

Starting material				Products		
Intermediate 1 / Q	**Structure**	**Intermediate 2/ Q**	**Route**	**Intermediate 3/ Q**	**Structure**	**Analytical Data**
G1-1 20.8g	 CAS 944561-44-8	F-1 20g	Scheme 3 then SFC chiral separation of I1-1*	I1-1 3.44g		485.2 $[M+H]^+$ SFC 1.59min
G1-2 1.52 g	 CAS 2411548-12-2	F-1 1.35 g	Scheme 3	I1-2* 732 mg		483.5 $[M+H]^+$
G1-3 0.97 g		F-1 1.17 g	Scheme 3	I1-3* 635 mg		499.0 $[M+H]^+$

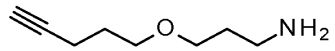
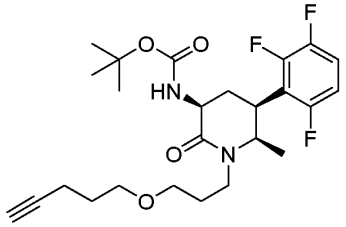
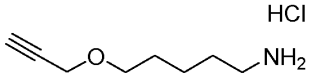
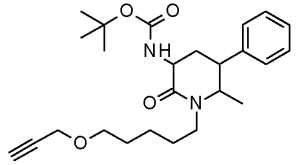
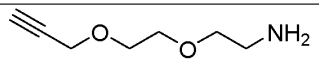
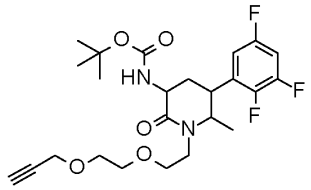
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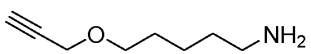
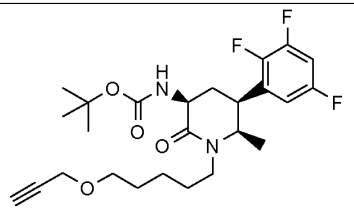
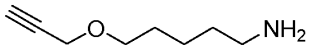
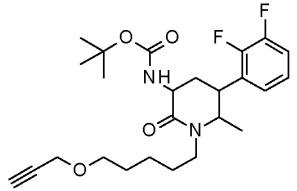
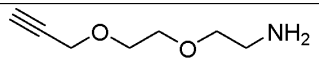
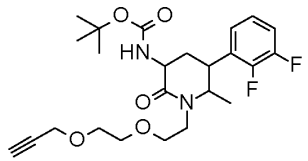
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G1-4 662 mg		F-1 600 mg	Scheme 3	I1-4* 324 mg		499.1 $[M+H]^+$
G1-5 406 mg	 CAS 1858472-14-6 US20190192668	F-1 600 mg	Scheme 3	I1-5* 333 mg		483.1 $[M+H]^+$
G1-6 571.0 mg		F-1 600.0 mg	Scheme 3	I1-6* 355.2 mg		499.1 $[M+H]^+$
G1-7 650 mg	 CAS 1564790-72-2	F-1 960 mg	Scheme 3	I1-7* 553 mg		483.1 $[M+H]^+$

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G1-7 15g	 CAS 1564790-72-2	F-1 18g	Scheme 3 then SFC chiral separation of I1-7*	I1-1 1.93g		483.1 $[M+H]^+$ SFC 1.52min
G1-2 482 mg	 CAS 2411548-12-2	F-3 649 mg CAS 1456803-33-0	Scheme 3	I2-2* 373 mg		429.9 $[M+H]^+$
G1-1 13.5g	 CAS 944561-44-8	F-6 12g	Scheme 4	I3-1* 650 mg		485 [M+H]+

G1-2 16.5g	HCl  CAS 2411548-12-2	F-5 20.5g	Scheme 3 then SFC chiral separation of I3-2*	I3-2 3.32g		483.6 $[M+H]^+$ SFC 1.56min
G1-2 11g	HCl  CAS 2411548-12-2	F-7 15g	Scheme 4	I4-1* 860 mg		465.3 $[M+H]^+$
G1-1 2.34 g	 CAS 944561-44-8	F-7 5.0g	Scheme 4	I4-2* 1.0 g		467.6 $[M+H]^+$

SFC preparative methods for I1-1, I1-7 and I3-2

Instrument: Sepiatec Prep SFC 100 with Prep SFC 100 control software and UV/Vis detector.

Solvents: Primary mobile phase = CO_2

I1-1

Column: Phenomenex Lux Amylose-1, 5 µm, 250 x 21.2 mm at 40°C.

UV monitoring: 210nm

Flow: 50ml/min. Modifier: 20% MeOH with 0.2% NH_3.

I1-7

Column: Phenomenex Lux Amylose-1, 5 µm, 250 x 21.2 mm at 40°C.

UV monitoring: 210nm

Flow: 50ml/min. Modifier: 30% MeOH.

I3-2

Column: Phenomenex Lux Amylose-1, 5 µm, 250 x 21.2 mm at 40°C.

UV monitoring: 210nm

Flow: 50ml/min. Modifier: 30% MeOH.

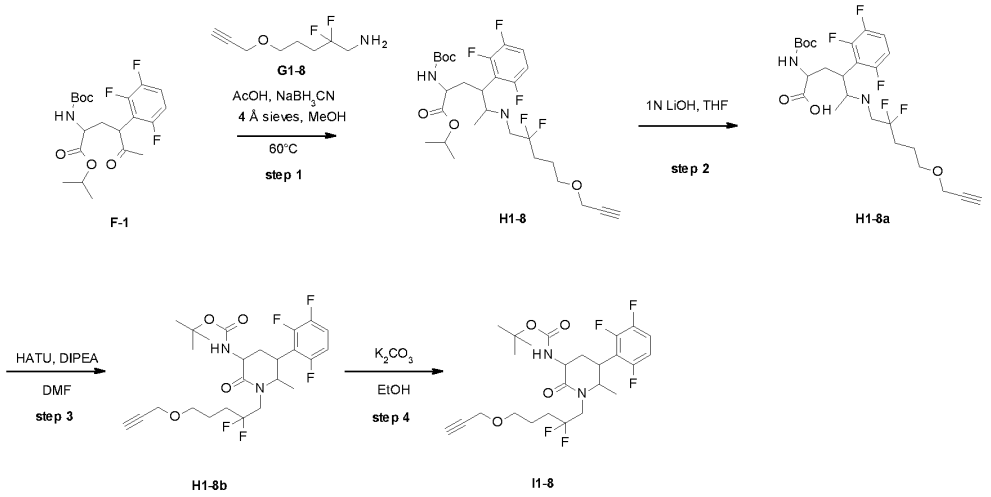
Analytical SFC method for I1-1, I1-7 and I3-2

Instrument: Waters Acquity UPC2 with Masslynx software, PDA detector and a QDa mass detector.

Column: Phenomenex Lux Amylose-1, 3µm, 50 x 2 mm, 45 °C., 1.5ml/min

Solvents: Primary mobile phase = CO_2 with MeOH modifier

Scheme 5. Synthesis of Intermediate I1-8*



Experimental procedure of synthesis of Intermediate I1-8*

Step 1. Synthesis of isopropyl 2-(*tert*-butoxycarbonylamino)-5-[(2,2-difluoro-5-prop-2-ynoxy-pentyl)amino]-4-(2,3,6-trifluorophenyl)hexanoate (H1-8)

Same procedure as for step 1 in synthesis of **Intermediate I1-1***, starting from compound **F-1** (CAS 1488326-89-1) (855 mg, 2.05 mmol) and compound **G1-8** (726 mg, 4.10 mmol). The desired crude product **H1-8** (m=1.46 g) was obtained as a yellow oil.

LC-MS (ES+): 579.1 $[M+H]^+$.

Step 2.Synthesis 2-(*tert*-butoxycarbonylamino)-5-[(2,2-difluoro-5-prop-2-ynoxy-pentyl)amino]-4-(2,3,6-trifluorophenyl)hexanoic acid (H1-8a)

Same procedure as step 3 in synthesis of **Example 1-1**, starting with **H1-8** ((1.1 g, 1.90 mmol). The desired product **H1-8a** (546 mg, 87 %) was obtained and used as is in the next reaction step.

LC-MS (ES+): 537.0 $[M+H]^+$.

Step 3. Synthesis *tert*-butyl N-[1-(2,2-difluoro-5-prop-2-ynoxy-pentyl)-6-methyl-2-oxo-5-(2,3,6-trifluorophenyl)-3-piperidyl]carbamate (H1-8b*)

Same procedure as step 5 in synthesis of **Example 1-1**, starting with **H1-8a** (504 mg, 0.940 mmol). The crude product **H1-8b*** (426 mg) was obtained as a sticky light orange solid.

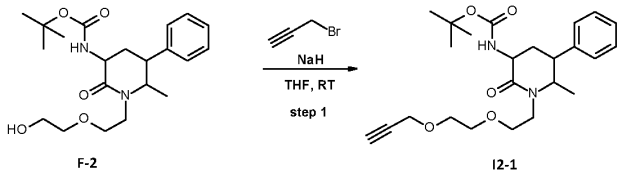
LC-MS (ES+): 519.1 $[M+H]^+$.

Step 4. Synthesis *tert*-butyl (1-(2,2-difluoro-5-prop-2-ynoxy-pentyl)-6-methyl-2-oxo-5-(2,3,6-trifluorophenyl)-3-piperidyl)carbamate (I1-8*)

Same procedure as step 2 in the synthesis of **Intermediate I1-1*** starting from **H1-8b*** (426 mg, 0.822 mmol). Desired product **I1-8*** was obtained (247 mg, 58%).

LC-MS (ES+): 519.0 $[M+H]^+$.

Scheme 6. Synthesis of Intermediate I2-1



F-2 I2-1

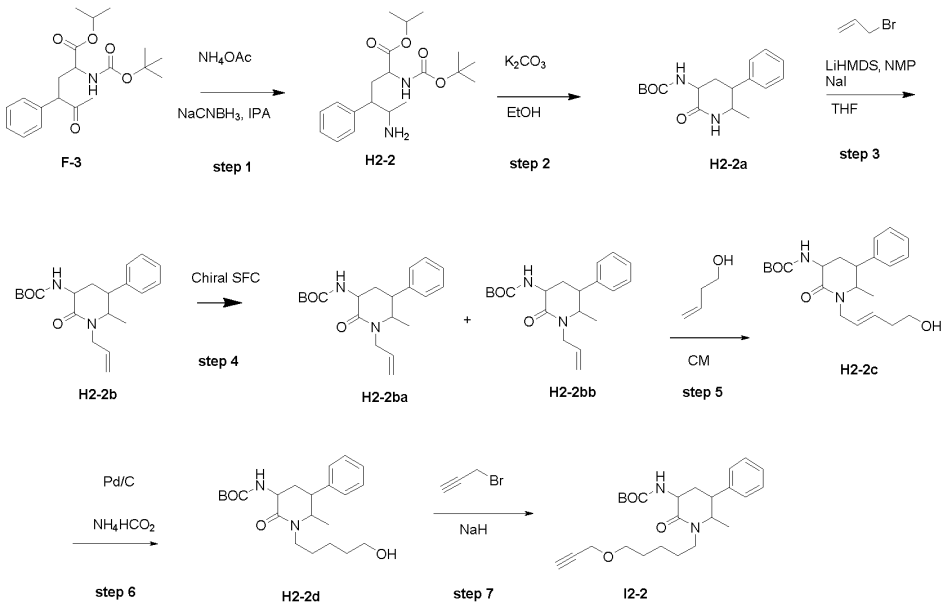
Experimental procedure of synthesis of Intermediate I2-1

Step 1. Synthesis of *tert*- butyl N-[6-methyl-2-oxo-5-phenyl-1-[2-(2-prop-2-ynoxyethoxy)ethyl]-3-piperidyl]carbamate (I2-1)

To the ice cooled solution of **F-2** (658 mg, 1.67 mmol) in THF (8 mL), under argon, NaH (60% suspension in mineral oil, 74.3 mg, 1.86 mmol) was added portionwise. The resulted mixture was stirred at 0 C for 15 minutes upon which compound propargyl bromide (80% in toluene, 186 µL, 2.61 mmol) was added dropwise during 5 min. Stirring was continued at 0 °C for 5 minutes then at room temperature overnight. The reaction mixture was quenched with *sat* NH_4Cl (40 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford crude product (723 mg). The crude material was loaded and purified on a silica column (Interchim 12 g, 15 µm, SiO_2) using Interchim PuriFlash 450 instrument with a flow of 20 mL/min starting with cyclohexane (100%) and going to 100% EtOAc in 20 CVs. Hold 100% EtOAc for 5 CVs The appropriate fractions were collected, the solvent removed to yield **I2-1** (472 mg, 65.6%).

LC-MS (ES+): 431.8 $[M+H]^+$.

Scheme 7. Synthesis of Intermediate I2-2



Experimental procedures of synthesis of Intermediate I2-2

Step 1. Synthesis of isopropyl 5-amino-2-((tert-butoxycarbonyl)amino)-4-phenylhexanoate (H2-2)

To a stirred solution of isopropyl 2-((*tert*-butoxycarbonyl)amino)-5-oxo-4-phenylhexanoate, **F-3** (CAS 1456803-33-0) (40 g, 110.19 mmol), NH_4OAc (84.84 g, 1.1mol) and 4Å molecular sieves (40 g) in IPA (1000 mL) at RT was added $NaCNBH_3$ (10.38 g, 165.28 mmol) and the resultant reaction mixture was stirred at RT for 12 h. The reaction mixture was filtered through Celite, and the filtrate was evaporated and diluted with 10% $NaHCO_3$ (aq) solution, extracted with 10% MeOH in DCM, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude compound was purified by flash column chromatography using silica gel (230-400 mesh) and compound was eluted with 0-5% MeOH in DCM gradient to afford isopropyl 5-amino-2-((*tert*-butoxycarbonyl)amino)-4-phenylhexanoate **H2-2** (20g, 49%).

LC-MS (ESI+): 365.3 $[M+H]^+$.

Step 2. Synthesis of tert-butyl (6-methyl-2-oxo-5-phenylpiperidin-3-yl)carbamate (H2-2a)

To a stirred solution of isopropyl 5-amino-2-((*tert*-butoxycarbonyl)amino)-4-phenylhexanoate **H2-2** (20 g, 54.94 mmol) in EtOH (500 mL) was added K_2CO_3 (15.16 g, 109.89 mmol) at RT. The reaction mixture was stirred at 80°C for 1 h and the reaction mixture was filtered through Celite. The filtrate was evaporated and diluted with water, extracted with EtOAc, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to obtain crude compound. The crude compound was purified by flash column chromatography using silica gel (230-400 mesh) and compound was eluted with 0-30% EtOAc in petroleum-ether gradient to afford *tert*-butyl (6-methyl-2-oxo-5-phenylpiperidin-3-yl)carbamate **H2-2a** (13g, 77.8%).

LC-MS (ESI+): 249.2 $[M+H-tBu]^+$

Step 3. Synthesis of tert-butyl (1-allyl-6-methyl-2-oxo-5-phenylpiperidin-3-yl)carbamate (H2-2b)

To a stirred solution of *tert*-butyl (6-methyl-2-oxo-5-phenylpiperidin-3-yl)carbamate **H2-2a** (8 g, 26.31 mmol) in THF: NMP (2:1) (100 ml) was dropwise added LiHMDS (28.94 ml, 28.94 mmol). The reaction mixture was allowed to stir and after 15 min allyl bromide (15.91 g, 131.55 mmol) and NaI (3.94 g, 26.31 mmol) were added. The resulting mixture was stirred at 0°C for 2 h and then warmed to RT for an additional 18 h.The reaction mixture was diluted with water and extracted with EtOAc (2 x 500 mL), dried over anhydrous Na_2SO_4, concentrated to obtain crude compound, which was purified by flash column chromatography using silica gel (230-400 mesh) and compound was eluted with 0-20% EtOAc in petroleum-ether gradient to afford *tert*-butyl (1-allyl-6-methyl-2-oxo-5-phenylpiperidin-3-yl)carbamate **H2-2b** (7g, 77.34%).

LC-MS (ESI+): 344.5 $[M+H]^+$.

Step 4 Preparative Chiral SFC:

Instrument: PICLab PREP 100
Solvents: Primary mobile phase = CO_2 Modifier: 30% MeOH
Column: YMC Cellulose-SC 5um, 250x30mm, at 35°C. UV monitoring: 210nm
Flow: 80g/min.

Product fractions combined and evaporated to give cis isomers 1.45g **H2-2ba** Isomer 1 and 1.18g **H2-2b** Isomer 2.

Step 5. Synthesis of tert-butyl (E)-(1-(5-hydroxypent-2-en-1-yl)-6-methyl-2-oxo-5-phenylpiperidin-3-yl)carbamate (H2-2c)

tert-butyl (1-allyl-6-methyl-2-oxo-5-phenylpiperidin-3-yl)carbamate **H2-2ba** (1.0g, 2.90 mmol) is dissolved in DCM (18.5 mL), reaction mixture was purged with argon then but-3-en-1-ol (628 mg, 8.71 mmol) was added followed by Ti(iPrO)4 (0.258 mL, 0.871 mmol) and the reaction mixture was stirred for 30 minutes at room temperature. Then Hoveyda-Grubbs 2nd gen (182 mg, 0.290 mmol) was added and RM was stirred rt, overnight (green colour was changed to red). RM was diluted with DCM (15 mL), sat $NaHCO_3$ was added (10 mL), layers were separated, aqueous layer was extracted with DCM, organics collected, dried and concentrated to get crude product that was purified by column chromatography (normal phase [Interchim cartridge 25 g, 25 µm, using DCM/MeOH = 90/10 in DCM, 0-40%, 20CV, 40-80% 20 CV, 100% 3CV, 10 mL/min flow rate]), to get tert-butyl (E)-(1-(5-hydroxypent-2-en-1-yl)-6-methyl-2-oxo-5-phenylpiperidin-3-yl)carbamate **H2-2c** (520 mg, 46%) that was used in next step as is.

LC-MS (ESI+): 389.3 $[M+H]^+$.

Step 6. Synthesis of *tert*-butyl (1-(5-hydroxypentyl)-6-methyl-2-oxo-5-phenylpiperidin-3-yl)carbamate, H2-2d

H2-2c (168 mg, 0.43 mmol) was dissolved in EtOH (6 mL) in a vial, the reaction mixture was purged with argon then Pd/C (16 mg) was added followed by ammonium formate (189 mg, 3 mmol) and the reaction mixture was heated at 70°C for 2 hours. The reaction mixture was filtered through a pad of Celite, filtrate was concentrated to give crude. Crude was purified by column chromatography (normal phase [Biotage, Interchim cartridge 12 g, 25 um, 0-50%, 10CV, 50-100% 20 CV, 100% 3CV, 10 mL/min flow rate DCM/MeOH= 9/1 in DCM, 20 mL/min flow rate]) to give tert-butyl (1-(5-hydroxypentyl)-6-methyl-2-oxo-5-phenylpiperidin-3-yl)carbamate **H2-2d** (123 mg, 74 %).

LC-MS (ESI+): 391.3 $[M+H]^+$.

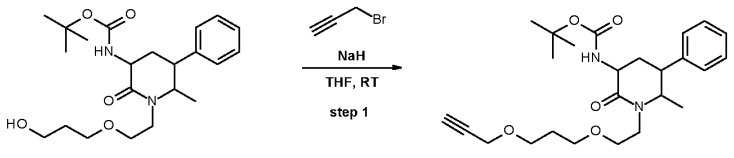
1H NMR (600MHz, DMSO-d_6): δ/ppm: = 0.81 (d, *J*=6.5 Hz, 3 H), 1.24 - 1.32 (m, 2H), 1.41 - 1.51 (m, 3H), 1.55 - 1.64 (m, 1H), 1.94 - 2.00 (m, 1H), 2.32 - 2.42 (m, 1H), 2.71 - 2.79 (m, 1H), 3.38 - 3.44 (m, 3H), 3.58 – 3.64 (m, 1H), 3.64 - 3.72 (m, 1H), 3.95 – 4.02 (m, 1H), 4.37 (t, *J*=5.0 Hz, 1H), 7.03 (d, *J*=4.9 Hz, 1H), 7.21 – 7.27 (m, 3H), 7.34 (t, *J*=8.7 Hz, 2H).

Step 7 Synthesis of tert-butyl (6-methyl-2-oxo-5-phenyl-1-(5-(prop-2-yn-1-yloxy)pentyl)piperidin-3-yl)carbamate, I2-2.

H2-2d (420 mg, 1.08 mmol) was dissolved in THF (3.4 mL), the reaction mixture was cooled down to 0°C and purged with argon, then NaH (60.0 %, 55.9 mg, 1.40 mmol), was added portion wise, the reaction mixture was stirred for 10 minutes then propargyl bromide (80.0 %, 0.144 mL, 1.29 mmol) was added and the reaction mixture was stirred overnight at rt. The reaction mixture was quenched with sat. Aq NH_4Cl (5 mL) and EtOAc (15 mL), layers were separated, aqueous layer was extracted with EtOAc (2x 10 mL), organics collected, dried and concentrated to give crude. Crude was purified by column chromatography (normal phase [Interchim cartridge, 25 g, 25 µm, eluting with DCM/MeOH=9/1 in MeOH 0-50%, 30CV, 50% 3CV, 20 mL/min flow rate]) to give tert-butyl (6-methyl-2-oxo-5-phenyl-1-(5-(prop-2-yn-1-yloxy)pentyl)piperidin-3-yl)carbamate, **I2-2.** (250 mg, 54%).

LC-MS (ESI+): 429.2 $[M+H]^+$.

Scheme 8. Synthesis of Intermediate I2-3



F-4 I2-3

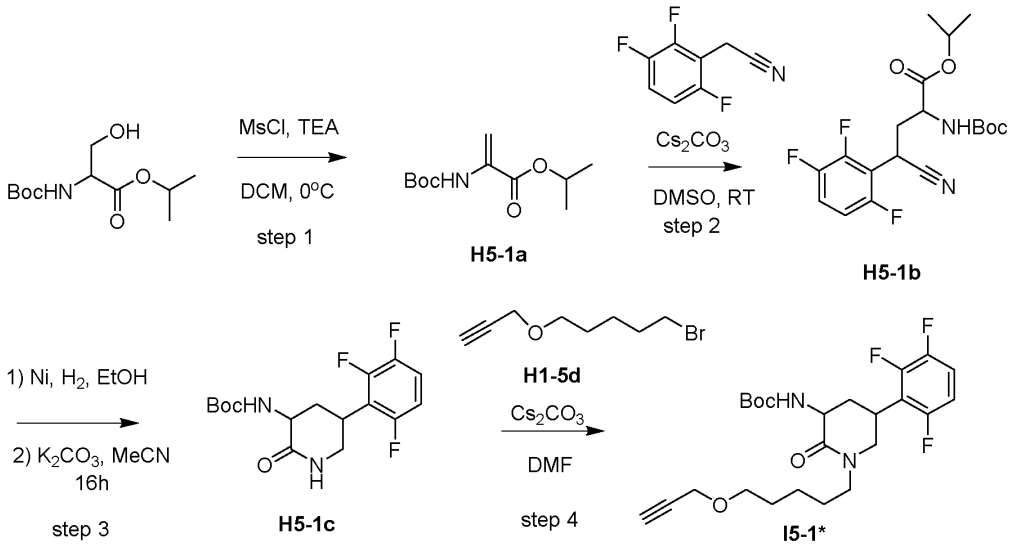
Experimental procedure of synthesis of Intermediate I2-3

Step 1. Synthesis of *tert*-butyl N-[6-methyl-2-oxo-5-phenyl-1-[2-(3-prop-2-ynoxypropoxy)ethyl]-3-piperidyl]carbamate (I2-3)

Same procedure as synthesis of Intermediate **I2-1** starting from **F-4** (412.6 mg, 1.015 mmol). Desired product **I2-3** was obtained (171.8 mg, 38.1%).

