

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

(19) World Intellectual Property

Organization

International Bureau

(43) International Publication Date

14 May 2020 (14.05.2020)



(10) International Publication Number

WO 2020/096916 A2

(51) International Patent Classification:

A61K 31/47 (2006.01)

(21) International Application Number:

PCT/US2019/059582

(22) International Filing Date:

04 November 2019 (04.11.2019)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/757,422

08 November 2018 (08.11.2018) US

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(81) Designated States (unless otherwise indicated, for every

kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ,

CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO,

DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,

HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP,

KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME,

MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ,

OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA,

SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN,

TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every

kind of regional protection available): ARIPO (BW, GH,

GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ,

UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

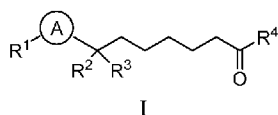
Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: INHIBITORS OF HISTONE DEACETYLASE USEFUL FOR THE TREATMENT OR PREVENTION OF HIV INFECTION



(57) Abstract: The present invention relates to Compounds of Formula I: and pharmaceutically acceptable salts or prodrug thereof, wherein R^1 , R^2 , R^3 , R^4 and A are as defined herein. The present invention also relates to compositions comprising at least one compound of Formula I, and methods of using the compounds of Formula I for treating or preventing HIV infection in a subject.

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INHIBITORS OF HISTONE DEACETYLASE USEFUL FOR THE TREATMENT OR PREVENTION OF HIV INFECTION

FIELD OF THE INVENTION

5 The present invention relates to inhibitors of histone deacetylase, compositions comprising at least one inhibitor of histone deacetylase, and methods of using the inhibitors of histone deacetylase for treating or preventing HIV infection in a subject.

BACKGROUND OF THE INVENTION

10 DNA in the nucleus of the cell exists as a hierarchy of compacted chromatin structures. The basic repeating unit in chromatin is the nucleosome, which consists of a histone octamer of proteins in the nucleus of the cell around which DNA is wrapped twice. The orderly packaging of DNA in the nucleus plays an important role in the functional aspects of gene regulation. Covalent modifications of the histones have a key role in altering chromatin higher
15 order structure and function, and ultimately, gene expression. The covalent modification of histones, such as acetylation, occurs by enzymatically mediated process.

 Regulation of gene expression through the inhibition of the nuclear enzyme histone deacetylase (HDAC) is one of the several possible regulatory mechanisms whereby chromatin actively can be affected. The dynamic homeostasis of the nuclear acetylation of
20 histone can be regulated by the opposing activity of the enzymes histone acetyl transferase (HAT) and histone deacetylase (HDAC). Transcriptionally silent chromatin can be characterized by nucleosomes with low levels of acetylated histones. Acetylation reduces the positive charge of histones, thereby expanding the structure of the nucleosome and facilitating the interaction of transcription factors with the DNA. Removal of the acetyl group restores the positive charge,
25 condensing the structure of the nucleosome. While histone acetylation can activate DNA transcription, enhancing gene expression, histone deacetylase can reverse the process and can serve to repress gene expression. Inhibition of the histone deacetylase (HDAC inhibition) can also increase the activation of DNA transcription. See, for example, Grunstein, Nature, 389, 349-352 (1997); Pazin et al., Cell 89, 325-328 (1997); Wade et al., Trends Biochem Sci. 22, 128-
30 132 (1997); and Wolffe, Science 272, 371-372 (1996).

 With the introduction of combination antiretroviral therapy (ART), HIV became a controllable chronic disease. The combination of ART (cART) targets specific stages of the viral life cycle, and is effective at combatting active viral load down to undetectable levels. However, HIV persists within the body of infected individuals undergoing therapy, and cessation

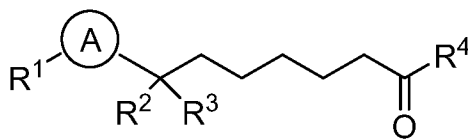
of ART leads to a viral rebound within 3-4 weeks. The HIV can persist in resting memory and naïve CD4⁺ T cells and other long-lived cells, such as infected astrocytes and cells of macrophage lineage. HIV can persist in these resting cells by establishing a latent or “silent” infection. In these cells, virus is integrated into the host genome, but viral production does not occur as a result of inhibition of both viral transcriptions from proteins. However, these latently infected cells still do contain replication competent virus, and once cART is stopped, rebound in plasma HIV RNA is observed in nearly all patients.