LC-MS (ES+): 445.1 $[M+H]^+$.

Scheme 9. Synthesis of intermediates I5-1* and I5-1



Experimental procedure for synthesis of Intermediates I5-1* and I5-1

Step 1 Synthesis of isopropyl 2-((tert-butoxycarbonyl)amino)acrylate H5-1a

To a stirred solution of isopropyl (tert-butoxycarbonyl)serinate (50 g, 202.4 mmol) and TEA (84 mL, 607 mmol) in DCM (500 mL) at 0 °C was added methane sulfonyl chloride (23.38 mL, 303.3 mmol) dropwise and the resultant the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was quenched with ice water (200 mL) and extracted with DCM (300 mL). Organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtained crude material, which was purified by Biotage-Isolera using silica snap (230-400 mesh) and eluted with (0-10 %) EtOAc in petroleum-ether gradient to afford isopropyl 2-((tert-butoxycarbonyl)amino)acrylate **H5-1a** as a colourless gum (45g, 96%).

^{1}H NMR (400MHz, DMSO-d6) δ: 8.36 (s, 1H), 5.60 (s, 1H), 5.46 (s, 1H), 5.0 – 4.94 (m, 1H), 1.42 (s, 9H), 1.24 (d, J= 6.4 Hz, 6H)

Step 2 Synthesis of isopropyl 2-((tert-butoxycarbonyl)amino)-4-cyano-4-(2,3,6-trifluorophenyl)butanoate H5-1b

To a stirred solution of 2-(2,3,6-trifluorophenyl)acetonitrile (CAS 114152-21-5) (40 g, 233.91 mmol) and isopropyl 2-((tert-butoxycarbonyl)amino)acrylate **H5-1a** (53.56 g, 233.91 mmol) in DMSO (800 mL) at 0 °C was added Cs_2CO_3 (38.01 g, 116.95 mmol) portion wise and the resultant the reaction mixture was stirred at the same temperature for 10 min. After the completion of starting material, monitored by TLC, the reaction mixture was diluted with EtOAc (1 L) and washed with water (3x500 mL). Organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude mass. The crude compound was purified by flash column chromatography using silica gel (230-400 mesh) and eluted with (0-10%) EtOAc in petroleum-ether gradient to afford isopropyl 2-((tert-butoxycarbonyl)amino)-4-cyano-4-(2,3,6-trifluorophenyl)butanoate **H5-1b** as an off-white solid (85g, 90%).

LC-MS (ESI+): 300.9 $[M+H]^+$.

Step 3 Synthesis of tert-butyl (2-oxo-5-(2,3,6-trifluorophenyl)piperidin-3-yl)carbamate H5-1c

To a stirred solution of isopropyl 2-((tert-butoxycarbonyl)amino)-4-cyano-4-(2,3,6-trifluorophenyl)butanoate **H5-1b** (85 g, 212 mmol) in ethanol (1.5 L) was added Raney Ni (90 g) (Raney Ni was washed with ethanol 200 mL and decanted) and the resultant reaction mixture was hydrogenated under 8 kg/cm^2 hydrogen pressure in an autoclave instrument at rt for 48 h. Reaction mixture was filtered through Celite pad, rinsed with EtOH (500 mL) and the filtrate was concentrated under reduced pressure. Residue obtained was dissolved in acetonitrile (1 L), potassium carbonate (47.8 g, 346 mmol) was added and the resultant reaction mixture was heated at 80 °C for 16h. After the completion of starting material monitored by TLC, the reaction mixture concentrated under reduced pressure to remove EtOH. Residue obtained was partitioned between EtOAc (1 L) and with water (500 mL). Organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude compound which was purified by flash column chromatography using silica gel (230-400 mesh) eluted with (0-50%) EtOAc in petroleum-ether gradient to afford tert-butyl (2-oxo-5-(2,3,6-trifluorophenyl)piperidin-3-yl)carbamate **H5-1c** as a white solid (55g, 75%).

LC-MS (ESI+): 245.1 $[M+H\ -Boc]^+$

Step 4 synthesis of tert-butyl (2-oxo-1-(5-(prop-2-yn-1-yloxy)pentyl)-5-(2,3,6-trifluorophenyl)piperidin-3-yl)carbamate I5-1*

To a stirred solution of tert-butyl (2-oxo-5-(2,3,6-trifluorophenyl)piperidin-3-yl)carbamate **H5-1c** (32 g, 93.02 mmol) and 1-bromo-5-(prop-2-yn-1-yloxy)pentane **H5-1d** (22.88 g, 111.6 mmol) in DMF (350 mL), Cs_2CO_3 (45.94 g, 139.5 mmol) was added and the resultant reaction mixture was stirred at 60 °C for 16 h. After the completion of starting material, monitored by TLC, the reaction mixture was partitioned between EtOAc (1 L) and water (3x500 mL). Organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude mass. Crude compound was purified by flash column chromatography using silica gel (230-400 mesh) and eluted with (0-20%) EtOAc in petroleum-ether gradient to afford tert-butyl (2-oxo-1-(5-(prop-2-yn-1-yloxy)pentyl)-5-(2,3,6-trifluorophenyl)piperidin-3-yl)carbamate **I5-1*** as a colourless gum (35 g, 80%).

Preparative Chiral SFC:

Instrument: PICLab PREP 100
Solvents: Primary mobile phase = CO_2 Modifier: 40% IPA
Column: YMC Cellulose-SC 5um, 250x30mm, at 35°C. UV monitoring: 210nm
Flow: 80g/min.

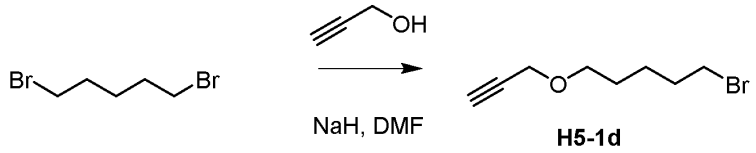
Pure fractions were concentrated under reduced pressure and lyophilized to give products.

Isomer 1 (the first eluting peak) tert-butyl ((3S,5S)-2-oxo-1-(5-(prop-2-yn-1-yloxy)pentyl)-5-(2,3,6-trifluorophenyl)piperidin-3-yl)carbamate **I5-1** as white solid 5.0g

Chiral SFC analytical YMC Cellulose-SC, 250×4.6 mm 5µ at 35 °C, 3 ml/min, 40% Methanol 35 °C. Isomer-1 3.07 min

^{1}H NMR (400MHz, $CDCL_3$) δ 7.13-7.02 (m, 1H), 6.89-6.82 (m, 1H), 5.63-5.55 (m, 1H), 4.15 (d, J = 2.4 Hz, 3H), 3.80-3.72 (m, 1H), 3.60-3.40 (m, 5H), 3.35-3.27 (m, 1H), 2.74-2.65 (m, 1H), 2.43 (t, J = 2.4 Hz, 1H), 2.32-2.22 (m, 1H), 1.68-1.53 (m, 4H), 0.73 (s, 9H), 1.40-1.35 (m, 2H).

Experimental procedure of synthesis of Intermediate H5-1d



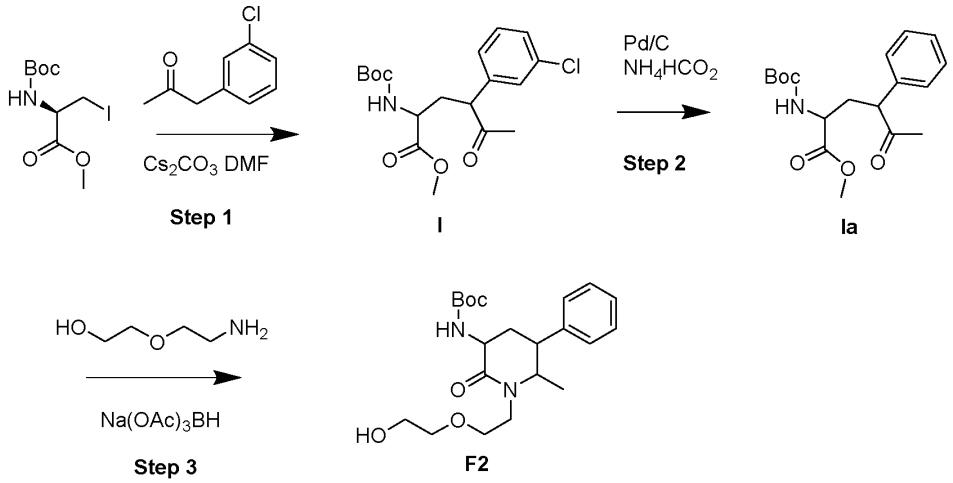
H5-1d

To a stirred solution of prop-2-yn-1-ol (20 g, 357.14 mmol) and 1,5-dibromopentane (163 g, 714 mmol) in DMF (120 mL) at 0 °C was added NaH (27.38 g, 714 mmol) portion wise and the resultant reaction mixture was stirred at room temperature for 15 h. The reaction mixture was quenched by the dropwise addition of water (500 mL) and extracted with EtOAc (2x500 mL). Combined organic layers were washed with brine solution (2x500 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by Biotage-Isolera using 340 g silica gel Snap cartridge (230-400 mesh) and eluted with (0-5%) EtOAc in petroleum-ether gradient to afford 1-bromo-5-(prop-2-yn-1-yloxy)pentane **H5-1d** as a colourless gum (90g, 33.5%).

^{1}HNMR (400MHz, DMSO-d6) δ: 4.16 (d, J = 2.4 Hz, 2H), 3.55 (t, J = 6.4 Hz, 2H), 3.44 (t, J = 6.8 Hz, 2H), 2.45 (t, J = 2.4 Hz, 1H), 1.95-1.85 (m, 2H), 1.70-1.60 (m, 2H), 1.57-1.50 (m, 2H)

Synthesis of Intermediates F-X

Scheme 10. Synthesis of intermediate F-2



Experimental procedure for synthesis of F-2

Step-1 Synthesis of methyl 2-(tert-butoxycarbonylamino)-4-(3-chlorophenyl)-5-oxo-hexanoate (I).

Into a solution of Boc-3-Iodo-D-Ala-OMe (6.0 g, 18 mmol) in dry DMF (40 mL), 3-chlorophenylacetone (3.36 g, 20. mmol) and cesium carbonate (6.5g 20mmol) were added and stirred at room temp. under argon for 45 min. Further 3-chlorophenylacetone (3.36 g, 20.18 mmol) and cesium carbonate (6.5g 20mmol) were added. The reaction mixture was stirred at room temp. under argon for 2.5 h. EtOAc (50 mL and water (200 mL) were added, and the layers separated. The organic layer was washed with $NaHCO_3$ (aq, sat.) (2 x 40 mL) and brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated to afford the desired product **I** (5.98 g, 80%) used as is in the next step.

LC-MS (ES+): 392.6 $[M+Na]^+$.

Step-2 Synthesis of methyl 2-(tert-butoxycarbonylamino)-5-oxo-4-phenyl-hexanoate (Ia).

A solution of **I** (5.97 g, 16.14 mmol) and ammonium formate (4.07 g, 64.56 mmol) in EtOH (42 mL) was degassed with argon in a ultrasonic bath for 15 min. Palladium on carbon (10%, 1.37 g, 1.29 mmol) was added and the mixture was stirred at 60 °C for 1.5 h. The reaction mixture was filtered through a pad of Celite. The Celite was washed with EtOH and the sample concentrated. The yellow residue was dissolved in EtOAc (100 mL) and the undissolved solids filtered off. The solvent was evaporated to afford the crude product 5 (5.1 g) as a sticky residue. The crude product was dry-loaded and purified on a silica column (Interchim 120 g, 15 µm, SiO_2) using an Interchim PuriFlash 450 instrument with a flowrate of 60 mL/min starting with cyclohexane (100%) and going to 100% cyclohexane/EtOAc (5/1) in 20 CVs. Hold 100% cyclohexane/EtOAc (5/1) for 10 CVs The appropriate fractions were collected, the solvent removed to yield the desired product **Ia** (3.1 g, 57.3%).

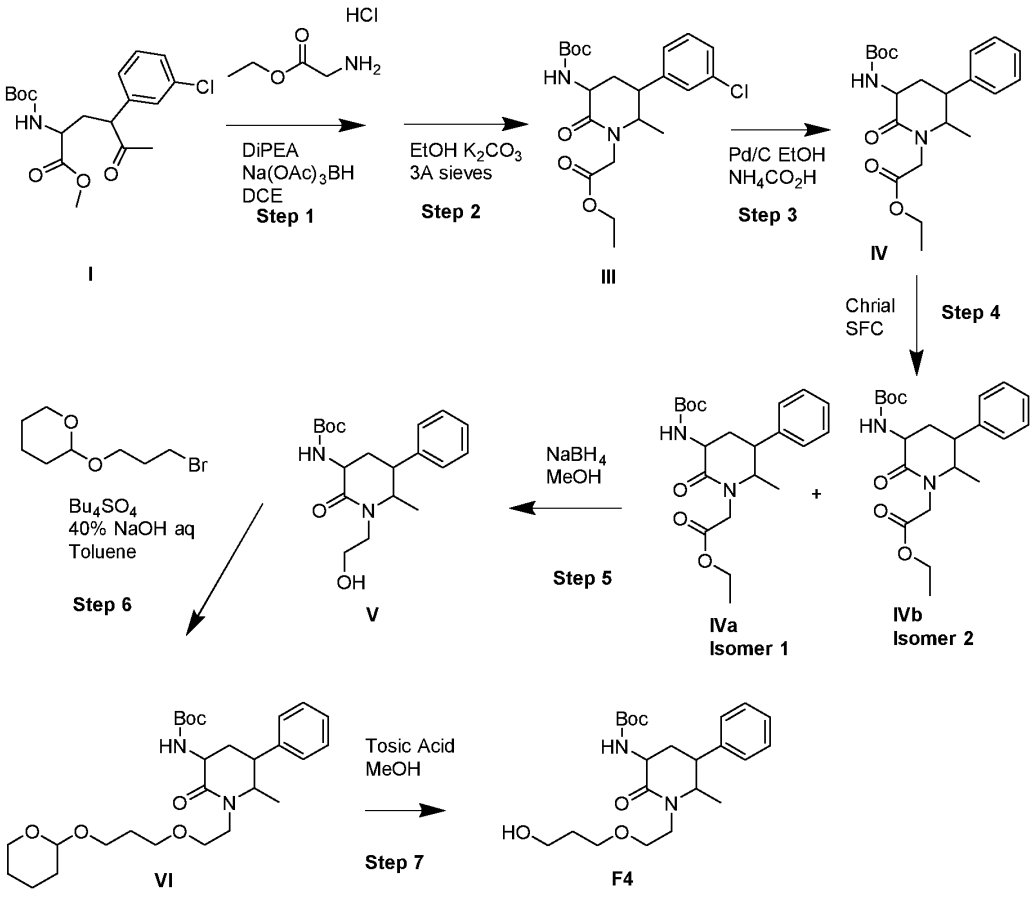
LC-MS (ES+): 358.6 $[M+Na]^+$.

Step-3 Synthesis of tert-butyl N-[1-[2-(2-hydroxyethoxy)ethyl]-6-methyl-2-oxo-5-phenyl-3-piperidyl]carbamate (F-2).

Into a solution of 2-(2-aminoethoxy)ethanol (3.43 g, 32.6 mmol) in dry DCE (40 mL) was added a solution of **Ia** (2.73 g, 8.15 mmol) in dry DCE (40 mL), followed by acetic acid (1.4 mL, 24.45 mmol), 4 Å powdered molecular sieves (2 g) and sodium triacetoxyborohydride (6.91 g, 32.61 mmol). This mixture was stirred at room temp. under argon for 2 days. A new amount of 2-(2-aminoethoxy)ethanol (1.71 g, 16.3 mmol) was added followed by sodium triacetoxyborohydride (3.46 g, 16.3 mmol). The reaction was continued at room temp. for further 2 days. DCM (80 mL) and water (80 mL) were added with vigorous stirring. The organic layer was separated, washed with water (80 mL) and brine, dried over anhydrous Na_2SO_4, filtered and the solvent evaporated to afford the desired product **F-2** (2.9 g, 90.6%) as a sticky yellow residue.

LC-MS (ES+): 393.7 $[M+H]^+$.

Scheme 11. Synthesis of Intermediate F-4



Experimental procedure for synthesis of Intermediate F-4

Step 1 and 2 . Synthesis of ethyl 2-[5-(*tert*-butoxycarbonylamino)-3-(3-chlorophenyl)-2-methyl-6-oxo-1-piperidyl]acetate (III)

1) Ethylaminoacetate hydrochloride (34.7g, 249mmol) was suspended in DCE (200 mL), DIPEA (43ml, 248mmol) was added dropwise and suspension was stirred for 15 minutes, then was added solution of **I** (23g, 62mmol) in DCE (250 mL) followed by acetic acid, 4 Å molecular sieves (0.25 g), $Na(OAc)_3BH$ (52.7g, 248mmol) and the reaction mixture was stirred overnight at room temperature. LCMS showed traces of SM, and formation of intermediate M= 457, in a mixture with final cyclized compound. An additional amount of ethylaminoacetate hydrochloride (2 eq), DIPEA (2 eq), and $Na(OAc)_3BH$ (3 eq) were added and the was stirred for two additional days. LCMS showed completed reaction. The reaction mixture was diluted with DCM (200 mL), water was added (600 mL), molecular sieves were removed by filtration, layers were separated and organic layer was washed with water (3x500mL), dried (Na_2SO_4) and concentrated to obtain intermediate (m= 30.3 g).

2) Epimerisation step. Into a solution of product from step 1 (29.17g, 68.65 mmol) in dry EtOH (400 mL), potassium carbonate (28.46 g, 205.95 mmol) and 3 Å molecular sieves (10 g) were added and stirred at 60°C for 2 hours and overnight at RT. The reaction mixture was concentrated, and the residue dissolved in EtOAc (200 mL). The organic layer was carefully separated and the solid residue washed again with EtOAc (4×50 mL). The combined organic layer was washed with sat. $NaHCO_3$ (100 mL), brine (4×50 mL), dried over anhydrous Na_2SO_4, and evaporated to yield product **III** (23.85 g) that was used as is in the next reaction step.

Step 3. Synthesis of ethyl 2-[5-(*tert*-butoxycarbonylamino)-2-methyl-6-oxo-3-phenyl-1-piperidyl]acetate (IV)

A solution of **III** (23.85 g, 56.12 mmol) and ammonium formate (17.69 g, 280.64 mmol) in ethanol (500 mL) was flushed with argon. To this solution 10% Palladium on Charcoal (4.77 g) was added and the reaction mixture heated at 60°C for 30 min. The reaction mixture was filtered through a pad of Celite. The solvent was evaporated to yield m=20.20 g of crude product. It was dissolved in DCM and loaded on a Interchim (300 g, 50 µm, SiO_2) column and purified using a Interchim Puriflash 450 system with a flowrate of 120 ml/min starting with cyclohexane (100%) and

going to 65% cyclohexane/EtOAc (1/1) in 15 CVs, hold 100% for 10 CVs. The fractions containing the desired product mixture were evaporated to yield m=4.87 g and m=10.89 g of crude material that was repurified on a Interchim (120 g, HC-15 µm, SiO_2) column using the same method as above (flowrate of 50 ml/min) to yield m=1.45 g of desired product mixture and m=7.69 g of crude material. Additional chromatography yielded batches of m=1.38 g, m=0.87 g and m= 0.26 g of desired compound. All product batches combined and further dried to yield 8.2g of product mixture.

Step 4. SFC chiral

System Details

Column Details Lux C4 (21.2mm x 250mm, 5um)

Column Temperature 40°C

Flow Rate 50 mL/min

Detector Wavelength 215 nm

Injection Volume 1500 uL (62 mg) in ethanol

Isocratic Conditions 35:65 EtOH:CO_2 (0.1% v/v NH_3)

Combined product fractions were concentrated, transferred to final vessels with DCM, further dried under nitrogen at 40°C and then under vacuum for 16 hour at 40°C to give **IVa Isomer 1** 3.7g (enantiomeric excess 100%) and **IVb Isomer 2** 3.6g (enantiomeric excess 98.6%)

Step 5. Synthesis of *tert*-butyl N-[1-(2-hydroxyethyl)-6-methyl-2-oxo-5-phenyl-3-piperidyl]carbamate (V)

To a solution of **IVa** (1.0 g, 2.561 mmol) in dry MeOH (10.0 mL) cooled at 0°C, $NaBH_4$ (387.6 mg, 10.244 mmol) was added. The reaction mixture was stirred at room temperature for 90 minutes. Added new amount of $NaBH_4$ (193.8 mg, 5.122 mmol) and stirring was continued at 45 °C. After 2 hours a new amount of $NaBH_4$ (193.8 mg, 5.122 mmol) was added and stirring at 45 °C continued. After 2 hours new amount of $NaBH_4$ (193.8 mg, 5.122 mmol) was added and stirring was continued at room temperature for 15 hours. To the reaction mixture *sat.* NH_4Cl (50 mL) and DCM (25 mL) were added, the layers separated, and the aqueous layer extracted with DCM (2 × 25 mL). The combined organic layers were dried over

Na_2SO_4 and concentrated under reduced pressure to afford the raw product (986.5 mg). The crude material was loaded and purified on a silica column (Interchim 25 g, 15 µm, SiO_2) using Interchim PuriFlash 450 instrument with a flowrate of 20 mL/min starting with DCM (100%) and going to 100% [DCM/MeOH (20:1)] in 20 CVs. Hold 100% for 10 CVs. The appropriate fractions were collected, the solvent removed to yield the desired product **V** (821.2 mg, 92.0%).

LC-MS (ES+): 349.2 $[M+H]^+$.

Step 7. Synthesis of *tert*-butyl N-[6-methyl-2-oxo-5-phenyl-1-[2-(3-tetrahydropyran-2-yloxypropoxy)ethyl]-3-piperidyl]carbamate (VI)

To a solution of **V** (700.0 mg, 2.009 mmol) and 2-(3-bromopropoxy)tetrahydropyran (458.1 µL, 2.566 mmol) in toluene (1.75 mL), NaOH (40% in water, 1.75 mL) and tetrabutylammonium hydrogensulfate (695.9 mg, 2.009 mmol) was added and the resultant reaction mixture was stirred at 43 °C for 3 hours. Added new amount of 2-(3-bromopropoxy)tetrahydropyran (229.1 µL, 1.284 mmol) and tetrabutylammonium hydrogensulfate (348.0 mg, 1.005 mmol) and stirring at 43°C was continued. After 17 hours, new amount of 2-(3-bromopropoxy)tetrahydropyran (117.5 µL, 0.658 mmol) and tetrabutylammonium hydrogensulfate (178.9 mg, 0.517 mmol) was added and stirring at 43°C was continued for 4 hours. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with *sat.* NH_4Cl (2 × 15 mL) aq. and brine (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product (1.27 g). The crude material was loaded and purified on a silica column (Interchim 25 g, 15 µm, SiO_2) using Interchim PuriFlash 450 instrument with a flowrate of 20 mL/min starting with DCM (100%) and going to 70% [DCM/MeOH (20:1)] in 20 CVs. Hold 70% for 10 CVs. The clean fractions were collected, and the mixed fractions purified again. This process was repeated five times to give compound **VI** (598.8 mg, 60.1%).

LC-MS (ES+): 491.1 $[M+H]^+$.

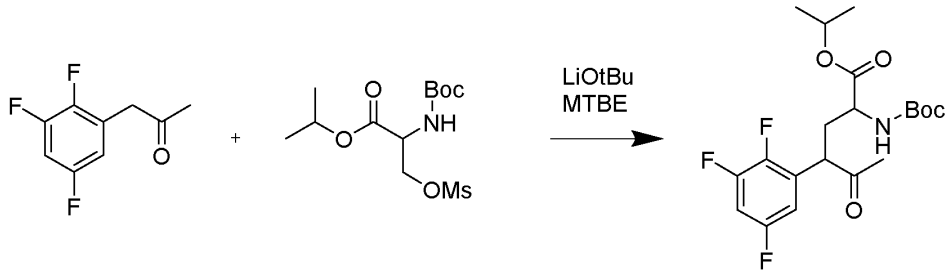
Step 8. Synthesis of *tert*-butyl N-[1-[2-(3-hydroxypropoxy)ethyl]-6-methyl-2-oxo-5-phenyl-3-piperidyl]carbamate (F-4)

To a solution of **VI** (597.2 mg, 1.217 mmol) in dry MeOH (10.7 mL), *p*-toluenesulfonic acid (11.0 mg, 0.061 mmol) was added. The reaction mixture was stirred at room

temperature for 5 hours. The reaction mixture was quenched with a mixture of *sat.* $NaHCO_3/H_2O$ 1:1 (30 mL), and DCM (30 mL) and stirred for 10 minutes. The layers were separated, and the aqueous layer extracted with DCM (2 × 25 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the raw product (545.0 mg). The crude material was loaded and purified on a silica column (Interchim 25 g, 15 µm, SiO_2) using Interchim PuriFlash 450 instrument with a flowrate of 20 mL/min starting with DCM (100%) and going to 100% [DCM/MeOH (20:1)] in 20 CVs. Hold 100% for 10 CVs. The appropriate fractions were collected, the solvent removed to yield the desired product **F-4** (412.6 mg, 83.4%).

LC-MS (ES+): 407.2 $[M+H]^+$.

Scheme 12. Synthesis of Intermediate F-5



F-5

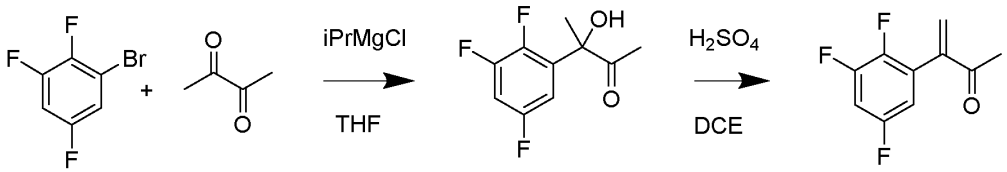
Experimental procedure for synthesis of isopropyl 2-((tert-butoxycarbonyl)amino)-5-oxo-4-(2,3,5-trifluorophenyl)hexanoate F-5

To a solution of isopropyl N-(tert-butoxycarbonyl)-O-(methylsulfonyl)serinate (35.9 g, 110.1 mmol) in dry MTBE (258 ml) molecular sieves (4Å) and 1-(2,3,5-Trifluorophenyl)-2-propanone (CAS 1305323-99-2) (17.8 g, 94.8 mmol) were added and the solution was stirred at room temperature for 30 min. After that the mixture was cooled to 0°C and lithium tert-butoxide (28.5 g, 355.4 mmol) was added in several portions. The reaction mixture was stirred at room temperature for 20h. The reaction mixture was filtered through a pad of silica, washed with EtOAc (420 ml) and water (1 L) was added. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 315 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (3 × 170 mL) and brine (3 × 170 mL), dried over anhydrous Na_2SO_4 and concentrated to yield the crude product which was loaded and purified on a

silica column (Interchim, HP columns, 30 µm, SiO_2, loading: 0.05) using Interchim PuriFlash 430 instrument starting with cyclohexane (100%) for 2 CVs and going to 30% [cyclohexane/EtOAc (5:1)] in 10 CVs. Increasing to 70% [cyclohexane/EtOAc (5:1)] in 15 CVs. Hold 70% [cyclohexane/EtOAc (5:1)] for 10 CVs. The appropriate fractions were collected, the solvent removed to yield the desired product **F-5** (20.5 g, 51.8%).

LC-MS (ES+): 440.3 $[M+Na]^+$.

Scheme 13. Synthesis of Intermediate F-6



Step 1 F6a Step 2 F6

Experimental procedure for synthesis of 3-(2,3,5-trifluorophenyl)but-3-en-2-one F6.

Step 1 synthesis of 3-hydroxy-3-(2,3,5-trifluorophenyl)butan-2-one F6a

To a stirred solution of 1-bromo-2,3,5-trifluorobenzene (20.00 g, 95mmol) in THF (200 mL) was added iPrMgCl-LiCl (1.3 M in THF) (80mL, 104mmol) dropwise at -20~-30°C under nitrogen atmosphere. The mixture was stirred for 1h at -20 °C under nitrogen atmosphere. The above mixture was added to a solution of diacetyl (9.42 g, 110mmol) in THF (80 mL) at -20~-30 °C. The resulting mixture was stirred for an additional 1.5 h at -10~-20 °C. The reaction was quenched with sat. NH_4Cl (aq.) at 0 °C. The resulting mixture was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 3-hydroxy-3-(2,3,5-trifluorophenyl)butan-2-one **F6a** (20 g, 92mmol) as a brown oil

Step 2 synthesis of 3-(2,3,5-trifluorophenyl)but-3-en-2-one F6

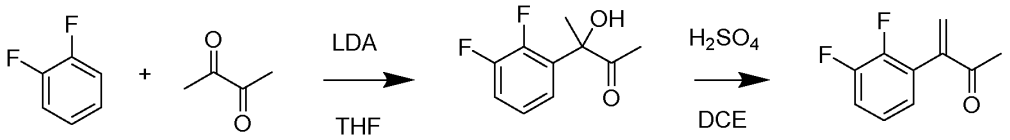
To a stirred mixture of H_2SO_4 (67.50 g, 0.7mol) in DCE (500mL) was added a solution of 3-hydroxy-3-(2,3,5-trifluorophenyl)butan-2-one **F6a** (50 g, 229mmol) in DCE(100 mL) dropwise at 70 °C. The resulting mixture was stirred for 0.5 h at 70 °C. The mixture was allowed to cool down to 0-10 °C. The reaction was quenched with

Water/Ice. The resulting mixture was extracted with MTBE (2 x 300mL). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (100:1) to afford 3-(2,3,5-trifluorophenyl)but-3-en-2-one **F6** (10.5g, 53mmol) as an orange solid.

LCMS (ES, m/z): 201 $[M+H]^+$.

1H NMR (300 MHz, Chloroform-d) δ 6.94 (dddd, J = 10.0, 8.1, 6.1, 3.1 Hz, 1H), 6.75 (dddd, J = 8.3, 4.7, 3.1, 2.1 Hz, 1H), 6.44 (s, 1H), 6.10 (s, 1H), 2.48 (s, 3H).

Scheme 14. Synthesis of Intermediate F-7



Experimental procedure for synthesis of 3-(2,3-difluorophenyl)but-3-en-2-one F-7.

Step 1

To a stirred solution of 1,2-difluorobenzene (200 g, 1.75mol) in THF (1 L) was added 2M LDA in (965.00 mL, 1.93mol) dropwise at -40~-50 °C under nitrogen atmosphere. The mixture was stirred for 1h at -30 °C and then added to a solution of diacetyl (173.5 g, 2.02mol) in THF (1600 mL) at -70 °C. The result mixture was stirred for 2 h at -10 °C. The reaction was quenched with HOAc (126 g) and H_2O (2 L). The resulting mixture was extracted with MTBE (3 x 1 L). The combined organic layers were washed with brine (500 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (10:1) to afford 3-(2,3-difluorophenyl)-3-hydroxybutan-2-one **F7a** (230 g 1.15mol) as a brown oil.

Step 2

To a stirred solution of 3-(2,3-difluorophenyl)-3-hydroxybutan-2-one **F7a** (70 g, 0.35mol) in DCE (700 mL) was added H_2SO_4 (72.1 g, 0.74mmol) dropwise at 30 °C

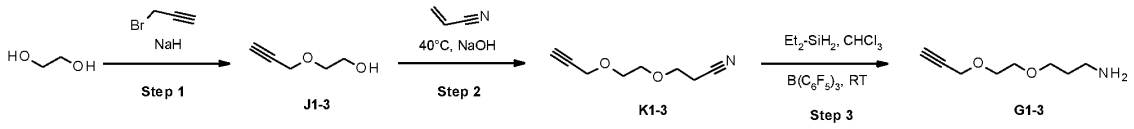
under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 40 °C under nitrogen atmosphere. The reaction was quenched with water at 0-10 °C. DCE was removed under reduced pressure. The resulting mixture was extracted with MTBE (3 x 500mL). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (100:1) to afford 3-(2,3-difluorophenyl)but-3-en-2-one **F-7** (18 g) as a brown oil.

LCMS (ES, m/z): 183 $[M+H]^+$.

^{1}H NMR (300 MHz, Chloroform-d) δ 7.25 – 6.91 (m, 3H), 6.40 (s, 1H), 6.06 (s, 1H), 2.46 (s, 3H).

Synthesis of Intermediates G1-X

Scheme 15. Synthesis of Intermediate G1-3



Experimental procedures for synthesis of Intermediate G1-3

Step 1. Synthesis of 2-prop-2-ynoxyethanol (J1-3)

Into ethylene glycol (44.61 mL, 0.814 mol) a dispersion of NaH (8.13 g, 0.203 mol, 1 equiv., 60 % in mineral oil) was carefully added in portions. After all the bubbling stopped, to the white suspension propargyl bromide (21.9 mL, 0.203 mol, 80% in toluene) was added. After the initial bubbling subsided the flask was sealed and the reaction stirred overnight at RT. DCM (20 mL) and water (200 mL) were added. The organic layer was separated and the aqueous layer extracted with with DCM/i-PrOH (1:1, 10×20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to yield the desired product **J1-3** (m=19.59 g) as a yellowish liquid. The product was used as is in the next step.

TLC (cyclohexane-EtOAc 1:1): rf=0.23

Step 2. Synthesis of 2-prop-2-ynoxyethanol (K1-3)

Into a flask containing compound **J1-3** (18.5 g, 166 mmol) a freshly prepared solution of 2.5 M NaOH in water(1.99 mL) was added, followed by a dropwise addition of acrylonitrile (43,6 mL, 665mmol), (very carefully so the temp did not exceed 45°C). The reaction mixture was stirred at 45°C overnight. Additional 2.5 M NaOH in water (2.0 mL) added and stirring continued at 45°C over the weekend. Added a new amount of acrylonitrile (10 mL) and continued over the night. The reaction mixture was diluted with sat. $NaHCO_3$/water (1:1, 50 mL) and EtOAc (250 mL). The aqueous layer was separated and the organic layer washed with sat. $NaHCO_3$ (3×50 mL), dried over anhydrous Na_2SO_4 and concentrated to yield the crude product (m=27.3 g). The crude material was dry loaded and purified on a silica column (Interchim, 330 g, 50 µm, SiO_2) using an Interchim PuriFlash 430 instrument with a flowrate of 127 mL/min starting with cyclohexane (100%). Hold 100% cyclohexane for 2 CVs. Increasing to 60% [cyclohexane/EtOAc (1:1)] in 20 CVs. Hold 60% for 5 CVs. Increasing to 75% [cyclohexane:EtOAc (1:1)] in 10 CVs. Hold 75% for 5 CVs. Fractions containing the desired product were combined, the solvent removed to yield the desired product **K1-3** (m=13.29 g, 52%).

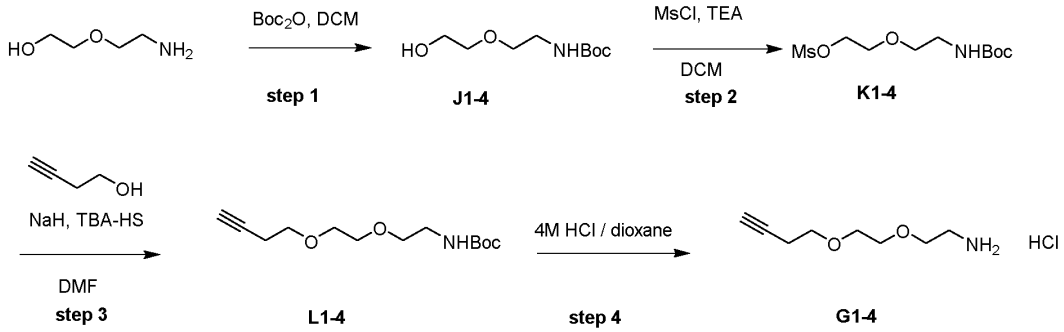
TLC (cyclohexane-EtOAc 1:1): rf=0.54

Step 3. Synthesis of 3-(2-prop-2-ynoxyethoxy)propan-1-amine (G1-3)

A solution of tris(pentafluorophenyl)borane (369 mg, 70.56 mmoL) in chloroform (22.5 mL) was bubbled with argon for 5 minutes. To this solution diethylsilane (8.23 mL, 61.74 mmol) was added while bubbling argon through the solution. The reaction mixture was stirred briefly for 5 min after which a solution of compound **K1-3** (2.7 g, 17.62 mmol) in dry $CHCl_3$ (5.94 mL) was added. The reaction was stirred under argon for 15 minutes. The reaction mixture was concentrated under reduced pressure to afford the crude material (m=7.05 g). The crude product was loaded and purified on a silica column (Interchim 40 g, 15 µm, SiO_2) using an Interchim PuriFlash 430 instrument with a flowrate of 27 mL/min starting with DCM (100%) Hold 100% DCM for 2CVs and increasing to 100% E-system (DCM/MeOH/NH_4OH) (90/9/1.5) in 10 CVs. Hold 100% E-system for 15 CVs. The desired fractions were combined, and the solvent removed to yield the desired product **G1-3** (m=2.19 g, 79.1%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 2 H), 1.72 (quint, *J*=6.6 Hz, 2 H), 2.40 - 2.41 (t, *J*=2.4 Hz, 1 H), 2.78 (t, *J*=6.8 Hz, 2 H), 3.53 (t, *J*=6.3 Hz, 2 H), 3.56-3.62 (m, 2 H), 3.63-3.70 (m, 2 H), 4.18 (d, *J*=2.3 Hz, 2 H) ppm

Scheme 16. Synthesis of Intermediate G1-4



Experimental procedure for synthesis of 2-(2-but-3-ynoxyethoxy)ethanamine, hydrochloride (G1-4).

Step 1. Synthesis of *tert*-butyl N-[2-(2-hydroxyethoxy)ethyl]carbamate (J1-4)

To a solution of compound 2-(2-aminoethoxy)ethanol (CAS 929-06-6) (5.00 g, 47.6 mmol) in dry DCM (125 mL) cooled at 0°C, Boc_2O (12.5 g, 57.1 mmol) was added portion wise. The reaction mixture was stirred at room temperature for 2 hours. The solvent was evaporated to yield the crude material (m=12.0 g). The crude product was loaded and purified on a silica column (Interchim 120 g, 15 µm, SiO2) using an Interchim PuriFlash 430 instrument with a flowrate of 60 mL/min starting with cyclohexane (100%) and going to 100% cyclohexane/EtOAc (1/1) in 25 CVs. Hold 100% cyclohexane/EtOAc (1/1) for 5CVs. The appropriate fractions were collected, the solvent removed to yield the desired product **J1-4** (7.59 g, 78%).

LC-MS (ES+): 206.1 $[M+H]^+$.

Step 2. Synthesis of 2-[2-(*tert*-butoxycarbonylamino)ethoxy]ethyl methanesulfonate (K1-4)

To a solution of compound **J1-4** (4.10 g, 20.0 mmol) and methanesulfonyl chloride (1.78 mL, 23.0 mmol) in dry DCM (100 mL), triethylamine (3.34 mL, 24.0 mmol) was added slowly under an ice bath. The reaction mixture was stirred at room

temperature for 75 minutes. The reaction mixture was quenched with NH_4Cl (aq. sat.) (150 mL), the organic layer separated, washed with brine (2×10 mL), dried over anhydrous Na_2SO_4, and concentrated to yield the desired product **K1-4** (m=5.38 g, 95%).

LC-MS (ES+): 284.1 $[M+H]^+$.

Step 3. Synthesis of *tert*-butyl N-[2-(2-but-3-ynoxyethoxy)ethyl]carbamate (L1-4)

Into a solution of but-3-yn-1-ol (2.9 mL, 38. mmoL) in dry DMF (60 mL) cooled at 0°C, NaH (840 mg, 21 mmol) was added portion wise. The reaction mixture was stirred at 0°C for 10 minutes. After that a solution of **K1-4** (5.38 g, 19.0 mmol) in dry DMF (5 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 24 hours. The reaction was cooled to 0°C and tetrabutylammonium hydrogen sulphate (2.0 mL 55 wt. % in H_2O) was added. After 20 minutes NaH (160 mg, 4 mmol) was added in portions and the reaction continued at room temperature overnight. The reaction mixture was quenched with saturated NH_4Cl (360 mL) and DCM (50 mL). The layers were separated, and the aq. layer extracted with DCM (2×50 mL). The combined organic layer was concentrated to yield a solution of the crude product **L1-4** in DMF.

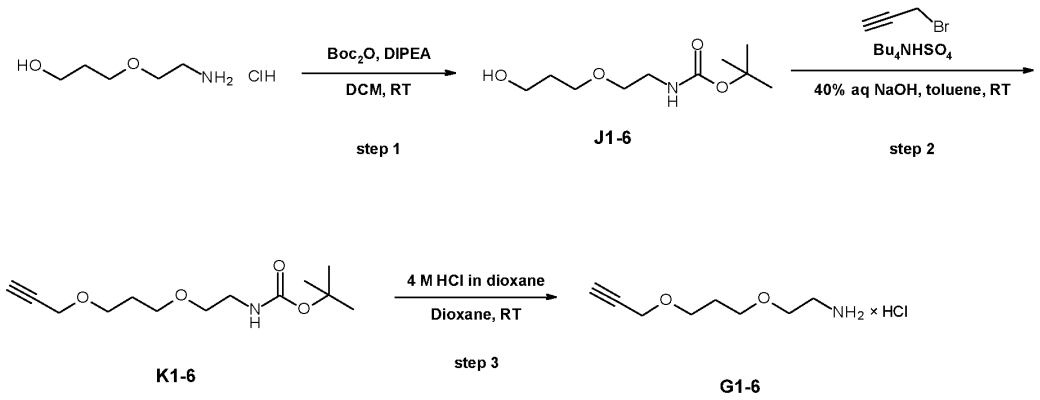
LC-MS (ES+): 258.1 $[M+H]^+$.

Step 4. Synthesis of 2-(2-but-3-ynoxyethoxy)ethanamine, hydrochloride (G1-4)

A DMF solution of compound **L1-4** (4950 mg, 19.2 mmol – from step before) was cooled in an ice bath. Into this solution a 4 M HCl solution in dioxane (193 mL) was added dropwise over a period of 30 minutes. The reaction was stirred ice cooled for 2 hours, concentrated and the residue treated with n-hexane (4×30 ml) to yield the desired product **G1-4** (m=2.86 g) as a HCl salt.

LC-MS (ES+): 158.0 $[M+H]^+$.

Scheme 17. Synthesis of Intermediate G1-6



Experimental procedure for synthesis of 2-(2-but-3-ynoxyethoxy)ethanamine, hydrochloride (G1-6)

Step 1. Synthesis of *tert*-butyl *N*-[2-(3-hydroxypropoxy)ethyl]carbamate (J1-6)

To a solution of compound 3-(2-aminoethoxy)propan-1-ol hydrochloride (CAS 947664-36-0) (1.0 g, 6.426 mmol) in DCM (11.3 mL), di-*tert*-butyl dicarbonate (3.09 g, 14.137 mmol) and DIPEA (1.23 mL, 7.068 mmol) were added. The reaction was stirred at room temperature overnight. The reaction mixture was poured into *sat.* $NaHCO_3$ (50 mL) and extracted with DCM (3×25 mL). The organic layer was washed with 10% citric acid (25 mL), brine (25 mL), dried over anhydrous $MgSO_4$ and concentrated to yield the crude material (2.81 g) as a colorless oil. The crude material was loaded and purified on a silica column (Interchim 40 g, 30 µm, SiO_2) using Interchim PuriFlash 450 instrument with a flowrate of 27 mL/min starting with cyclohexane (100%) for 2 CVs and going to 50% ethylacetate in 15 CVs. Hold 50% for 5 CVs. Increasing to 70 % in 10 CVs. Hold 70% for 10 CVs. The appropriate fractions were collected, the solvent removed to yield the desired product **J1-6** (1.12 g, 79.5%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 1.81 (quint, *J*=5.7 Hz, 2 H), 1.97 (br, 1 H), 3.29 (m, 2 H), 3.48 (t, *J*=5.0 Hz, 2 H), 3.60 (t, *J*=5.7 Hz, 2 H), 3.74 (t, *J*=5.6 Hz, 2 H), 4.82 (br, 1 H) ppm.

Step 2. Synthesis of *tert*-butyl *N*-[2-(3-prop-2-ynoxypropoxy)ethyl]carbamate (K1-6)

To a solution of **J1-6** (788.0 mg, 3.594 mmol) and propargyl bromide (445.3 µL, 4.133 mmol) in toluene (3.14 mL), NaOH (40% in water, 3.14 mL) and tetrabutylammonium hydrogensulfate (1.25 g, 3.594 mmol) was added and the resulted reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was diluted with water (100 mL) and extracted with EtOAc (3×25 mL). The combined organic layers were washed with *sat.* NH_4Cl (2×50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product (842.6 mg). The crude material was loaded and purified on a silica column (Interchim 25 g, 15 µm, SiO_2) using Interchim PuriFlash 450 instrument with a flowrate of 20 mL/min starting with cyclohexane (100%) and going to 70% [cyclohexane/EtOAc (1:1)] in 20 CVs. Hold 70% for 10 CVs. The appropriate fractions were collected and the solvent removed to yield the desired product **K1-6** (579.0 mg, 62.6%).

LC-MS (ES+): 280.1 $[M+Na]^+$.

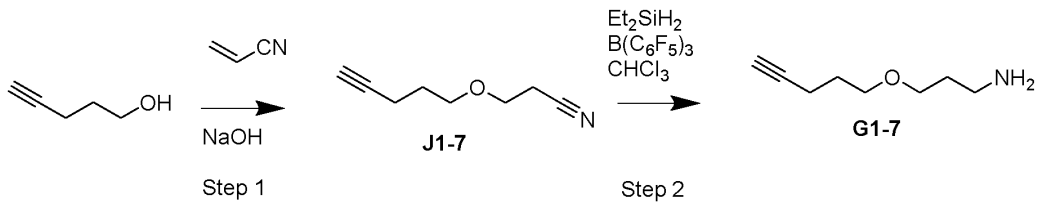
^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.43 (s, 9H), 1.84 (quint, *J*=6.4 Hz, 2H), 2.42 (t, *J*=2.3 Hz, 1H), 3.21 - 3.35 (m, 2H), 3.46 (t, *J*=5.2 Hz, 2H), 3.51 (t, *J*=6.4 Hz, 2H), 3.59 (t, *J*=6.3 Hz, 2H), 4.13 (d, *J*=2.4 Hz, 2H), 4.89 (b.s., 1H) ppm.

Step 3. Synthesis of 2-(3-prop-2-ynoxypropoxy)ethanamine hydrochloride (G1-6)

To the solution of compound **K1-6** (747.4 mg, 2.904 mmol) in dioxane (8.22 mL), HCl (4.0 M in dioxane, 29.0 mL, 116.180 mmol) was added. The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated to yield the desired product **G1-6** (595.0 mg) which was used as is in the next reaction step.

LC-MS (ES+): 407.2 $[M+H]^+$.

Scheme 18. Synthesis of Intermediate G1-7



Experimental procedure for synthesis of 3-pent-4-ynoxypropan-1-amine (G1-7)

Step 1, Synthesis of 3-pent-4-ynoxypropanenitrile (J1-7)

Into a flask containing pent-4-yn-1-ol (CAS 5390-04-5) (10 g, 119 mmol) a freshly prepared solution of 2.5 N NaOH in water (1.43 mL) was added, followed by a dropwise addition of acrylonitrile (31.1 mL, 476 mmol), (very carefully so the temp did not exceed 45°C). The reaction mixture was stirred at 45°C overnight. The reaction mixture was diluted with sat. $NaHCO_3$/water (1:1, 100 mL) and EtOAc (250 mL). The aqueous layer was separated and the organic layer washed with sat. $NaHCO_3$ (3×50 mL), dried over anhydrous Na_2SO_4 and concentrated to yield the crude product (m=19.68 g) as a pale yellow oil. The crude material was dry loaded and purified on a silica column (Interchim, 330 g, 50 µm, SiO_2) using an Interchim PuriFlash 430 instrument with a flowrate of 100 mL/min starting with cyclohexane (100%). Hold 100% cyclohexane for 2 CVs. Increasing to 100% [cyclohexane/EtOAc (5:1)] in 20 CVs. Hold 100% for 5 CVs. Fractions containing the desired product were combined, the solvent removed to yield the desired **J1-7** (m=10.42 g, 63.9%)

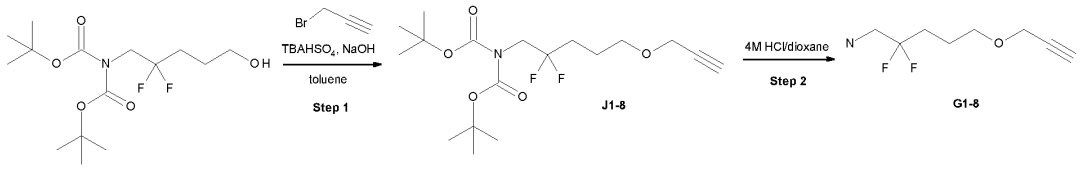
TLC (cyclohexane-EtOAc 1:1): rf=0.5

Step 2, Synthesis of 3-pent-4-ynoxypropan-1-amine (G1-7)

A solution of tris(pentafluorophenyl)borane (427 mg, 0.816 mmoL) in chloroform (18.2 mL) was bubbled with argon for 1 minute. To this solution diethylsilane (8.78 mL, 65.7 mmol) was added followed by the immediate addition of a solution of 3-pent-4-ynoxypropanenitrile **J1-7** (2.8 g, 20.4 mmol) in dry $CHCl_3$ (7.4 mL). The reaction was stirred for 30 minutes. The reaction mixture was concentrated under reduced pressure to afford the crude material. The crude product was loaded and purified on a silica column (Interchim 120 g, 15 µm, SiO_2)) using an Interchim PuriFlash 430 instrument with a flowrate of 37 mL/min starting with DCM (100%) Hold 100% DCM for 2CVs and increasing to 100% E-system (DCM/MeOH/NH_4OH) (90/9/1.5) in 20 CVs. Hold 100% E-system for 10 CVs. The desired fractions were combined, and the solvent removed to yield the desired **G1-7** (m=2.01 g, 70.1%) as a yellow oil.

TLC (DCM/MeOH/NH_4OH = 90/9/1.5): rf=0.13

Scheme 19. Synthesis of Intermediate G1-8



Experimental procedures of synthesis of 2,2-difluoro-5-prop-2-ynoxy-pentan-1-amine, G1-8

Step 1. Synthesis of *tert*-butyl N-*tert*-butoxycarbonyl-N-(2,2-difluoro-5-prop-2-ynoxy-pentyl)carbamate (J1-8)

To a solution of compound *tert*-butyl N-*tert*-butoxycarbonyl-N-(2,2-difluoro-5-hydroxy-pentyl)carbamate (2.89 g, 8.52 mmol) and propargyl bromide (1.06 mL, 9.79 mmol) in toluene (7.46 mL), NaOH (40% in water, 7.43 mL) and tetrabuthyl ammonium hydrogen sulfate (2.95 g, 8.52 mmol) was added and the reaction mixture was stirred at room temperature over the night. The reaction mixture was diluted with water (200 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were washed with *sat.* NH_4Cl (50 mL) aq.and brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford the raw product **J1-8** (2.68 g) as a light orange oil.

TLC (cyclohexane-EtOAc 5:1): rf=0.38

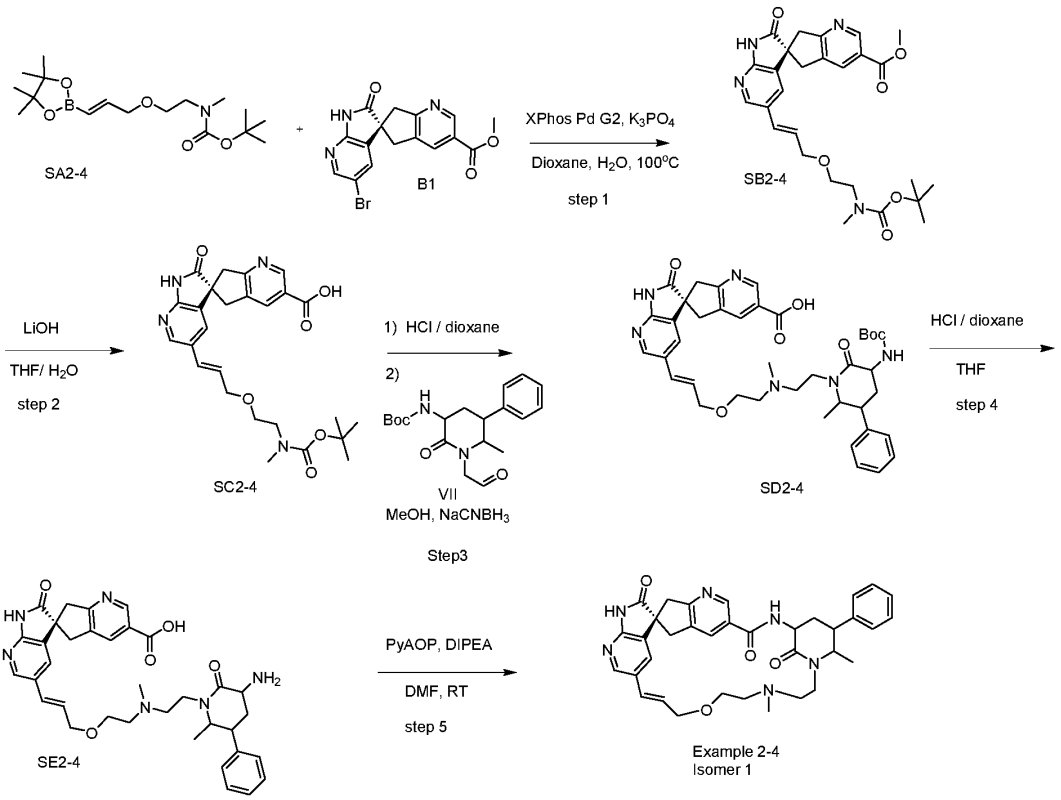
Step 2. Synthesis of 2,2-difluoro-5-prop-2-ynoxy-pentan-1-amine (G1-8)

Into a flask, containing compound **J1-8** (2.58 g, 6.84 mmol) a 4M HCl in dioxane (68.4 mL, 273 mmol) was added. The reaction was stirred fat RT over the night. The reaction mixture was concentrated and washed with toluene to yield the desired crude product (2.45 g) as a brown oil. The crude product was dry loaded and purified on a silica column (Interchim 40 g, 15 µm, SiO_2) using an Interchim PuriFlash 430 instrument with a flowrate of 26 mL/min starting with DCM (100%) Hold 100% DCM for 2CVs and increasing to 80% E1-system (DCM/MeOH/NH_4OH) (90/9/0.5) in 20 CVs. Hold 80% E-system for 10 CVs. The desired fractions were combined, and the solvent removed to yield the desired product **G1-8** (m=726 mg, 68%) as a yellow oil.

LC-MS (ES+): 178.0 $[M+H]^+$.

Final Examples with different synthetic pathway than general scheme 2

Scheme 20. Synthesis of Example 2-4



Experimental procedures of synthesis of Example 2-4

Step 1. Synthesis of Methyl (3S)-5-[(E)-3-[2-[tert-butoxycarbonyl(methyl)amino]ethoxy]prop-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylate (SB2-4)

Synthesized using the same experimental procedures as described for synthesis of the Intermediate **C1-1**, starting from **B-1** (300 mg, 0.8 mmol) and compound **SA2-4** (410 mg, 1.2 mmol). The desired product was obtained **SB2-4** (160 mg, 40%).

LC-MS (ESI+): 509.7 $[M+H]^+$.

Step 2. Synthesis of (3S)-5-[(E)-3-[2-[*tert*-butoxycarbonyl(methyl)amino]ethoxy]prop-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylic acid (SC2-4)

Methyl (3S)-5-[(E)-3-[2-[*tert*-butoxycarbonyl(methyl)amino]ethoxy]prop-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylate (**SB2-4)** (110 mg, 0.22 mmol) was dissolved in THF/water (4/1 mL) and LiOH (16 mg, 0.66 mmol) was added. reaction mixture was stirred at room temperature and occasionally checked by UPLC until full conversion to product (3 hours). The reaction mixture was concentrated water was added (3 mL) and acidified to pH 4 by dropwise addition of HCl (aq, 0.2M). Product was extracted with DCM/iPrOH=2/1, organics collected dried and concentrated to give crude (3S)-5-[(E)-3-[2-[*tert*-butoxycarbonyl(methyl)amino]ethoxy]prop-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylic acid, **SC2-4** (84 mg, 78%). It was used in next step as is.

LC-MS (ESI+): 495.3 $[M+H]^+$.

Step 3. Synthesis of (3S)-5-[(E)-3-[2-[2-[5-(*tert*-butoxycarbonylamino)-2-methyl-6-oxo-3-phenyl-1-piperidyl]ethyl-methyl-amino]ethoxy]prop-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylic acid (SD2-4)

SC2-4 (84 mg, 0.17 mmol) was dissolved in THF (5 mL) the reaction mixture was cooled down to 0°C, then HCl in dioxane (5 mL, 4M) was added. The reaction mixture was stirred at rt until full consumption of starting material. The reaction mixture was concentrated, then suspended in MeOH (4 mL) and DIPEA (119 µL, 0.68 mmol) was added followed by **VII** (117 mg, 0.34 mmol) dissolved in DCM (4 mL), acetic acid (19 µL, 0.34 mmol) and $NaCNBH_3$ (16 mg, 0.255 mmol). The reaction mixture was stirred at rt for 2 hours then was added additional amount of $NaCNBH_3$ (16 mg, 0.255 mmol) and the reaction mixture was stirred for an additional 30 minutes. The reaction mixture was concentrated and redissolved in sat. NH_4Cl and DCM, layers were separated, aqueous layer was extracted with DCM (2*5 mL), organics collected, dried and concentrated to give crude product. Crude product was purified by column chromatography (normal phase [Biotage, Interchim cartridge 12 g, 25 um, 0% 3CV, 0-100%, 20 CV DCM/MeOH/HCOOH= 9/1/0.01 in DCM and then DCM/MeOH/AcOH= 9/1/1 6CV, 10 mL/min flow rate]) to give (3S)-5-[(E)-3-[2-[2-[5-(*tert*-butoxycarbonylamino)-2-methyl-6-oxo-3-phenyl-1-piperidyl]ethyl-methyl-amino]ethoxy]prop-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-

dihydrocyclopenta[b]pyridine]-3'-carboxylic acid, **SD2-4** (180 mg, >100%, theoretically 123 mg). It was used in next step as is.

LC-MS (ESI+): 725.5 $[M+H]^+$.

Step 4. Synthesis of (3S)-5-[(E)-3-[2-[2-(6-amino-2-methyl-3-phenyl-1-piperidyl)ethyl-methyl-amino]ethoxy]prop-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylic acid; tetrahydrochloride (SE2-4)

SD2-4 (180 mg, theor. 123 mg, 0.17 mmol) was dissolved in THF (4 mL) the reaction mixture was cooled down to 0°C and HCl in dioxane (2 mL, 4M) was added. The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated to give crude (3S)-5-[(E)-3-[2-[2-(5-amino-2-methyl-6-oxo-3-phenyl-1-piperidyl)ethyl-methyl-amino]ethoxy]prop-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylic acid;tetrahydrochloride, **SE2-4** (180 mg, theoretical yield 131 mg, 100%). It was used in next step as is.

LC-MS (ESI+): 625.4 $[M+H]^+$.

Step 5. Synthesis of (1S,22E)-13,17-dimethyl-12-phenyl-20-oxa-5,9,14,17,26,28-hexazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione, Example 2-4, Isomer 1

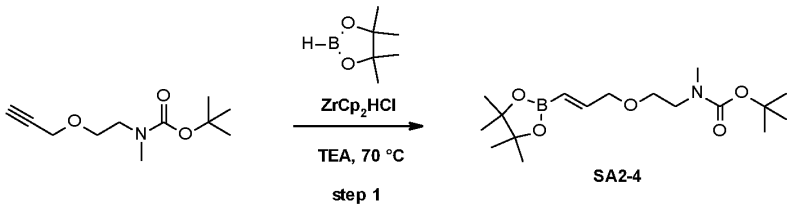
To a solution of PyAOP (134 mg, 0.255 mmol) and DIPEA (0.059 mL, 0.34 mmol) in DMF(30 mL) was added dropwise solution of 5-[(E)-3-[2-[2-(5-amino-2-methyl-6-oxo-3-phenyl-1-piperidyl)ethyl-methyl-amino]ethoxy]prop-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylic acid; tetrahydrochloride, **SE2-4** (180, theoretical yield 131 mg, 0.17 mmol) and DIPEA (0.118 mL, 0.68 mmol) in DMF (15 mL) over 20 minutes. The reaction mixture was stirred for 20 minutes then quenched with water (200 mL) and DCM (150 mL), layers were separated, aq. layer was extracted with DCM (3x 60 mL), organics collected washed with aq. sat. $NaHCO_3$, dried and concentrated affording crude. Crude was purified by column chromatography (normal phase [Biotage, Interchim cartridge 12 g, 25 µm, 0-50%, 10CV, 50-100% 20CV, 100% 3CV, DCM/MeOH/NH_4OH = 90/10/1 in DCM, 10 mL/min flow rate]) to give **Example 2-4, Isomer 1** (35 mg, 34%).

LC-MS (ESI+): 607.4 $[M+H]^+$, R_t = 4.52 min (Method 1)

^{1}H NMR (500 MHz, DMSO- d_6): δ ppm 0.92 (d, J = 6.4 Hz, 3 H), 2.09 - 2.17 (m, 1 H), 2.25 (br. s., 3 H), 2.54 - 2.61 (m, 1 H), 3.01 (d, J = 15.9 Hz, 1 H), 3.15 (d, J = 15.6 Hz, 1 H), 3.44 - 3.53 (m, 3 H), 3.56 (d, J = 13.4 Hz, 1 H), 3.65 (d, J = 15.9 Hz, 1 H), 3.71 - 3.76 (m, 1 H), 3.93 - 4.03 (m, 2 H), 4.57 - 4.69 (m, 1 H), 5.62 - 5.72 (m, 1 H), 6.41 (d, J = 15.9 Hz, 1 H), 6.47 (s, 1 H), 7.23 - 7.30 (m, 3 H), 7.33 - 7.41 (m, 2 H), 8.01 (d, J = 2.1 Hz, 1 H), 8.15 (s, 1 H), 8.73 (d, J = 7.6 Hz, 1 H), 8.88 (s, 1 H), 11.40 (br. s., 1 H) ppm.

^{13}C NMR (126 MHz, DMSO- d_6): δ ppm 14.5, 26.4, 39.8, 41.2, 42.9, 43.7, 50.4, 54.1, 59.4, 68.8, 71.4, 122.8, 125.3, 126.0, 126.6, 127.5, 127.6, 128.3, 129.1, 129.8, 131.4, 134.9, 141.1, 146.9, 155.5, 165.1, 178.1.

Scheme 21. Synthesis of Intermediate SA2-4



Experimental procedures for synthesis of Intermediate SA2-4

Synthesis of *tert*-butyl N-methyl-N-[2-[(E)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyloxy]ethyl]carbamate (SA2-4)

Synthesized using the same experimental procedures as described in the synthesis of Intermediate **A1-1***, starting from *tert*-butyl N-methyl-N-(2-prop-2-ynoxyethyl)carbamate (300 mg, 1.4 mmol). The desired product **SA2-4** was obtained (430 mg) and used as is in the next reaction step.

LC-MS (ESI+): 242.7 $[M+H\text{-}Boc]^+$

Scheme 22. Synthesis of Intermediate VII



V VII

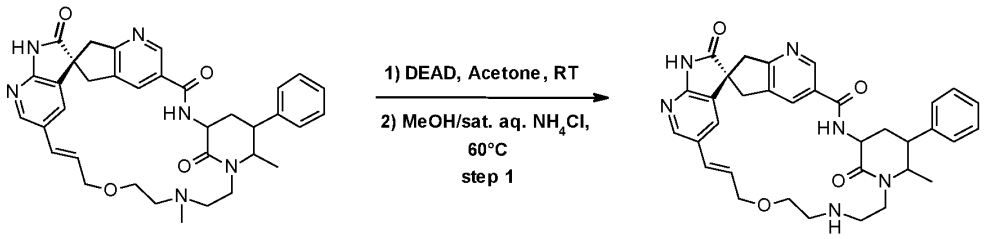
Experimental procedures of synthesis of Intermediate VII

Synthesis of *tert*-butyl N-[6-methyl-2-oxo-1-(2-oxoethyl)-5-phenyl-3-piperidyl]carbamate (VII)

V (118 mg, 0.34 mmol) was dissolved in DCM (4 mL), the reaction mixture was cooled to 0°C Dess Martin periodinane (216 mg, 0.51 mmol) was added and the reaction mixture was stirred at rt for 2 hours. Reaction was quenched by addition of sat. $NaHCO_3/Na_2S_2O_3$ (4/4 mL) mixture. Mixture was passed through the phase separator and product *tert*-butyl N-[6-methyl-2-oxo-1-(2-oxoethyl)-5-phenyl-3-piperidyl]carbamate (**VII**) was used as solution in DCM (theoretically 117 mg, 100%).

LC-MS (ESI+): 347.2 $[M+H]^+$.

Scheme 23. Synthesis of Example 2-5, Isomer 1



Example 2-4 Isomer 1 Example 2-5 Isomer 1

Experimental procedures of synthesis of Example 2-5

Step 1. Synthesis of (1S,22E)-13-methyl-12-phenyl-20-oxa-5,9,14,17,26,28-hexazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione, Example 2-5, Isomer 1

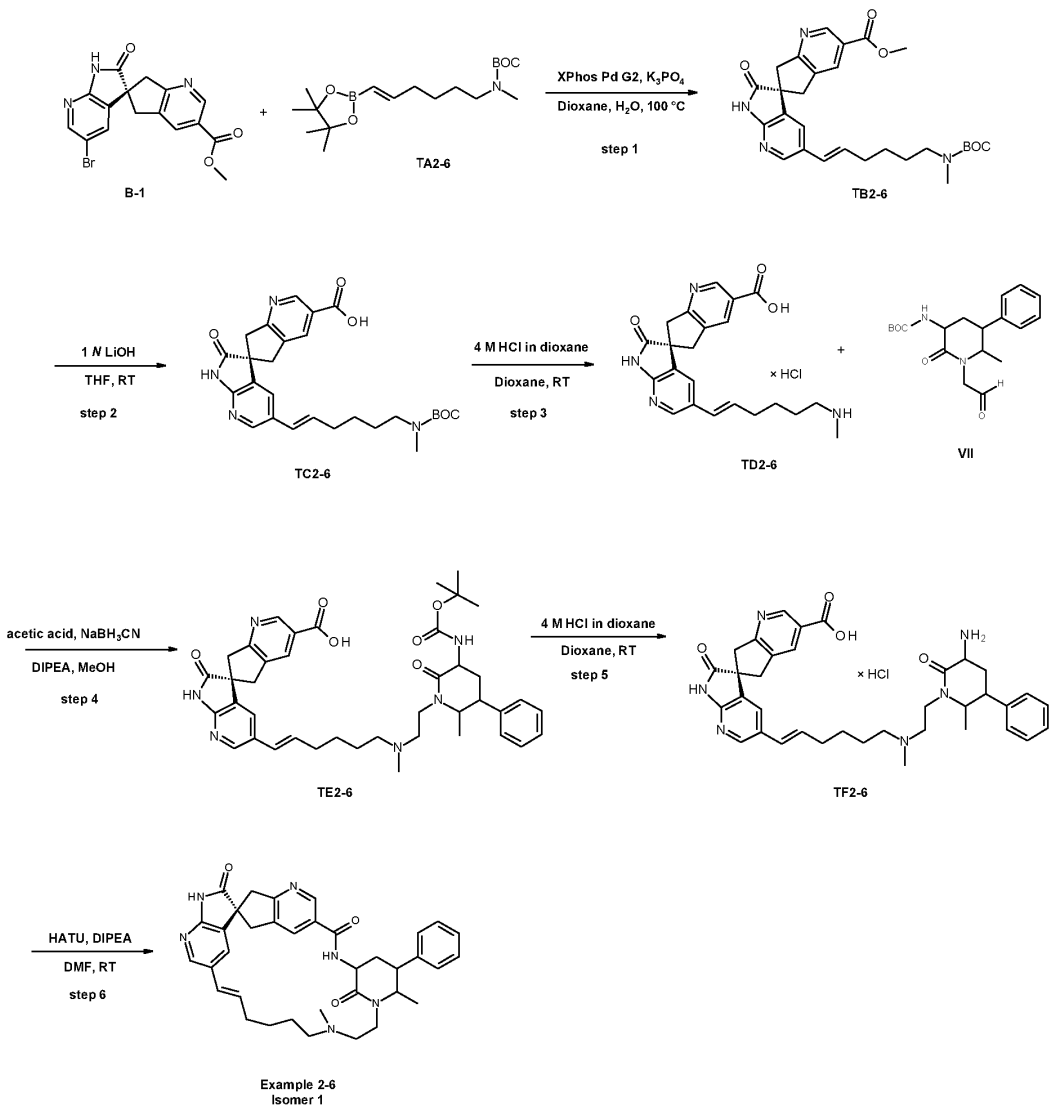
Example 2-4, Isomer 1 (10 mg, 0.017 mmol) was dissolved in acetone (1 mL) and DEAD (40% in toluene, 23 µL, 0.050 mmol) was added slowly, the reaction mixture was stirred at rt overnight. The reaction mixture was concentrated and redissolved in MeOH/sat. aq. NH_4Cl (1 /1 mL). The reaction mixture was heated at 60°C for 1 hour.

The reaction mixture was diluted with DCM, layers were separated, aq. layer was extracted with DCM (3x4mL) organics collected, washed with aq. sat. $NaHCO_3$, dried and concentrated to give crude. Crude was purified by column chromatography (normal phase [Biotage, Interchim cartridge 4g, 25 µm, 0-100%, 10CV, 100% 20 CV, DCM/MeOH/NH_4OH = 90/10/1 in DCM, 6 mL/min flow rate, to give **Example 2-5, Isomer 1** (3.3 mg, 33%).

LC-MS (ESI+): 593.3 $[M+H]^+$, R_t = 4.25 min (Method 1)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.89 (d, *J*=6.4 Hz, 3 H), 2.11 (dd, *J*=11.0, 7.3 Hz, 1 H), 2.51 - 2.60 (m, 1 H), 2.66 - 2.79 (m, 2 H), 2.97 - 3.11 (m, 2 H), 3.12 - 3.19 (m, 1 H), 3.26 - 3.31 (m, 1 H), 3.40 (t, *J*=4.7 Hz, 2 H), 3.47 - 3.53 (m, 1 H), 3.61 - 3.72 (m, 2 H), 3.72 - 3.76 (m, 2 H), 3.84 - 4.16 (m, 3 H), 4.42 - 5.12 (m, 1 H), 5.60 (dt, *J*=16.2, 6.0 Hz, 1 H), 6.39 - 6.47 (m, 1 H), 6.50 (d, *J*=2.1 Hz, 1 H), 7.22 - 7.33 (m, 1 H), 7.33 - 7.40 (m, 1 H), 7.99 (d, *J*=1.8 Hz, 1 H), 8.18 (s, 1 H), 8.87 (d, *J*=9.2 Hz, 1 H), 8.92 (s, 1 H), 11.40 (br. s., 1 H)

Scheme 24. Synthesis of Examples 2-6, Isomer 1



Experimental procedures of synthesis of Example 2-6, Isomer 1

Step 1. Synthesis of (3S)-5-[(E)-6-(methylamino)hex-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylic acid;hydrochloride (TB2-6)

Synthesized using the same experimental procedures as described for synthesis of the Intermediate **C1-1**, starting from **B-1** (600 mg, 1.60 mmol) and compound **TA2-6** (841 mg, 2.4 mmol). The desired product was obtained **TB2-6** (454 mg, 56%).

LC-MS (ES+): 507.2 $[M+H]^+$.

Step 2. Synthesis of (3S)-5-[(E)-6-[*tert*-butoxycarbonyl(methyl)amino]hex-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylic acid (TC2-6)

Synthesized using the same experimental procedures as described for synthesis of the Intermediate **D1-1**, starting from **TB2-6** (200 mg, 0.395 mmol). The desired product **TC2-6** was obtained (179 mg, 92%) and used as is in the next reaction step.

LC-MS (ES+): 493.2 $[M+H]^+$.

Step 3. Synthesis of (3S)-5-[(E)-6-(methylamino)hex-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylic acid (TD2-6)

Synthesized using the same experimental procedures as described for synthesis of the Intermediate **E1-1**, starting from **TC2-6** (179 mg, 0.248 mmol). The desired fractions were combined, and the solvent removed to yield the desired product **TD2-6** (197 mg, 98% yield as 4xHCl salt).

LC-MS (ES+): 393.4 $[M+H]^+$.

Step 4. Synthesis of (3S)-5-[(E)-6-[2-[5-(*tert*-butoxycarbonylamino)-2-methyl-6-oxo-3-phenyl-1-piperidyl]ethyl-methyl-amino]hex-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylic acid (TE2-6)

To a solution of crude compound **TD2-6** (218 mg, 0.301 mmol) in MeOH (6 mL) and DIPEA (0.206 mL, 1.2 mmol), powdered molecular sieves (200 mg) and a solution of compound **VII** (crude in DCM 6 mL) was added followed by acetic acid (34.4 µL, 0.601 mmol) and $NaCNBH_3$ (28.3 mg, 0.451 mmol). The reaction mixture was stirred at RT for 90 minutes. Added a new amount of $NaCNBH_3$ (13 mg) and continued over the night. The reaction mixture was concentrated and the residue dissolved in sat. NH_4CL (20 mL) and DCM (10 mL). The layers were separated, and the aq. layer extracted with DCM/i-PrOH (1/1, 3×10 mL). The combined organic layer was dried and concentrated to yield the crude product (506 mg) as a yellowish solid. The crude material was dry loaded and purified on a silica column (Interchim 12 g, 15 µm, SiO_2)

using an Interchim PuriFlash 450 instrument with a flowrate of 20 mL/min starting with DCM (100%) and going to 100% of DCM/MeOH/formic acid (10/2/1) in 20 CVs. Hold this 100% for further 20 CVs. The desired fractions were combined and the solvent removed to yield the desired product **TE2-6** (179.7 mg, 82% yield).

LC-MS (ES+): 723.5 $[M+H]^+$.

Step 5. Synthesis of (3S)-5-[(E)-6-[2-[5-amino-2-methyl-6-oxo-3-phenyl-1-piperidyl]ethyl-methyl-amino]hex-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylic acid; hydrochloride (TF2-6)

Synthesized using the same experimental procedures as described for synthesis of the Intermediate **E1-1**, starting from **TE2-6** (179 mg, 0.248 mmol). 197 mg of desired product **TF2-6** was obtained and was used in the next reaction step as is.

LC-MS (ES+): 623.4 $[M+H]^+$.

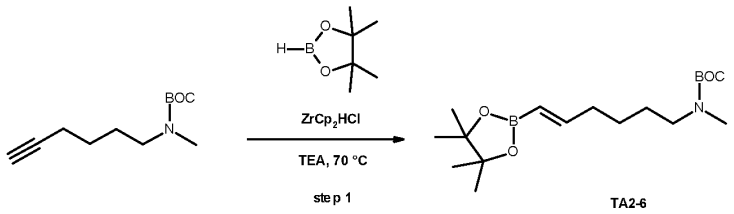
Step 6. Synthesis of (1S ,22E)-13,17-dimethyl-12-phenyl-5,9,14,17,26,28-hexazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione (Example 2-6, Isomer 1)

Synthesized using the same experimental procedures as described for synthesis of the **Example 1-1** (step 4), starting from **TF2-6** (191 mg, 0.248 mmol). The desired product was obtained **Example 2-6, Isomer 1** (67 mg, 52%).

LC-MS (ESI+): 605.3 $[M+H]^+$, R_t = 5.00 min (Method 1)

^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 0.95 (d, J=6.2 Hz, 3 H), 1.29 - 1.36 (m, 2 H), 1.37 - 1.44 (m, 1 H), 1.49 (br. s., 1 H), 2.14 (d, J=6.8 Hz, 2 H), 2.31 - 2.48 (m, 2 H), 2.57 - 2.72 (m, 2 H), 3.00 (d, J=16.0 Hz, 1 H), 3.07 - 3.16 (m, 1 H), 3.48 - 3.53 (m, 1 H), 3.56 - 3.63 (m, 1 H), 3.68 (br. s., 2 H), 3.65 (d, J=16.0 Hz, 1 H), 3.78 (br. s., 1 H), 4.57 (br. s., 1 H), 5.52 - 5.58 (m, 1 H), 6.31 (d, J=15.8 Hz, 1 H), 6.43 (br. s., 1 H), 7.26 - 7.32 (m, 3 H), 7.35 - 7.41 (m, 2 H), 7.94 (d, J=2.0 Hz, 1 H), 8.15 - 8.19 (m, 1 H), 8.86 (br. s., 1 H), 8.90 (s, 1 H), 11.35 (s, 1 H)

Scheme 25. Synthesis of Intermediate TA2-6



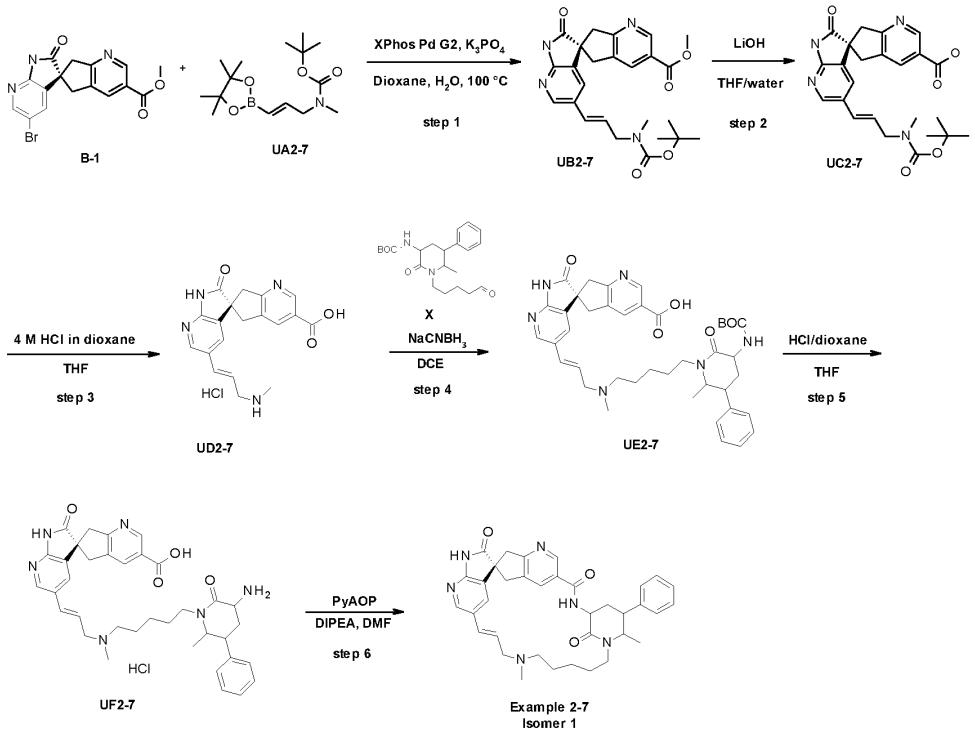
Experimental procedures of synthesis of Intermediate TA2-6

Step 1. Synthesis of *tert*-butyl N-methyl-N-[(E)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-enyl]carbamate (TA2-6)

Synthesized using the same experimental procedures as described in the synthesis of Intermediate **A1-1**, starting from *tert*-butyl N-hex-5-ynyl-N-methyl-carbamate (CAS 320367-00-8) (507 mg, 2.40 mmol). The desired product **TA2-6** was obtained (776 mg) and used as is in the next reaction step.

TLC (cyclohexane/EtOAc; 5/1); rf=0.30.

Scheme 26. Synthesis of Examples 2-7, Isomer 1



Experimental procedures of synthesis of Example 2-7

Step 1. Synthesis of methyl (3S)-5-[(E)-3-[*tert*-butoxycarbonyl(methyl)amino]prop-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylate (UB2-7)

Synthesised using the same experimental procedures as described for synthesis of the Intermediate **C1-1**, starting from **B-1** (300 mg, 0.8 mmol) and compound **UA2-7** (356 mg, 1.2 mmol). The desired product was obtained **UB2-7** (168 mg, 47%).

Step 2. Synthesis of (3S)-5-[(E)-3-[*tert*-butoxycarbonyl(methyl)amino]prop-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylic acid (UC2-7)

Synthesized using the same experimental procedures as described for synthesis of the Intermediate **D1-1**, starting from **UB2-7** (110 mg, 0.24 mmol).The desired product **UC2-7** was obtained (95 mg, 88%) and used as is in the next reaction step.

Step 3. Synthesis of (3S)-5-[(E)-3-(methylamino)prop-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylic acid (UD2-7)

Synthesized using the same experimental procedures as described for synthesis of the Intermediate **E1-1**, starting from **UC2-7** (95 mg, 0.211 mmol). The desired fractions were combined and the solvent removed to yield the desired product **UD2-7** (104 mg, 100% yield as 4xHCl salt).

Step 4. Synthesis of (3S)-5-[(E)-3-[5-[5-(*tert*-butoxycarbonylamino)-2-methyl-6-oxo-3-phenyl-1-piperidyl]pentyl-methyl-amino]prop-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylic acid (UE2-7)

UD2-7 (104 mg, 0.211 mmol) was dissolved in MeOH (4 mL) and DIPEA (147 µL, 0.84 mmol) was added followed by *tert*-butyl N-[-6-methyl-2-oxo-1-(5-oxopentyl)-5-phenyl-3-piperidyl]carbamate **X** (122 mg, 0.315 mmol) dissolved in DCM (4 mL), acetic acid (24 µL, 0.42 mmol) and $NaCNBH_3$ (27 mg, 0.42mmol). The reaction mixture was stirred at rt for 1 hour. It was added additional amount of $NaCNBH_3$ (16 mg) and the reaction mixture was stirred for an additional 30 minutes. The reaction

mixture was concentrated and redissolved in sat. NH_4Cl and DCM, layers were separated, organics collected, dried and concentrated. Crude was purified by column chromatography (normal phase [Biotage, Interchim cartridge 12 g, 25 µm DCM/MeOH/AcOH= 9/2/2 in DCM, 0%, 3CV, 0-100% 20 CV, 10 mL/min flow rate]) to give 5-[(E)-3-[5-[5-(*tert*-butoxycarbonylamino)-2-methyl-6-oxo-3-phenyl-1-piperidyl]pentyl-methyl-amino]prop-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylic acid **UE2-7** (100 mg, 66%). Used as is in the next step.

LC-MS (ESI+): 723.5 $[M+H]^+$.

Step 5. Synthesis of (3S)-5-[(E)-3-[5-(5-amino-2-methyl-6-oxo-3-phenyl-1-piperidyl)pentyl-methyl-amino]prop-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylic acid;tetrahydrochloride, UF2-7

UE2-7 (100 mg, 0.139 mmol) was dissolved in THF (5 mL) the reaction mixture was cooled down to 0°C and HCl in dioxane (4 mL, 4M) was added. The reaction mixture was stirred at room temperature 2 hours. The reaction mixture was concentrated to give crude 5-[(E)-3-[5-(5-amino-2-methyl-6-oxo-3-phenyl-1-piperidyl)pentyl-methyl-amino]prop-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylic acid;tetrahydrochloride **UF2-7** (107 mg, 100%). It was used in next step as is.

LC-MS (ESI+): 623.4 $[M+H]^+$.

Step 6. Synthesis of Example 2-7, Isomer 1

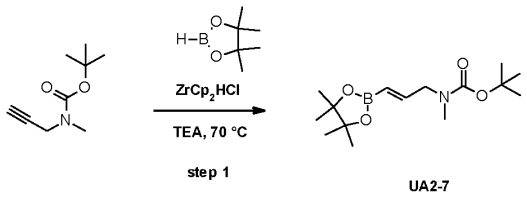
To a solution of PyAOP (109 mg, 0.208 mmol) and DIPEA (0.048 mL, 0.278 mmol) in DMF (27 mL) was added dropwise solution of **UF2-7** (107 mg, 0.139 mmol) and DIPEA (0.096 mL, 0.556 mmol) in DMF (12 mL) over 20 minutes. The reaction mixture was stirred for 20 minutes then quenched with water (100 mL) and DCM (60 mL), layers were separated, aq. layer was extracted with DCM (3x 30 mL), organics collected washed with aq. sat. $NaHCO_3$, dried and concentrated affording crude. Crude was purified by column chromatography (normal phase [Biotage, Interchim cartridge 12 g, 25 µm, 0-50%, 10CV, 50-100% 20CV, 100% 3CV,

DCM/MeOH/NH_4OH = 90/10/1 in DCM, 10 mL/min flow rate]) to give **Example 2-7, Isomer 1** (16 mg, 19%) as a single diastereoisomer.

LC-MS (ESI+): 605.3 $[M+H]^+$, R_t = 4.25 min (Method 1)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.96 (d, *J*=6.4 Hz, 3 H), 1.21 - 1.31 (m, 2 H), 1.32 - 1.43 (m, 1 H), 1.43 - 1.53 (m, 2 H), 1.55 - 1.68 (m, 1 H), 2.02 (br. s., 3 H), 2.08 - 2.15 (m, 1 H), 2.25 (br. s., 2 H), 2.64 (q, *J*=12.7 Hz, 1 H), 2.81 (dt, *J*=13.4, 6.6 Hz, 1 H), 2.89 (br. s., 1 H), 3.02 (d, *J*=16.2 Hz, 1 H), 3.14 (d, *J*=11.9 Hz, 1 H), 3.18 (d, *J*=15.9 Hz, 1 H), 3.46 - 3.57 (m, 2 H), 3.63 (d, *J*=16.2 Hz, 1 H), 3.66 - 3.74 (m, 1 H), 3.74 - 3.79 (m, 1 H), 4.58 - 4.65 (m, 1 H), 5.54 - 5.61 (m, 1 H), 6.40 (d, *J*=15.9 Hz, 1 H), 6.58 (d, *J*=1.8 Hz, 1 H), 7.21 - 7.31 (m, 3 H), 7.33 - 7.40 (m, 2 H), 7.99 (d, *J*=1.8 Hz, 1 H), 8.13 (s, 1 H), 8.76 (d, *J*=8.9 Hz, 1 H), 8.85 (s, 1 H), 11.39 (s, 1 H)

Scheme 27. Synthesis of Intermediate UA2-7

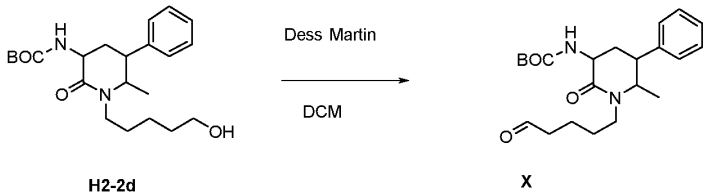


Experimental procedures of synthesis of Intermediate UA2-7

Step 1. Synthesis of *tert*-butyl N-methyl-N-[(E)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl]carbamate (UA2-7)

Synthesized using the same experimental procedures as described in the synthesis of Intermediate **A1-1**, starting from *tert*-butyl N-methyl-N-prop-2-ynyl-carbamate (204 mg, 1.2 mmol). The desired product **UA2-7** was obtained (356 mg) and used as is in the next reaction step.

Scheme 28. Synthesis of intermediate X



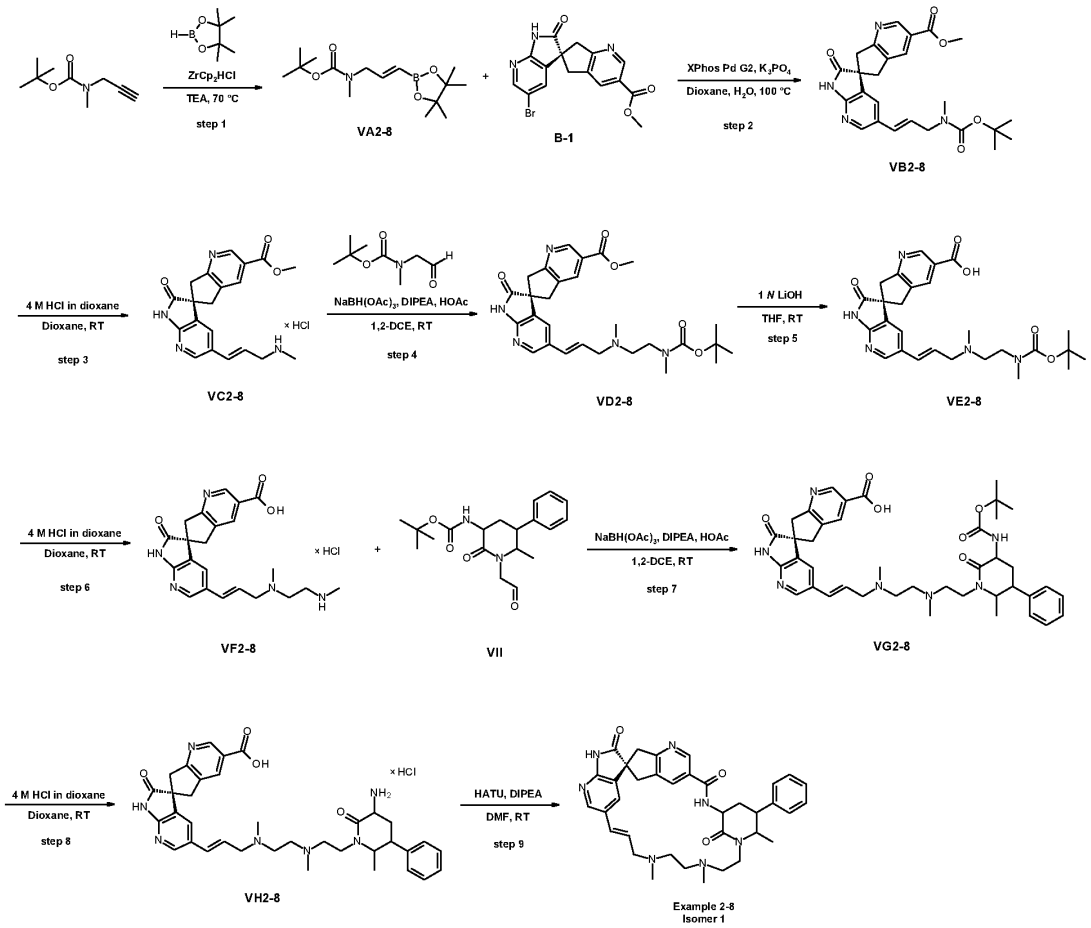
Experimental procedures of synthesis of Intermediate X

Synthesis of *tert*-butyl (6-methyl-2-oxo-1-(5-oxopentyl)-5-phenyl-3-piperidyl)carbamate, X

H2-2d (123 mg, 0.315 mmol) was dissolved in DCM (4 mL), the reaction mixture was cooled to 0°C Dess Martin periodinane (200 mg, 0.472 mmol) was added and the reaction mixture was stirred at rt for 2 hours. Reaction was quenched by addition of sat. $NaHCO_3/Na_2S_2O_3$ (4/4 mL) aq. mixture. Mixture was passed through the phase separator and product *tert*-butyl (6-methyl-2-oxo-1-(5-oxopentyl)-5-phenyl-3-piperidyl)carbamate **X** was used as solution in DCM (theoretically 122 mg, 100%).

LC-MS (ESI+): 389.3 $[M+H]^+$.

Scheme 29. Synthesis of Example 2-8 Isomer 1



Step 1. Synthesis of *tert*-butyl *N*-methyl-*N*-[(*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl]carbamate (VA2-8)

Synthesized using the same experimental procedures as described in step 3 of the synthesis of Intermediate **A1-1**, starting from (Methyl)(2-propyn-1-yl)carbamic acid *tert*-butyl ester (CAS 124045-51-8) (642.0 mg, 3.794 mmol). The desired product **VA2-8** was obtained (776 mg) and used as is in the next reaction step.

LC-MS (ES+): 320.3 $[M+Na]^+$.

Step 2. Synthesis of methyl (3*S*)-5-[(*E*)-3-[*tert*-butoxycarbonyl(methyl)amino]prop-1-enyl]-2-oxo-spiro[1*H*-pyrrolo[2,3-*b*]pyridine-3,6'-5,7-dihydrocyclopenta[*b*]pyridine]-3'-carboxylate (VB2-8)

Synthesized using the same experimental procedure as described in the synthesis of Intermediate **C1-1**, starting from compound **VA2-8** (800.0 mg, 2.138 mmol) and compound **B-1** (1.16 g, 3.574 mmol). The desired product **VB2-8** (448.0 mg, 45.1%).

LC-MS (ES+): 465.4 $[M+H]^+$.

Step 3. Synthesis of methyl (3*S*)-5-[(*E*)-3-(methylamino)prop-1-enyl]-2-oxo-spiro[1*H*-pyrrolo[2,3-*b*]pyridine-3,6'-5,7-dihydrocyclopenta[*b*]pyridine]-3'-carboxylate hydrochloride (VC2-8)

Synthesized using the same experimental procedure as described in the synthesis of Intermediate **E1-1**, starting from compound **VB2-8** (152.4 mg, 0.328 mmol). The desired product **VC2-8** (172.6 mg) was obtained and used as is in the next reaction step.

LC-MS (ES+): 365.3 $[M+H]^+$.

Step 4. Synthesis of methyl (3*S*)-5-[(*E*)-3-[2-[*tert*-butoxycarbonyl(methyl)amino]ethyl-methyl-amino]prop-1-enyl]-2-oxo-spiro[1*H*-pyrrolo[2,3-*b*]pyridine-3,6'-5,7-dihydrocyclopenta[*b*]pyridine]-3'-carboxylate, (VD2-8)

To a suspension of compound **VC2-8** (172.6 mg, 0.3281 mmol), DIPEA (233.3 µL, 1.312 mmol) and 4 Å molecular sieves in DCE (8.40 mL) was added a solution of tert-butyl (2-oxoethyl)carbamate (CAS 1189711-08-0) (3.7 mg, 0.656 mmol) in DCE (5.50 mL) followed by acetic acid (75.1 µL, 1.312 mmol) and sodium

triacetoxyborohydride (278.2 mg, 1.312 mmol). The resulted mixture was left to stir at RT for 2 hours. The reaction mixture was filtered through pad of Celite pad and washed with DCM (3 × 10 mL). The filtrate was quenched with *sat.* $NaHCO_3$ (50 mL), layers were separated, and the aqueous layer additionally extracted with DCM (2 × 15 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford raw product (223.0 mg). The crude product was purified on an Interchim (12 g, 15 µm, SiO_2) column and using a flowrate of 20 mL/min starting with DCM (100%) and going to 100% [DCM/MeOH (10:1)] in 15 CVs. Hold 100% for 15 CVs. The appropriate fractions were collected, the solvent removed to yield the desired product **VD2-8** (139.3 mg, 81.4%).

LC-MS (ESI+): 522.4 $[M+H]^+$.

Step 5. Synthesis of (3*S*)-5-[(*E*)-3-[2-[*tert*-butoxycarbonyl(methyl)amino]ethyl-methyl-amino]prop-1-enyl]-2-oxo-spiro[1*H*-pyrrolo[2,3-*b*]pyridine-3,6'-5,7-dihydrocyclopenta[*b*]pyridine]-3'-carboxylic acid, (VE2-8)

Synthesized using the same experimental procedure as described in the synthesis of Intermediate **D1-1**, starting from compound **VD2-8** (152.4 mg, 0.328 mmol). The desired product **VE2-8** (135.6, 100.0%) was obtained and used as is in the next reaction step.

LC-MS (ESI+): 508.4 $[M+H]^+$.

Step 6. Synthesis of (3*S*)-5-[(*E*)-3-[methyl-[2-(methylamino)ethyl]amino]prop-1-enyl]-2-oxo-spiro[1*H*-pyrrolo[2,3-*b*]pyridine-3,6'-5,7-dihydrocyclopenta[*b*]pyridine]-3'-carboxylic acid hydrochloride (VF2-8),

Synthesized using the same experimental procedure as described in the synthesis of Intermediate **E1-1**, starting from compound **VE2-8** (53.0 mg, 0.1045 mmol). The desired product **VF2-8** (61.7 mg) was obtained and used in the next reaction step as is.

LC-MS (ES^+): 408.3 $[M+H]^+$.

Step 7. Synthesis of (3S)-5-[(E)-3-[2-[2-[5-(*tert*-butoxycarbonylamino)-2-methyl-6-oxo-3-phenyl-1-piperidyl]ethyl-methyl-amino]ethyl-methyl-amino]prop-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylic acid (VG2-8)

Synthesized using the same experimental procedure as described in the synthesis of Intermediate **VD2-8**, starting from compound **VF2-8** (61.7 mg, 0.1045 mmol) and a solution of **VII**. 55.8 mg (72.3%) of the desired product **VG2-8** (61.7 mg) was obtained.

LC-MS (ESI+): 738.7 $[M+H]^+$.

Step 8. Synthesis of (3S)-5-[(E)-3-[2-[2-(5-amino-2-methyl-6-oxo-3-phenyl-1-piperidyl)ethyl-methyl-amino]ethyl-methyl-amino]prop-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylic acid (VH2-8)

Synthesized using the same experimental procedure as described in the synthesis of Intermediate **E1-1**, starting from compound **VG2-8** (55.8 mg, 0.0756 mmol). The desired product **VH2-8** was obtained (64.8 mg) and used in the next reaction step as is.

LC-MS (ES^+): 638.6 $[M+H]^+$.

Step 9. Synthesis of (1*S*, 22*E*)-13,17,20-trimethyl-12-phenyl-5,9,14,17,20,26,28-heptazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione (Example 2-8, Isomer 1)

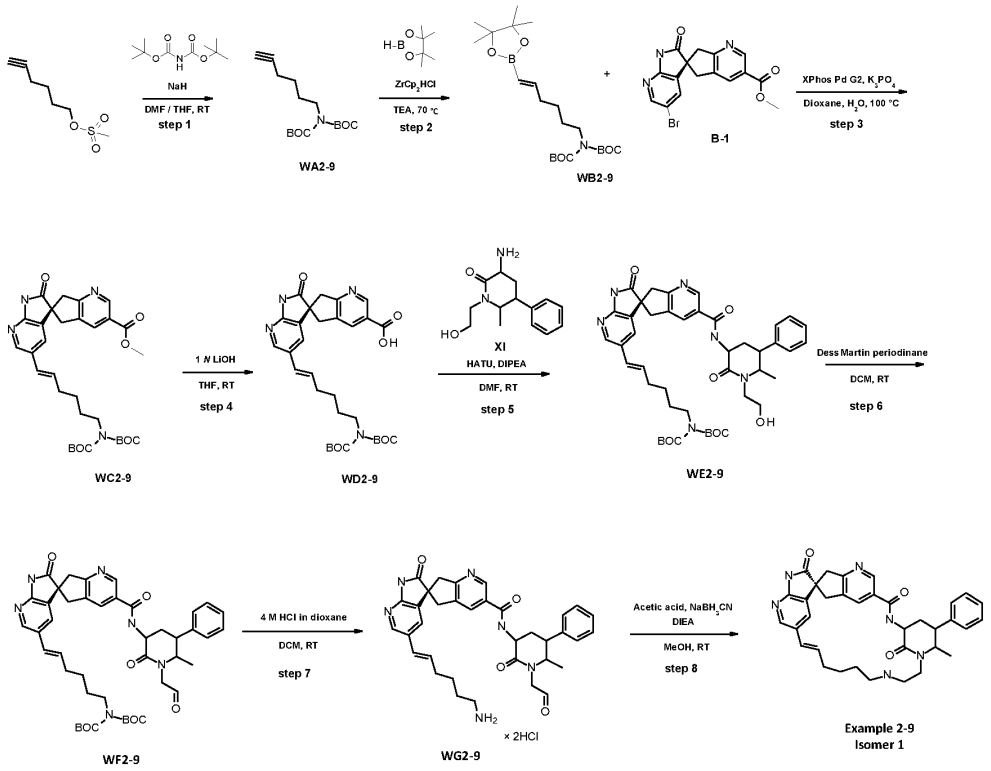
Synthesized using the same experimental procedure as described in the synthesis of Example **1-1**, starting from compound **VH2-8** (64.8 mg, 0.0756 mmol). 22.3 mg (52.9%) of desired product **Example 2-8** was obtained.

LC-MS (ESI+): 620.6 $[M+H]^+$. R_t = 3.53 min (Method 1)

^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 0.92 (d, *J*=6.4 Hz, 3 H), 2.03 (s, 3 H), 2.07 - 2.16 (m, 1 H), 2.20 (br. s., 3 H), 2.30 - 2.36 (m, 1 H), 2.36 - 2.45 (m, 2 H), 2.45 - 2.48 (m, 1 H), 2.56 - 2.68 (m, 2 H), 2.90 - 3.12 (m, 5 H), 3.12 - 3.22 (m, 1 H), 3.48 - 3.52 (m, 1 H), 3.56 (d, *J*=13.2 Hz, 1 H), 3.61 - 3.69 (m, 2 H), 3.70 - 3.76 (m, 1 H), 4.56 - 4.64 (m, 1 H), 5.55 - 5.62 (m, 1 H), 6.39 (d, *J*=15.8 Hz, 1 H), 6.51 (br. s., 1 H), 7.24 -

7.31 (m, 3 H), 7.37 (t, *J*=7.6 Hz, 2 H), 7.99 (d, *J*=1.8 Hz, 1 H), 8.18 (s, 1 H), 8.75 (br. s., 1 H), 8.90 (s, 1 H), 11.38 (br. s., 1 H)

Scheme 30. Synthesis of Example 2-9, Isomer 1



Experimental procedures of synthesis of Example 2-9

Step 1. Synthesis of *tert*-butyl N-*tert*-butoxycarbonyl-N-hex-5-ynyl-carbamate (WA2-9).

To a suspension of compound NaH (79.5 mg, 2.0 mmol) in DMF (8.4 ml) was added a solution of *tert*-butyl N-*tert*-butoxycarbonylcarbamate (360 mg, 1.66 mmol) in THF (1.4 mL) in a dropwise fashion. The reaction mixture was stirred at RT for 1 h, then cooled in ice bath to 0 °C. 5-Hexyn-1-ol 1-methanesulfonate (CAS 79496-61-0) (350 mg, 2.0 mmol) was added drop wise (dissolved in 0.2 ml of DMF). The stirring continued at RT for 16 h. The reaction mixture was quenched wit sat. aq. NH_4Cl (40 ml), extracted with EtOAc (3x30 ml), washed with water (30 ml) and brine (30 ml), dried under $MgSO_4$ and concentrated under reduced pressure to obtain crude product. The crude material was loaded and purified on a silica column (Interchim 12

g, 15 µm, SiO_2) using Interchim PuriFlash 430 instrument with a flowrate of 10 mL/min starting with cyclohexane (100%) and going to 10% of EtOAc/cyclohexane in 36 CVs. The appropriate fractions were collected, the solvent removed to yield the desired product **WA2-9** (288 mg, Y=58%) as a colourless liquid.

LC-MS (ES+): 320.2 $[M+Na]^+$.

Step 2. Synthesis of *tert*-butyl N-*tert*-butoxycarbonyl-N-[(E)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-enyl]carbamate (WB2-9)

Synthesized using the same experimental procedures as described in the synthesis of Intermediate **A1-1**, starting from **WA2-9** (288 mg, 0.97 mmol). The desired crude product **WB2-9** (285 mg, yellow oil) was obtained and used as is in the next reaction step.

LC-MS (ES+): 426.4 $[M+H]^+$.

Step 3. Synthesis of *ditert*-butyl 2-[(E)-6-[(3S)-3'-methoxycarbonyl-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-5-yl]hex-5-enyl]propanedioate (WC2-9)

Synthesized using the same experimental procedures as described in the synthesis of Intermediate **C1-1** starting from compound **B1** (167 mg, 0.44 mmol) and compound **WB2-9** (280.9 mg, 0.66 mmol). 158 mg (45.1%) of the desired product **WC2-9** was obtained.

LC-MS (ES+): 593.4 $[M+H]^+$.

Step 4. Synthesis of (3S)-5-[(E)-6-[bis(*tert*-butoxycarbonyl)amino]hex-1-enyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylic acid (WD2-9)

Synthesized using the same experimental procedures as described in the synthesis of Intermediate **D1-1** starting from compound **WC2-9** (158 mg, 0.27 mmol). The desired product **WD2-9** (86 mg, Y=55.8%, pale yellow solid) was obtained and used as is in the next reaction step.

LC-MS (ES+): 579.3 $[M+H]^+$.

Step 5. Synthesis of *tert*-butyl N-*tert*-butoxycarbonyl-N-[(E)-6-[(3S)-3'-[[1-(2-hydroxyethyl)-6-methyl-2-oxo-5-phenyl-3-piperidyl]carbamoyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-5-yl]hex-5-enyl]carbamate (WE2-9)

Synthesized using the same experimental procedure as described in the synthesis of Example **1-1**, starting from compound **WD2-9** (86 mg, 0.15 mmol) and compound **XI** (48.7 mg, 0.17 mmol). The desired product **WE2-9** was obtained (74 mg, Y=61.6%) as an off-white solid.

LC-MS (ES+): 809.5 $[M+H]^+$.

Step 6. Synthesis of *tert*-butyl N-*tert*-butoxycarbonyl-N-[(E)-6-[(3S)-3'-[[6-methyl-2-oxo-1-(2-oxoethyl)-5-phenyl-3-piperidyl]carbamoyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-5-yl]hex-5-enyl]carbamate (WF2-9)

A solution of compound **WE2-9** (16 mg, 0.02 mmol) in DCM (0.3 mL) was cooled to 0 °C, then Dess-Martin periodinane (12.6 mg, 0.03 mmol) was added and the reaction mixture stirred at RT for 5 hours. The reaction was quenched by adding 4 ml of a 1:1 mixture of sat. $NaHCO_3$/$Na_2S_2O_3$. The mixture was stirred for 10 minutes and then passed through a phase separator. The solution of the product **WF2-9** in DCM was used as is in the next reaction step as is.

LC-MS (ES+): 829.4 $[M+Na]^+$.

Step 7. Synthesis of (3S)-5-[(E)-6-aminohex-1-enyl]-N-[6-methyl-2-oxo-1-(2-oxoethyl)-5-phenyl-3-piperidyl]-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxamide; dihydrochloride (WG2-9)

Synthesized using the same experimental procedure as described in the synthesis of Intermediate **E1-1**, starting from compound **WF2-9** (16 mg, 0.019 mmol). The reaction mixture was concentrated to yield the desired product **WG2-9** (21 mg) which was used as is in the next reaction step.

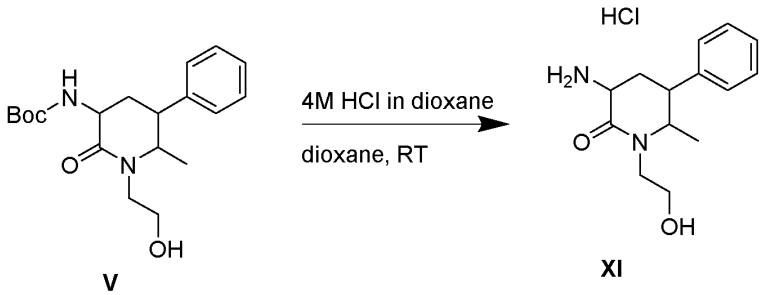
LC-MS (ES+): 607.3 $[M+H]^+$.

Step 8. Synthesis of (1S,22E)-13-methyl-12-phenyl-5,9,14,17,26,28-hexazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),22,24(31),25,27(30)-heptaene-8,29,32-trione (Example 2-9, Isomer 1)

To a solution of compound **WG2-9** (21mg, crude product) in methanol DIPEA (27 µL, 0.16 mmol) and powdered molecular sieves (40 mg) were added. The resulting brown mixture was stirred for 40 min at RT. Then acetic acid (2.3 µL, 0.04 mmol) and $NaBH_3CN$ (1.9 mg, 0.03 mmol) were added. The reaction mixture was stirred at RT for 2 h. The reaction mixture was concentrated, and the residue dissolved in *sat.* NH_4Cl (20 mL) and DCM/*i*-PrOH 1:1 (10 mL). The layers were separated, and the aqueous layer extracted with DCM/*i*-PrOH 1:1 (3×10 mL). The combined organic layers were dried under MgSO4 and concentrated under reduced pressure to afford m= 20 mg of the crude product. The crude material was loaded and purified on a silica column (Interchim 4 g, 15 µm, SiO_2) using Interchim PuriFlash 450 instrument with a flowrate of 8 mL/min starting with DCM (100%) and going to 100% DCM/MeOH/NH_3 (90:9:1.5) in 20 CVs. The appropriate fractions were collected, the solvent removed to yield the desired product **Example 2-9, Isomer 1** (1 mg, 8.6%) as a white solid.

LC-MS (ES+): 591.5 $[M+H]^+$.

Scheme 31. Synthesis of Intermediate XI



V **XI**

Experimental procedures of synthesis of Intermediate XI

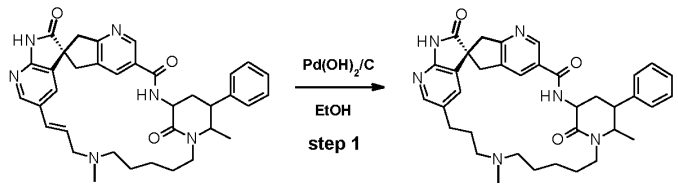
Synthesis of 3-amino-1-(2-hydroxyethyl)-6-methyl-5-phenyl-piperidin-2-one hydrochloride XI

To the solution of compound **V** (145 mg, 0.4 mmol) in 1,4-dioxane (4.2 mL) HCl (4.0 M in dioxane, 4.2 ml, 0.02 mmol) was added. The reaction mixture was stirred at RT

for 3 h. The reaction mixture was concentrated to yield the desired product **XI** (138 mg) which was used as is in the next reaction step.

LC-MS (ES+): 249.2 $[M+H]^+$.

Scheme 32. Synthesis of Example 2-10, Isomer 1



Example 2-7
Isomer 1

Example 2-10
Isomer 1

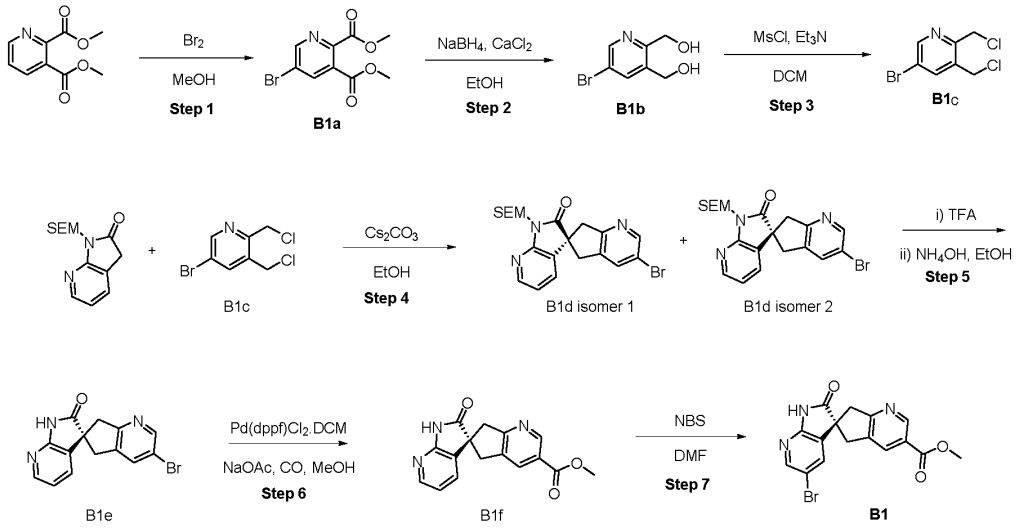
Step 1. Experimental procedures of synthesis of (1S)-13,20-dimethyl-12-phenyl-5,9,14,20,26,28-hexazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),24(31),25,27(30)-hexaene-8,29,32-trione (Example 2-10)

Example 2-7 (6.00 mg, 0.01 mmol) was dissolved in EtOH in a 5 mL flask, purged with argon, then $Pd(OH)_2/C$ (2.0 mg) was added. reaction mixture was stirred and hydrogenated under a balloon filled with hydrogen till full reduction of double bond, monitored by UPLC MS. The reaction mixture was filtered through syringe filter, and concentrated to give crude (1S)-13,20-dimethyl-12-phenyl-5,9,14,20,26,28-hexazahexacyclo[22.5.2.11,4.13,7.110,14.027,30]tetratriaconta-3,5,7(33),24(31),25,27(30)-hexaene-8,29,32-trione (4.4 mg, 73 %). Crude was purified by preparative HPLC to give final product **Example 2-10, Isomer 1** (1.3 mg, Y= 21%).

^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 1.11 (d, J=6.7 Hz, 3 H), 1.32 - 1.49 (m, 4 H), 1.49 - 1.68 (m, 4 H), 1.68 - 1.81 (m, 1 H), 2.24 - 2.30 (m, 2 H), 2.31 (s, 3 H), 2.36 - 2.47 (m, 2 H), 2.56 (t, J=7.2 Hz, 2 H), 2.82 - 2.95 (m, 2 H), 3.04 (d, J=16.2 Hz, 1 H), 3.11 (d, J=15.9 Hz, 1 H), 3.54 (d, J=13.4 Hz, 1 H), 3.67 (d, J=15.6 Hz, 1 H), 3.73 - 3.82 (m, 2 H), 3.97 (dt, J=13.9, 7.1 Hz, 1 H), 4.48 (dd, J=11.4, 7.2 Hz, 1 H), 6.57 (d, J=1.8 Hz, 1 H), 7.25 - 7.32 (m, 3 H), 7.37 (t, J=7.6 Hz, 2 H), 7.91 (d, J=1.8 Hz, 1 H), 8.16 - 8.20 (m, 1 H), 8.78 (s, 1 H)

Synthesis of Intermediates BX

Scheme 33. Synthesis of Intermediate B1



Experimental procedure for synthesis of methyl (S)-5'-bromo-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[b]pyridine-6,3'-pyrrolo[2,3-b]pyridine]-3-carboxylate B1

Step 1 synthesis of dimethyl 5-bromopyridine-2,3-dicarboxylate B1a

To a stirred solution of dimethyl pyridine-2,3-dicarboxylate (605-38-9) (100 g, 0.510 mol) in MeOH (500 mL) at 0 °C was added dropwise bromine (52.48 mL, 1.22 mol). The reaction mixture was then stirred at 55 °C overnight. The reaction mixture was quenched with ice cold H_2O and extracted with EtOAc (2 x 1 L). The combined organic layers were washed with sat. NaCl (aq) (500 mL) and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (SiO_2, petroleum ether - EtOAc) to give dimethyl 5-bromopyridine-2,3-dicarboxylate **B1a** (135 g, 96 %).

LC-MS (ESI+): 274.0 $[M+H]^+$.

Step 2 synthesis of(5-bromopyridine-2,3-diyl)dimethanol B1b

To a stirred solution dimethyl 5-bromopyridine-2,3-dicarboxylate **B1a** (135 g, 0.492 mol) in EtOH (2.5 L) at 0 °C was added portion wise sodium borohydride (112 g, 2.96 mol), followed by the dropwise addition of a solution of $CaCl_2$ (164 g, 1.48 mol) in EtOH (1.5 L) over a period of 40 mins. The temperature was maintained at 0 °C throughout the addition (exothermic reaction – efficient cooling was needed). The

reaction mixture was then stirred at room temperature for 20 h and then re-cooled to 0 °C. The reaction mixture was quenched with 2M HCl solution over a period of 30 mins to obtain a clear solution and was then allowed to warm to room temperature and stirred for 1 h. The reaction mixture was washed with EtOAc (1 L) and the organic layer was washed with further 1M HCL (0.2 L). The pH of the combined aqueous layers was adjusted to pH 7 using sat. $NaHCO_3$ (aq) and then extracted with EtOAc (2 x 1 L). The combined organic layers were washed with sat. NaCl (aq) (500 mL) and concentrated *in vacuo*. The crude residue was triturated with MeOH to obtain a solid. The solid was collected by filtration to give (5-bromopyridine-2,3-diyl)dimethanol **B1b** (48 g, 45 %).

LC-MS (ESI+): 218.0 $[M+H]^+$.

Step 3 synthesis of 5-bromo-2,3-bis(chloromethyl)pyridine B1c

To a solution of (5-bromopyridine-2,3-diyl)dimethanol **B1b** (35 g, 0.160 mol) and Et_3N (67 mL, 0.401 mol) in dry DCM (850 mL) at 0 °C was added methanesulfonyl chloride (31 mL, 0.481 mol). The reaction mixture was stirred at room temperature for 16 h and was then quenched with sat. NH_4Cl (aq) (500 mL) and extracted with DCM (500 mL). The organic layer was washed with sat. NaCl (aq) (150 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give 5-bromo-2,3-bis(chloromethyl)pyridine **B1c** (31.5 g, 77 %).

LC-MS (ESI+): 255.9 $[M+H]^+$.

Step 4 synthesis of (S)-3-bromo-1'-((2-(trimethylsilyl)ethoxy)methyl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,3'-pyrrolo[2,3-b]pyridin]-2'(1'H)-one B1d isomer 2.

To a suspension of 1-((2-(trimethylsilyl)ethoxy)methyl)-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (CAS 879132-48-6) (33 g, 0.125 mmol) and 5-bromo-2,3-bis(chloromethyl)pyridine **B1c** (44.6 g, 0.175 mol) in EtOH (900 mL) was added Cs_2CO_3 (113.75 g, 0.35 mol). The reaction mixture was stirred at room temperature for 16 h and was then quenched with ice cold H_2O (1 L) and extracted with EtOAc (2 x 1 L). The combined organic layers were washed with sat. NaCl (aq) (500 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (SiO_2, petroleum ether - EtOAc) to give 3-bromo-1'-((2-

(trimethylsilyl)ethoxy)methyl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,3'-pyrrolo[2,3-b]pyridin]-2'(1'H)-one **B1d**.

Purified by Chiral SFC

Instrument: PICLab PREP 400
Solvents: Primary mobile phase = CO_2 Modifier: 35% MeOH
Column: YMC Cellulose-SC 5um, 250x30mm, at 35°C. UV monitoring: 210nm
Flow: 120g/min..

To give

(R)-3-bromo-1'-((2-(trimethylsilyl)ethoxy)methyl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,3'-pyrrolo[2,3-b]pyridin]-2'(1'H)-one **B1d isomer 1** (4.0 g) **LC-MS (ESI+):** 446.2 $[M+H]^+$. **SFC** 2.34min and

(S)-3-bromo-1'-((2-(trimethylsilyl)ethoxy)methyl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,3'-pyrrolo[2,3-b]pyridin]-2'(1'H)-one (3.5 g) **B1d isomer 2 LC-MS (ESI+):** 446.2 $[M+H]^+$. **SFC** 3.25min

Chiral SFC analytical YMC Cellulose-SC, 250×4.6 mm 5µ at 35 °C, 3 ml/min, 40% Methanol 35 °C.

Step 5 synthesis of (S)-3-bromo-5,7-dihydrospiro[cyclopenta[b]pyridine-6,3'-pyrrolo[2,3-b]pyridin]-2'(1'H)-one B1e

A suspension of (S)-3-bromo-1'-((2-(trimethylsilyl)ethoxy)methyl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,3'-pyrrolo[2,3-b]pyridin]-2'(1'H)-one **B1d isomer 2** (19 g, 42.6 mmol) in TFA (100 mL) was heated at 60 °C for 3 h and then concentrated *in vacuo*. The resulting residue was dissolved in EtOH (100 mL) and to this was then added NH_4OH (100 ml). The reaction mixture was stirred at room temperature for 2 h. The resulting precipitate was collected by filtration to give (S)-3-bromo-5,7-dihydrospiro[cyclopenta[b]pyridine-6,3'-pyrrolo[2,3-b]pyridin]-2'(1'H)-one **B1e** (10.2 g, 76 %).

LC-MS (ESI+): 316.0 $[M+H]^+$.

Step 6 synthesis of methyl (S)-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[b]pyridine-6,3'-pyrrolo[2,3-b]pyridine]-3-carboxylate B1f

A stirred solution of (S)-3-bromo-5,7-dihydrospiro[cyclopenta[b]pyridine-6,3'-pyrrolo[2,3-b]pyridin]-2'(1'H)-one **B1e** (10 g, 31.62 mmol) and sodium acetate (5.24 g, 63.3 mmol) in MeOH (150 mL) in a mini clave vessel was degassed with argon, followed by the addition of $Pd(dppf)Cl_2$.DCM (3.87 g, 4.74 mmol). The reaction mixture was heated at 100 °C for 16 h under 5 Kg/cm^2 pressure of CO gas. The reaction mixture was partitioned between EtOAc (600 mL) and H_2O (200 mL). The organic layer was washed with sat. NaCl (aq) (200 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (SiO_2, petroleum ether - EtOAc) to give methyl (S)-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[b]pyridine-6,3'-pyrrolo[2,3-b]pyridine]-3-carboxylate **B1f** (5 g, 54 %).

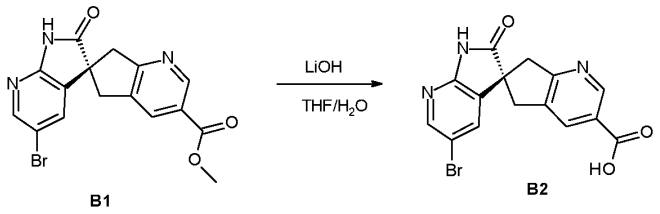
LC-MS (ESI+): 296.1 $[M+H]^+$.

Step 7 synthesis of methyl (S)-5'-bromo-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[b]pyridine-6,3'-pyrrolo[2,3-b]pyridine]-3-carboxylate B1

To a stirred solution of methyl (S)-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[b]pyridine-6,3'-pyrrolo[2,3-b]pyridine]-3-carboxylate **B1f** (5.0 g, 16.9 mmol) in DMF (50 mL) at 0 °C was added NBS (9.04 g, 50.8 mmol). The reaction mixture was stirred at room temperature for 3 h and was then quenched by ice cold H_2O. The resulting precipitate was collected by filtration, washed with cold H_2O, dried over high vacuum for 3 h to give methyl (S)-5'-bromo-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[b]pyridine-6,3'-pyrrolo[2,3-b]pyridine]-3-carboxylate **B1** (4.7 g, 74 %).

LC-MS (ESI+): 374.0 $[M+H]^+$.

Scheme 34. Synthesis of Intermediate B2

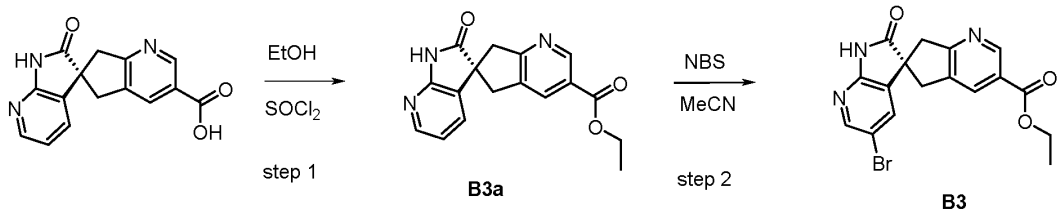


Experimental procedure for synthesis of (3S)-5-bromo-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylic acid (B2)

To the solution of compound **B1** (240 mg, 0.64 mmol) in THF (8.5 mL), LiOH (1.0 *N* in H_2O, 2.56 mL, 2.56 mmol) was added. The reaction mixture was stirred at room temperature for 40 minutes. The reaction mixture was concentrated under reduced pressure, diluted with water (20 mL) The pH value was adjusted to 3.5 using 1 *N* HCl, and extracted with a mixture of DCM/*i*-PrOH 1:1 (4 × 8 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford the desired product **B2** (207 mg, 89 %) which was used as is in the next reaction step.

LC-MS (ES+): 360.4, 362.4 $[M+H]^+$.

Scheme 35. Synthesis of Intermediate B3



Experimental procedures of synthesis of Intermediate B3

Step 1. Synthesis of ethyl (3S)-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylate

A solution of (3S)-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylic acid (CAS 1375541-21-1) (1.023 g, 3.63 mmol) in dry EtOH (50 mL) was cooled to 0°C. Into this solution $SOCl_2$ (1.057 mL, 14.5 mmol) was added dropwise. The mixture was stirred at the 75°C for 5 hours. The solvent was evaporated to yield ethyl (3S)-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylate (1.123 g, 100%). Product was used in next step as it is.

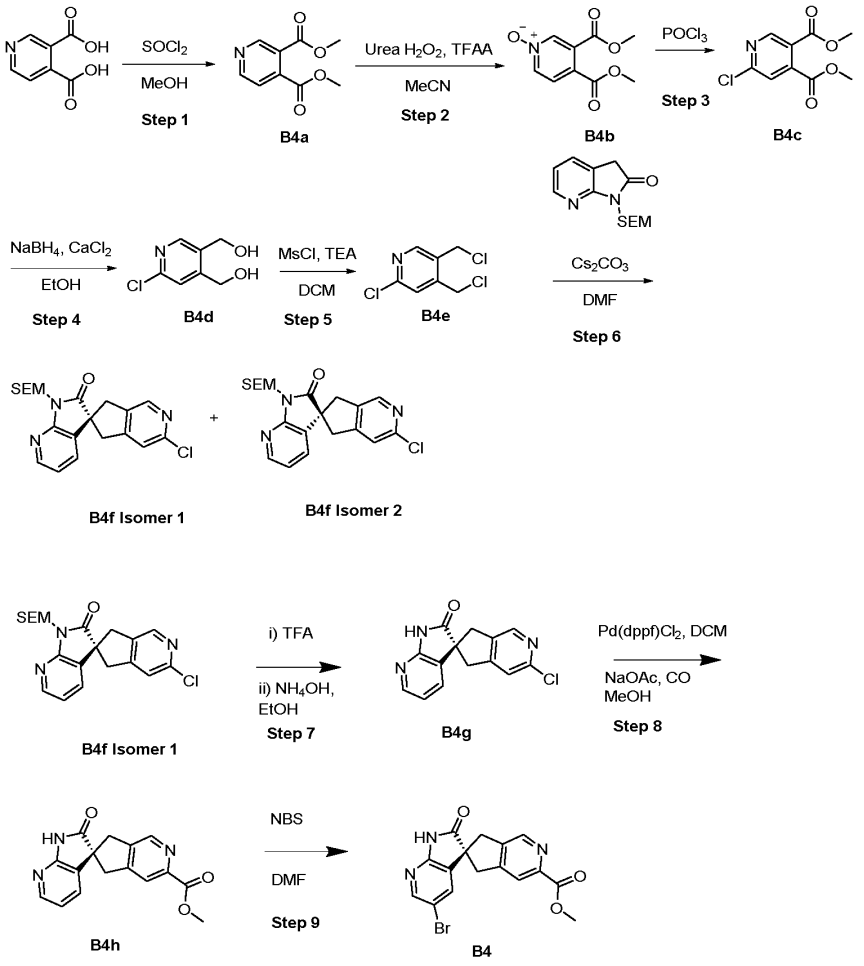
LC-MS (ES^+): 310.1 $[M+H]^+$

Step 2. Synthesis of ethyl (3S)-5-bromo-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylate B3

A suspension of ethyl (3S)-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b] pyridine]-3'-carboxylate (1.123 g, 0.363 mmol) in the dry ACN (20 mL) was cooled to 0°C. Into this solution NBS (1.292 g, 7.26 mmol) was added. The mixture was stirred at the RT ON. The reaction mixture was dropwise added into water (300 mL). The formed precipitation was filtered off, washed with water (50 mL) and dried overnight under vacuum at 45°C to give ethyl (3S)-5-bromo-2-oxo-spiro[1H-pyrrolo[2,3-b]pyridine-3,6'-5,7-dihydrocyclopenta[b]pyridine]-3'-carboxylate **B3** (1.4 g, 100%).

LC-MS (ES^+): 388 $[M+H]^+$

Scheme 36. Synthesis of Intermediate B4



Experimental procedures of synthesis of Intermediate B4

Step 1 Synthesis of dimethyl pyridine-3,4-dicarboxylate B4a

To stirred solution of pyridine-3,4-dicarboxylic acid (CAS 490-11-9) (500 g, 2.99 mol) in MeOH (4 L) at 0 °C was added dropwise $SOCl_2$ (1.1 L, 15.0 mol). The reaction mixture was stirred at 70 °C for 16 h. The reaction mixture was then concentrated *in vacuo* and the resulting residue was quenched with saturated aqueous $NaHCO_3$ (2 L) and extracted with EtOAc (2 x 2 L). The combined organic layers were washed with brine (1 L), dried (Na_2SO_4) and concentrated *in vacuo* to give dimethyl pyridine-3,4-dicarboxylate **B4a** (380 g, 65 %).

LC-MS (ESI+): 196.1 $[M+H]^+$.

Step 2 synthesis of 3,4-bis(methoxycarbonyl)pyridine 1-oxide B4b

To a stirred solution of dimethyl pyridine-3,4-dicarboxylate **B4a** (380 g, 1.94 mol) and urea hydrogen peroxide (366 g, 3.89 mol) in MeCN (3.5 L) at 0 °C was added dropwise TFAA (548 mL, 3.89 mol). The reaction mixture was stirred at 0 °C for 2 h and was then quenched with saturated aqueous $NaHCO_3$ (1 L) (cautiously) and extracted with DCM (2 x 2 L). The combined organic layers were washed with brine (1 L), dried (Na_2SO_4) and concentrated *in vacuo* to give 3,4-bis(methoxycarbonyl)pyridine 1-oxide **B4b** (390 g, 95 %).

LC-MS (ESI+): 212.0 $[M+H]^+$.

Step 3 synthesis of dimethyl 6-chloropyridine-3,4-dicarboxylate B4c

To a suspension of 3,4-bis(methoxycarbonyl)pyridine 1-oxide **B4b** (390 g, 1.84 mol) in toluene (3.5 L) at 0 °C was added $POCl_3$ (1.7 L,18.4 mol) and the reaction mixture was then heated at 110 °C for 12 h. The reaction mixture was concentrated *in vacuo* and the resulting residue was poured into ice cold H_2O (1 L), neutralized by the addition of saturated aqueous $NaHCO_3$ (~3.0 L) and extracted with EtOAc (2 x 2 L). The combined organic layers were washed with brine (2 L), dried (Na_2SO_4) and concentrated *in vacuo*. The crude was purified by flash chromatography (SiO_2, hexane - EtOAc) to give dimethyl 6-chloropyridine-3,4-dicarboxylate **B4c** (113 g, 27 %).

LC-MS (ESI+): 230.0 $[M+H]^+$.

Step 4 synthesis of (6-chloropyridine-3,4-diyl)dimethanol B4d

To a stirred solution of dimethyl 6-chloropyridine-3,4-dicarboxylate **B4c** (113 g, 0.49 mol) in EtOH (2.5 L) at 0 °C was added portion wise sodium borohydride (112 g, 2.95 mol), followed by the slow addition of a solution of $CaCl_2$ (164 g, 1.47 mmol) in EtOH (2.0 L) at 0 °C (over a period of 1.5 h, exothermic reaction-efficient cooling was needed). The reaction mixture was stirred at room temperature for 20 h and was then quenched by the addition of 4M HCl solution, over a period of 30 mins at 0 °C, to obtain a clear solution. The reaction mixture was then stirred at room temperature for 1 h. The reaction mixture was washed with EtOAc (3 L) and the organic layer was washed with further 1M HCL (2.0 L). The pH of the combined aqueous layers was adjusted to pH 7 using saturated aqueous $NaHCO_3$ and then extracted with EtOAc (2 x 5 L). The combined organic layers were washed with brine (3.0 L), dried (Na_2SO_4) and concentrated *in vacuo* to give (6-chloropyridine-3,4-diyl)dimethanol **B4d** (90 g, crude).

LC-MS (ESI+): 174.0 $[M+H]^+$.

Step 5 synthesis of 2-chloro-4,5-bis(chloromethyl)pyridine B4e

To a solution of (6-chloropyridine-3,4-diyl)dimethanol **B4d** (90 g, 0.518 mol) and Et_3N (216 mL, 1.56 mol) in dry DCM (1.8 L) at 0 °C was added slowly methanesulfonyl chloride (80 mL, 1.04 mol). The reaction mixture was stirred at room temperature for 2 h and was then quenched with saturated aqueous $NaHCO_3$ (1 L) and extracted with DCM (1.0 L). The organic layer was washed with brine (1.5 L), dried (Na_2SO_4) and concentrated *in vacuo* to give 2-chloro-4,5-bis(chloromethyl)pyridine **B4e** (105 g, crude).

LC-MS (ESI+): 209.9 $[M+H]^+$.

Step 6 synthesis of (S)-3-chloro-1'-((2-(trimethylsilyl)ethoxy)methyl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,3'-pyrrolo[2,3-b]pyridin]-2'(1'H)-one B4f isomer 1

To a suspension of 1-((2-(trimethylsilyl)ethoxy)methyl)-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (CAS 879132-48-5) (132 g, 0.498 mol) and 2-chloro-4,5-

bis(chloromethyl)pyridine **B4e** (105 g, 0.498 mol) in DMF (1.5 L) at room temperature was added Cs_2CO_3 (485 g, 1.49 mol). The reaction mixture was stirred for 16 h and was then quenched with ice cold H_2O (2.0 L) and extracted with EtOAc (2 x 2 L). The combined organic layers were washed with brine (2 x 2 L), dried (Na_2SO_4) and concentrated *in vacuo*. This was then purified by flash chromatography (SiO_2, petroleum ether - EtOAc) to give 3-chloro-1'-((2-(trimethylsilyl)ethoxy)methyl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,3'-pyrrolo[2,3-b]pyridin]-2'(1'H)-one **B4f** (60 g).

Purified by Chiral SFC

Instrument: PICLab PREP 150
Solvents: Primary mobile phase = CO_2 Modifier: 25% MeOH
Column: YMC Cellulose-SC 5um, 250x30mm, at 35°C. UV monitoring: 210nm
Flow: 100g/min..

To give

(S)-3-chloro-1'-((2-(trimethylsilyl)ethoxy)methyl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,3'-pyrrolo[2,3-b]pyridin]-2'(1'H)-one **B4f isomer 1** (20 g). **LC-MS (ESI+):** 402.1 $[M+H]^+$ **SFC** 3.14 min. and

(R)-3-chloro-1'-((2-(trimethylsilyl)ethoxy)methyl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,3'-pyrrolo[2,3-b]pyridin]-2'(1'H)-one **B4f isomer 2** (19 g). **LC-MS (ESI+):** 402.1 $[M+H]^+$. **SFC** 3.73 min.

Chiral SFC analytical YMC Cellulose-SC, 250×4.6 mm 5µ at 35 °C, 3 ml/min, 40% Methanol 35 °C.

Step 7 synthesis of (S)-3-chloro-5,7-dihydrospiro[cyclopenta[c]pyridine-6,3'-pyrrolo[2,3-b]pyridin]-2'(1'H)-one B4g

A suspension of (S)-3-chloro-1'-((2-(trimethylsilyl)ethoxy)methyl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,3'-pyrrolo[2,3-b]pyridin]-2'(1'H)-one **B4f** (10 g, 0.024 mol) in TFA (70 mL) was heated at 60 °C for 1 h. The reaction mixture was concentrated *in vacuo* and dried under high vacuum. The resulting residue was dissolved in EtOH (70 mL) and to this was then added NH_4OH (50 ml). The reaction mixture was stirred at 60 °C for 2 h. The resulting precipitate was collected by

filtration, washed with H_2O (100 mL) and dried under high vacuum to give (S)-3-chloro-5,7-dihydrospiro[cyclopenta[c]pyridine-6,3'-pyrrolo[2,3-b]pyridin]-2'(1'H)-one **B4g** (6.2 g, 82 %).

LC-MS (ESI+): 272.0 $[M+H]^+$.

Step 8 synthesis of methyl (S)-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[c]pyridine-6,3'-pyrrolo[2,3-b]pyridine]-3-carboxylate B4h

A stirred solution of (S)-3-chloro-5,7-dihydrospiro[cyclopenta[c]pyridine-6,3'-pyrrolo[2,3-b]pyridin]-2'(1'H)-one **B4g** (6.2 g, 0.0228 mol) and sodium acetate (3.79 g, 0.457 mol) in MeOH (120 mL) was degassed with argon and to this was added $Pd(dppf)Cl_2$.DCM (2.8 g, 0.0034 mol). The reaction mixture was heated at 100 °C for 16 h in a mini clave vessel under 5 Kg/cm^2 pressure of CO gas. The reaction mixture was concentrated *in vacuo* and the resulting residue was purified by flash chromatography (SiO_2, petroleum ether - EtOAc). The solid obtained was triturated with MeOH (20 mL) and the solids were collected by filtration to give methyl (S)-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[c]pyridine-6,3'-pyrrolo[2,3-b]pyridine]-3-carboxylate **B4h** (3.2 g, 48 %).

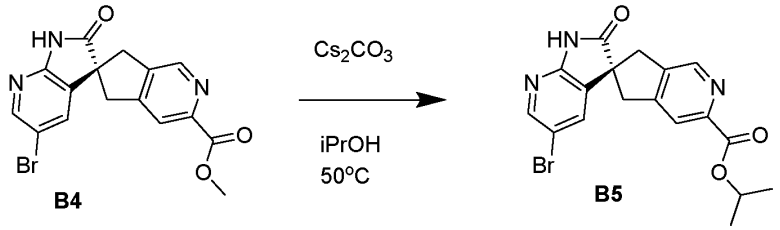
LC-MS (ESI+): 296.2 $[M+H]^+$.

Step 9 synthesis of methyl (S)-5'-bromo-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[c]pyridine-6,3'-pyrrolo[2,3-b]pyridine]-3-carboxylate B4

To a stirred solution of methyl (S)-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[c]pyridine-6,3'-pyrrolo[2,3-b]pyridine]-3-carboxylate **B4h** (2.4 g, 8.1 mmol) in DMF (25 mL) at 0 °C was added NBS (1.9 g, 10.5 mmol). The reaction mixture was stirred at room temperature for 5 h and was then quenched by the addition of ice-cold H_2O (100 mL). The resulting precipitate was collected by filtration, washed with cold H_2O and dried under high vacuum to give methyl (S)-5'-bromo-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[c]pyridine-6,3'-pyrrolo[2,3-b]pyridine]-3-carboxylate **B4** (1.33 g, 44 %).

LC-MS (ESI+): 374.0 $[M+H]^+$.

Scheme 37. Synthesis of Intermediate B5

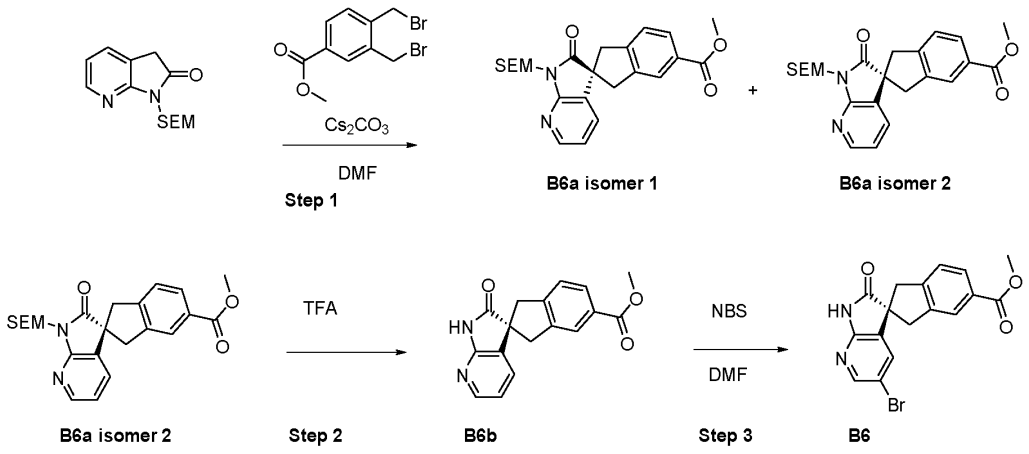


Synthesis of isopropyl (3*S*)-5-bromo-2-oxo-spiro[1*H*-pyrrolo[2,3-*b*]pyridine-3,6'-5,7-dihydrocyclopenta[*c*]pyridine]-3'-carboxylate B5

To a suspension of **B4** (1.175 g, 3.140 mmol) in a dry 2-propanol (78.0 mL), Cs_2CO_3 (413.5 mg, 1.256 mmol) was added. The resulting mixture was stirred at 50 °C for 13 hours. The reaction mixture was concentrated, water was added (50 mL) and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford raw product (1.17 g). The raw material was loaded and purified on a silica column (Interchim 25 g, 15 µm, SiO_2) using Interchim PuriFlash 450 instrument with a flowrate of 20 mL/min starting with DCM (100%) and going to 100% [DCM/MeOH (20:1)] in 30 CVs. Hold 100% for 10 CVs. The appropriate fractions were collected, the solvent removed to yield the desired product **B5** (1.07 g, 84.7%).

LC-MS (ES+): 402.10, 404.10 $[M+H]^+$.

Scheme 38. Synthesis of intermediate B6



Step 1 Synthesis of dimethyl pyridine-3,4-dicarboxylate B6a

To a suspension of 1-((2-(trimethylsilyl)ethoxy)methyl)-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (CAS 879132-48-6) (60 g, 0.22 mol) and methyl 3,4-bis(bromomethyl)benzoate (CAS 20896-23-5) (87.2 g, 0.27 mol) in DMF (1.5 L) was added Cs_2CO_3 (222 g, 0.68 mol). The reaction mixture was stirred at room temperature for 16 h and was then quenched with ice cold H_2O (5 L) and extracted with EtOAc (2 x 3 L). The combined organic layers were washed with brine (3 L), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (SiO_2, petroleum ether – EtOAc) to give methyl 2'-oxo-1'-((2-(trimethylsilyl)ethoxy)methyl)-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-b]pyridine]-5-carboxylate **B6a**.

Purified by Chiral SFC

Instrument: PICLab PREP 400
Solvents: Primary mobile phase = CO_2 Modifier: 25% MeOH
Column: YMC Amylose-C 5um, 250x30mm, at 35°C. UV monitoring: 210nm
Flow: 100g/min..

To give

Methyl (S)-2'-oxo-1'-((2-(trimethylsilyl)ethoxy)methyl)-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-b]pyridine]-5-carboxylate (**B6a isomer 1**) (11.5 g) **LC-MS (ESI+):** 425.1 $[M+H]^+$ **SFC** 1.52 min.

and

Methyl (R)-2'-oxo-1'-((2-(trimethylsilyl)ethoxy)methyl)-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-b]pyridine]-5-carboxylate (**B6a isomer 2**) (9.8 g) **LC-MS (ESI+):** 425.1 $[M+H]^+$.**SFC** 2.02 min.

Chiral SFC analytical YMC Amylose-C, 250×4.6 mm 5µ at 35 °C, 3 ml/min, 40% Methanol 35 °C.

Step 2 synthesis of methyl (R)-2'-oxo-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-b]pyridine]-5-carboxylate B6b

A suspension of methyl (R)-2'-oxo-1'-((2-(trimethylsilyl)ethoxy)methyl)-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-b]pyridine]-5-carboxylate **B6a isomer 2** (9.8 g, 23.12 mmol) in TFA (100 mL) was heated at 60 °C for 2 h. The reaction mixture was concentrated in vacuo and dried over high vacuum. The crude mass was dissolved in MeOH (100 mL) and to this was then added DIPEA (9.8 g, 23.12 mmol). The reaction mixture was heated at 60 °C for 2 h. The resulting precipitate was collected by filtration and dried to give methyl (R)-2'-oxo-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-b]pyridine]-5-carboxylate **B6b** (5.6 g, 84 %).

LC-MS (ESI+): 295.1 $[M+H]^+$.

Step 3 synthesis of methyl (R)-5'-bromo-2'-oxo-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-b]pyridine]-5-carboxylate B6

To a stirred solution of methyl (R)-2'-oxo-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-b]pyridine]-5-carboxylate (5.6 g, 19.04 mmol) in DMF (60 mL) at 0 °C was added NBS (10.17 g, 57.14 mmol). The reaction mixture was stirred at room temperature for 5 h and was then quenched with ice cold H_2O. The reaction mixture was stirred for 1 h and the resulting precipitate was collected by filtration, washed with ice cold H_2O and dried under high vacuum. The solid was triturated with MeOH to give methyl (R)-5'-bromo-2'-oxo-1,1',2',3-tetrahydrospiro[indene-2,3'-pyrrolo[2,3-b]pyridine]-5-carboxylate **B6** (6.0 g, 85 %).

LC-MS (ESI+): 373.0 $[M+H]^+$

BIOLOGICAL ACTIVITY

cAMP Functional Assay

cAMP production following receptor activation was determined using the Homogeneous Time-Resolved Fluorescence (HTRF) cAMP dynamic-2 assay (Cisbio, France). The human neuroblastoma cell line SK-N-MC endogenously expressing the human CGRP receptor was seeded at a density of 12,500 cells/well in solid walled 96 well half area plates (Costar, Catalog Number 3688, Corning Life Sciences, Germany). After 16 h incubation at 37ºC media was removed and cells were incubated at 37°C for 30 min in serum free media containing 500 µM IBMX (Tocris, Abingdon, UK, Catalog Number 2845) and increasing concentrations of test

antagonist. Following this cells were challenged with an EC_{80} concentration of human CGRP (0.3 nM) for a further 30 min at 37°C and then cAMP production was determined as manufacturer's instructions before plates were read on a PheraStar fluorescence plate reader (BMG LabTech, Germany). IC_{50} values were derived from the inhibition curve. The pIC_{50} values (where $pIC_{50} = -\log_{10} IC_{50}$) were converted to a functional pK_b value using a modified Cheng-Prussoff equation where K_d = agonist EC_{50} and L hot = agonist challenge concentration. The pK_b values of certain compounds of the invention are detailed in Table 5.

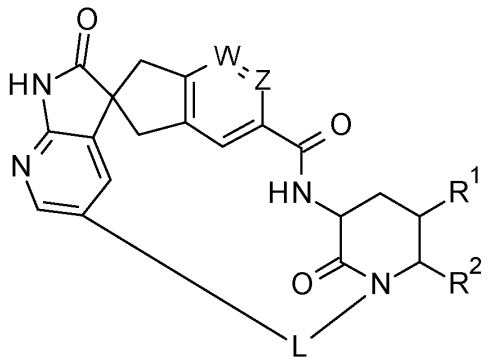
Table 5 - CGRP pK_b values

Example	isomer(s)	CGRP pK_b
Example 1-1	Isomer 1	11.2
Example 1-1	Isomer 2	9.3
Example 1-1	Isomer 3	9.3
Example 1-2	Isomer 1	11.3
Example 1-2	Isomer 2	9.3
Example 1-3	Isomer 1	11.1
Example 1-3	Isomer 2	9.3
Example 1-4	Isomer 1	11.1
Example 1-4	Isomer 2	9.9
Example 1-5	Isomer 1	11.6
Example 1-5	Isomer 2	7.7
Example 1-6	Isomer 1	11.1
Example 1-6	Isomer 2	8.9
Example 1-7	Isomer 1	11.4
Example 1-7	Isomer 2	8.9
Example 1-7	Isomer 3	9.1
Example 1-8	Isomer 1	11.3
Example 1-8	Isomer 2	9.2
Example 2-1	Single Isomer	9.9
Example 2-2	Isomer 1	10.5
Example 2-2	Isomer 2	8.0
Example 2-3	Single Isomer	10.6
Example 2-4	Single Isomer	9.8
Example 2-5	Single Isomer	10.3
Example 2-6	Single Isomer	10.2
Example 2-7	Single Isomer	10.6
Example 2-8	Single Isomer	10.0
Example 2-9	Single Isomer	10.7

Example 2-10	Single Isomer	10.5
Example 3-1	Isomer 1	11.1
Example 3-1	Isomer 2	8.2
Example 3-2	Isomer 1	11.4
Example 3-2	Isomer 2	8.9
Example 4-1	Isomer 1	11.9
Example 4-1	Isomer 2	9.7
Example 4-2	Isomer 1	11.1
Example 4-2	Isomer 2	9.2
Example 5-1	Isomer 1	10.8
Example 5-1	Isomer 2	8.8
Example 5-1	Isomer 3	8.9
Example 6-1	Isomer 1	6.3
Example 6-1	Isomer 2	8.5
Example 6-2	Isomer 1	7.5
Example 6-2	Isomer 2	8.9
Example 6-3	Single Isomer	8.4
Example 6-4	Single Isomer	8.3
Example 7-1	Mixture diastereomers	9.7
Example 8-1	Single Isomer	9.4
Example 8-2	Single Isomer	9.6
Example 9-1	Mixture (Isomer 2)	9.9
Example 9-1	Mixture (Isomer 1)	7.9
Example 10-1	Isomer 1	7.6
Example 10-1	Isomer 2	6.9
Example 10-2	Mixture diastereomers	7.9

Claims

1. A compound of Formula (1a):



(1a)

or a salt thereof, wherein;

W is CH or N;

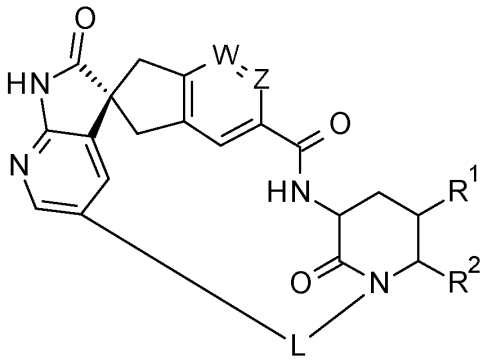
Z is CH or N;

R^1 is an aryl or heteroaryl group optionally substituted with one or more halo groups or C_{1-3} alkyl groups which are themselves optionally substituted with one or more F atoms;

R^2 is H or C_{1-3} alkyl optionally substituted with one or more F atoms;

and L is a C_{4-15} linker group optionally substituted with one or more F atoms, wherein one, two or three, but not all, of the carbon atoms of the linker group may be optionally replaced by a heteroatom selected from O and N.

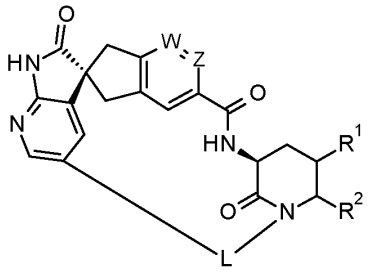
2. The compound according to claim 1, which is a compound of Formula (2a):



(2a)

or a salt thereof.

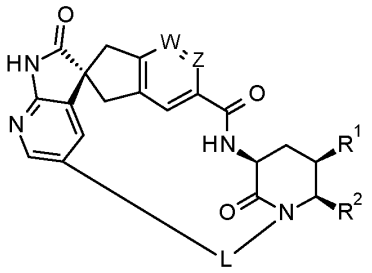
3. The compound according to claim 1, which is a compound of Formula (3a):



(3a)

or a salt thereof.

4. The compound according to claim 1, which is a compound of Formula (4a):



(4a)

or a salt thereof.

5. The compound according to any one of claims 1 to 4, wherein W is N and Z is CH.

6. The compound according to any one of claims 1 to 4, wherein W is CH and Z is N.

7. The compound according to any one of claims 1 to 4, wherein W and Z are both CH.

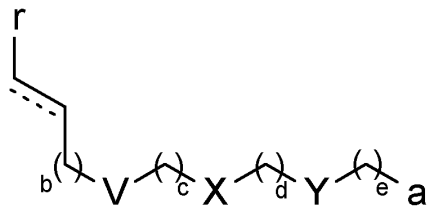
8. The compound according to any one of claims 1 to 7, wherein R^1 is a phenyl ring optionally substituted with one or more F atoms or C_{1-3} alkyl groups which are themselves optionally substituted with one or more F atoms;

9. The compound according to claim 8, wherein R^1 is a phenyl ring optionally substituted with 1-5 F atoms.

10. The compound according to any one of claims 1 to 9, wherein R^2 is H or methyl.

11. The compound according to claim 10, wherein R^2 is methyl.

12. The compound according to any one of claims 1 to 11, wherein L is a linker group of the formula:



wherein "r" indicates the point of attachment to the pyridine ring and "a" indicates the point of attachment to N; V, X and Y are independently selected from a bond, O, CH_2, NH and NMe; b, c, d and e are independently 1, 2 or 3 and the dotted line indicates that a single or double bond may be present.

13. The compound according to claim 12, wherein L is selected from the group consisting of:

-CHCHCH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$-;

-CHCHCH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$-;

-CH$_2$CH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$-;

-CH$_2$CH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$-;

-CHCHCH$_2$OCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$-;

-CHCHCH$_2$OCH$_2$CH$_2$N(CH$_3$)CH$_2$CH$_2$-;

-CHCHCH$_2$OCH$_2$CH$_2$NHCH$_2$CH$_2$-;

-CHCHCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_3$)CH$_2$CH$_2$-;

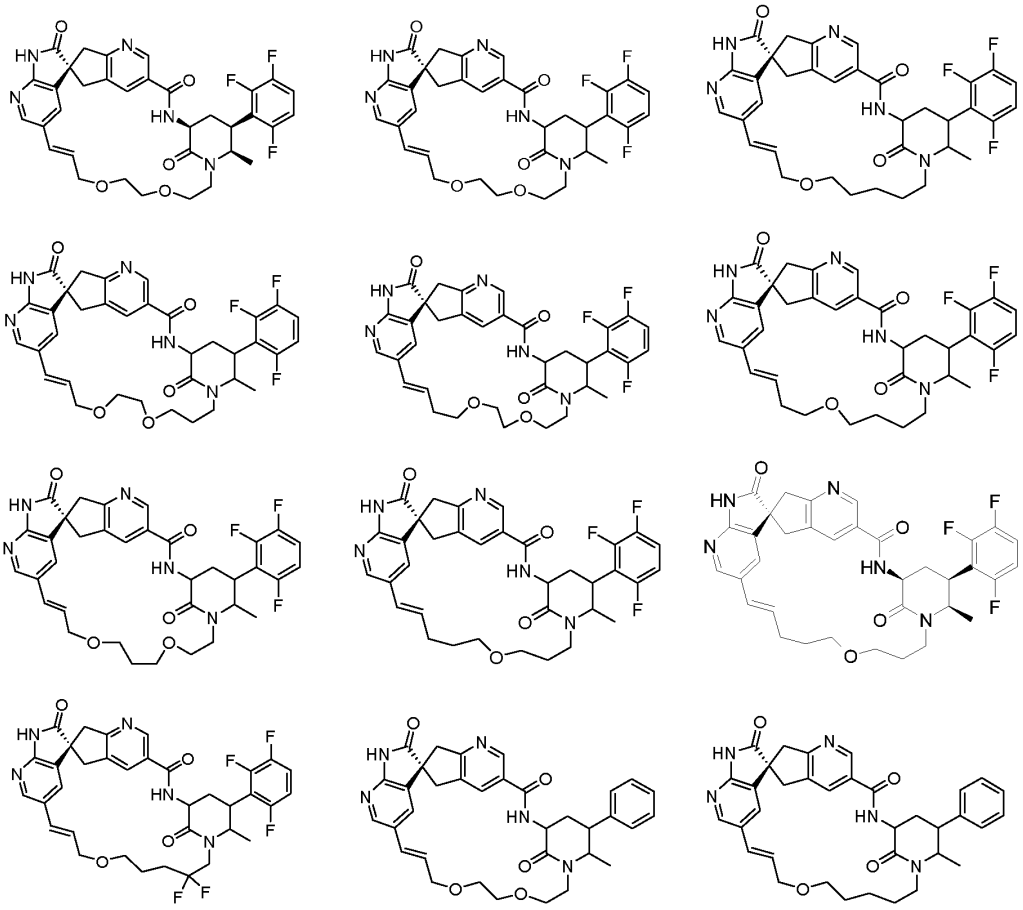
-CHCHCH$_2$N(CH$_3$)CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$-;

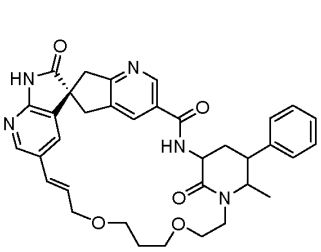
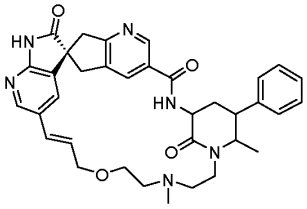
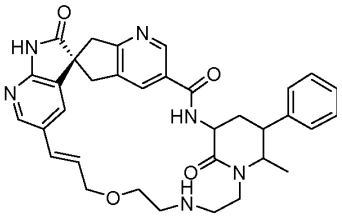
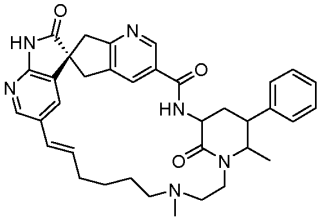
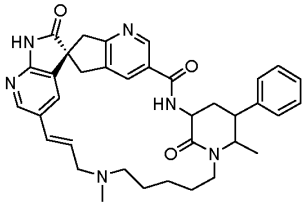
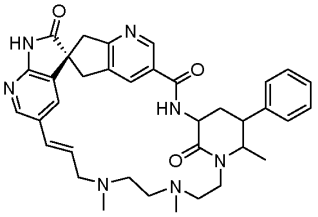
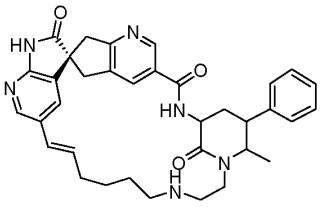
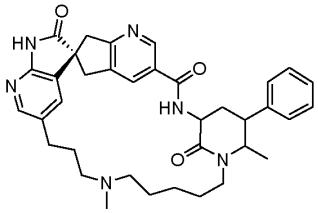
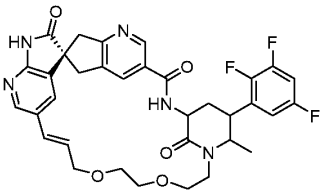
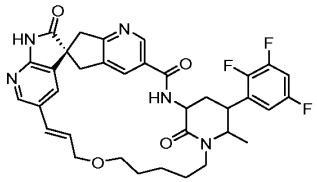
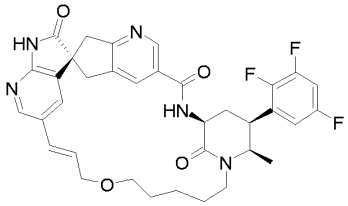
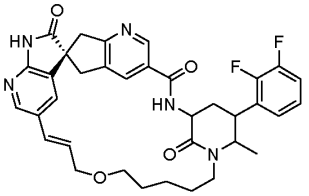
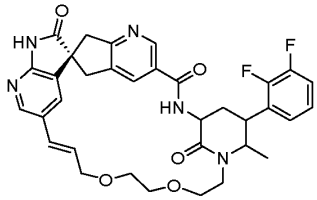
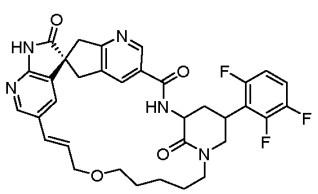
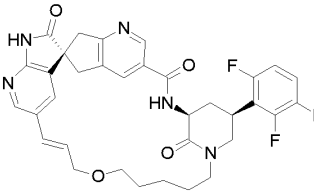
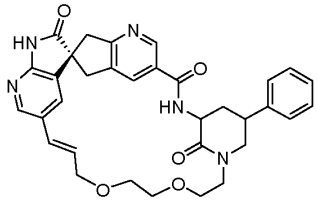
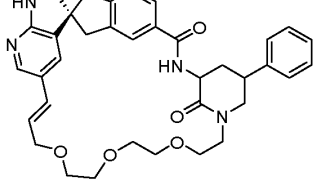
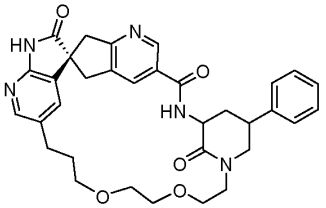
-CH$_2$CH$_2$CH$_2$N(CH$_3$)CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$-;

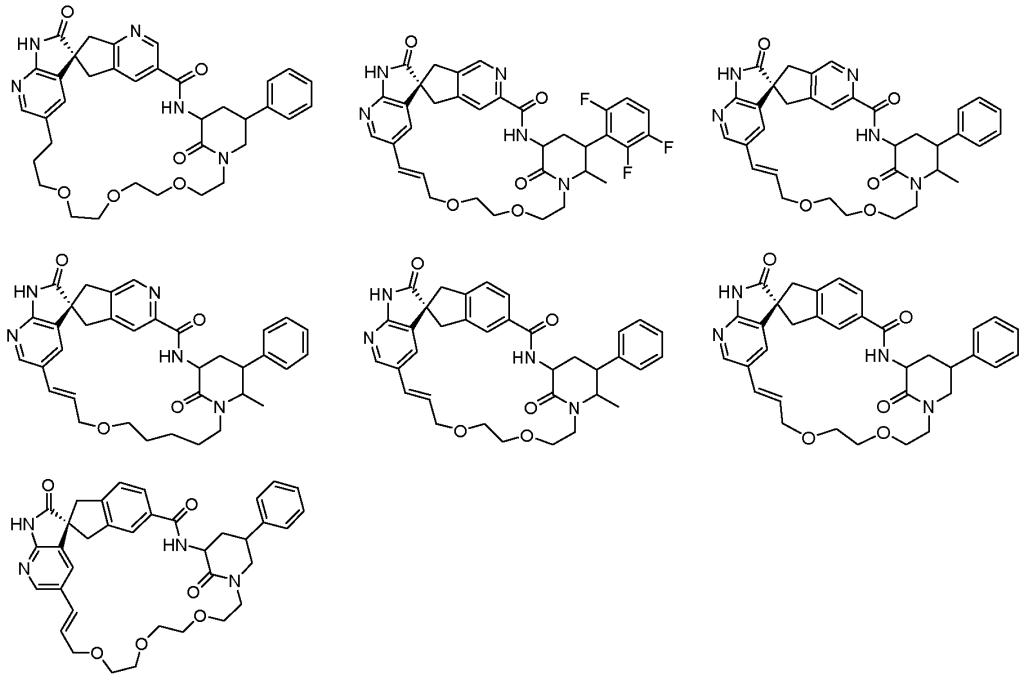
-CHCHCH$_2$CH$_2$CH$_2$CH$_2$NHCH$_2$CH$_2$-;

-CHCHCH$_2$N(CH$_3$)CH$_2$CH$_2$N(CH$_3$)CH$_2$CH$_2$-;
-CHCHCH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$CH$_2$-;
-CHCHCH$_2$OCH$_2$CH$_2$CH$_2$OCH$_2$CH$_2$-;
-CHCHCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$-;
-CHCHCH$_2$CH$_2$OCH$_2$CH$_2$CH$_2$CH$_2$-;
-CHCHCH$_2$CH$_2$CH$_2$OCH$_2$CH$_2$CH$_2$-
and
-CHCHCH$_2$OCH$_2$CH$_2$CH$_2$CF$_2$CH$_2$-.

14. The compound according to claim 1 which is selected from the group consisting of:





and salts thereof.

15. The compound according to any one of claims 1 to 14 having CGRP receptor antagonist activity.

16. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 15 and a pharmaceutically acceptable excipient.

17. The compound or composition according to any one of claims 1 to 16 for use medicine.

18. The compound or composition according to any one of claims 1 to 16 for use in the treatment of cerebrovascular or vascular disorders including migraine (with or without aura), chronic migraine, pure menstrual migraine, frequent episodic migraine, menstrually-related migraine, migraine with aura, familial hemiplegic migraine, sporadic hemiplegic migraine, basilar-type migraine, cyclical vomiting, abdominal migraine, benign paroxysmal vertigo of childhood, retinal migraine, status migrainosus, cluster headache, dialysis headache, chronic headaches of unknown origin, tension/stress induced

headaches, allergy induced headaches, paroxysmal hemicrania, osteoarthritis and associated osteoporotic fracture pain, hot flashes associated with menopause or medically induced menopause due to surgery or drug treatment, hemicrania continua, cyclic vomiting syndrome, opiate withdrawal syndrome, morphine tolerance, neurodegenerative disease, epilepsy, allergic rhinitis, rosacea, dental pain, earache, middle ear inflammation, sunburn, joint pain associated with osteoarthritis and rheumatoid arthritis and gout, cancer pain, neuropathic pain (including but not limited to cancer pain in all its various forms including of unexplained origin), dystonic pain, inflammatory pain, post-operative incision pain, sciatica, fibromyalgia, trigeminal neuralga, diabetic neuropathy, complex regional pain syndrome, Behçet's disease, endometriosis pain, back pain, phantom limb pain, menstrual period pain, pain associated with labour, pain resulting from burns to skin, or visceral pain associated with inflammatory bowel disease (including Crohn's disease, ileitis and ulcerative colitis), gastro-esophageal reflux disease, dyspepsia, irritable bowel syndrome, renal colic, cystitis, gout, pancreatitis and prostatitis or in the treatment of inflammatory and immune inflammation associated disorders including chronic fatigue syndrome, skin diseases, neurogenic cutaneous redness, skin rosaceousness, erythema, bronchial hyperreactivity, asthma, mast cell activation syndrome, mastocytosis, mast cell degranulation disorder, vascular disorders, shock, sepsis, non-insulin dependent diabetes mellitus, and infectious diseases including those of a respiratory and gastrointestinal origin.

19. Use according to claim 18, wherein the disorder is a migraine disorder.