One approach currently being explored to eliminate latently infected CD4⁺ T cells is to activate viral production from these cells in the presence of cART, when the production of the virus should kill the infected cells. Histone deacetylase inhibitors have shown promise in vitro in activating virus production from latent infected cells, and therefore this class of drugs is being studied as part of a strategy aimed at a cure of HIV.

Eleven members of the HDAC family has been identified in humans, which share a conserved catalytic domain and are grouped into two classes: class I (1,2,3,8), homologous to yeast Rpd3; and class IIa (4,5,7,9) and IIb (6, 10), homologous to yeast Hda1. HDAC 11 shares homology with both classes, but is at the same time distinct from all the other ten subtypes. The first generation of HDAC inhibitors (HDACi) are promising therapeutic agents against cancer and other diseases, and showed in vitro activation of virus production from latent infected cells. However, due to their poor selectivity, those that entered clinical trials, all show similar adverse effects. The poorly selective HDACi's are not suitable for healthy HIV patients on cART, thus the interest is high for the discovery and development of novel and subtype selective HDAC inhibitors.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides Compounds of Formula I:



wherein A is a five-membered heteroaryl ring which is optionally substituted with halo, cyano, R^5 , R^6 , $(\text{C}=\text{O})\text{N}(\text{R}^5)_2$, $\text{NR}^5(\text{C}=\text{O})\text{N}(\text{R}^5)_2$, $(\text{C}=\text{O})\text{R}^6$ or $(\text{C}_{1-3} \text{ alkyl})\text{O}(\text{C}=\text{O})\text{R}^5$;

R^1 is phenyl, bicyclic aryl, tricyclic aryl or heteroaryl, which may be monocyclic, bicyclic or tricyclic, wherein said phenyl and heteroaryl groups are optionally substituted with one to four groups independently selected from the group consisting of halo, oxo, cyano, C_{2-3} alkenyl, R^5 ,

R^6 , OR^5 , $N(R^5)_2$, $(C=O)NHR^6$, $NR^5(C=O)N(R^5)_2$, $NR^5(C=NR^5)N(R^5)_2$, SO_2R^5 , $SO_2N(R^5)_2$, $NR^5SO_2R^5$, and $NR^5SO_2N(R^5)_2$;

R^2 is selected from the group consisting of hydrogen, $N(R^5)_2$, $NR^5(C=O)R^5$, $NR^5(C=O)N(R^5)_2$, $NR^5(C=NR^5)N(R^5)_2$, $NR^5(C=O)R^6$, $NR^5(C_{1-3}alkyl)R^6$ and $NR^5(C=O)(C_{1-3}alkyl)R^6$;

5 R^3 is selected from hydrogen, C_{1-6} alkyl or CH_2OR^5 ;

R^4 is C_{1-6} alkyl, or C_{3-6} cycloalkyl, which is optionally substituted with one to three substituents independently selected from the group consisting of halo and hydroxyl, or C_{3-6} cycloalkyl; each R^5 is independently hydrogen, cyano, or C_{1-6} alkyl, which is optionally substituted with NH_2 , $N(CH_3)_2$, $NH(CH_3)_2$, $N(CH_2CH_3)_2$, or one to three halo;

10 R^6 is

- (a) heterocyclyl, which may be monocyclic, bicyclic or tricyclic,
- (b) C_{3-6} cycloalkyl,
- (c) phenyl, or
- (d) heteroaryl, which may be monocyclic, bicyclic or tricyclic,

15 wherein said heterocyclyl, cycloalkyl, phenyl and heteroaryl groups are optionally substituted with one to four groups independently selected from the group consisting of halo, cyano, oxo, R^5 , OR^5 , $(C=O)R^5$, $(C=O)OR^5$, $N(R^5)_2$, $(C=O)N(R^5)_2$, $NR^5(C=O)R^5$, $NR^5(C=O)N(R^5)_2$, $NR^5(C=NR^5)N(R^5)_2$, SO_2R^5 , $SO_2N(R^5)_2$, $NR^5SO_2R^5$, $NR^5SO_2N(R^5)_2$, C_{2-3} alkenyl, benzyl, benzyl- OR^5 , $CH_2(C_{3-6} cycloalkyl)$, $CH_2(heteroaryl)$, heteroaryl, heterocyclyl and $C_{3-6} cycloalkyl$.

20 The Compounds of Formula I and pharmaceutically acceptable salts or prodrugs thereof may be useful, for example, for activating HIV latency for potential complete cure of HIV infection alone or in combination with cART and/or other HIV treatments.

Accordingly, the present invention provides methods for treating or preventing HIV infection in a subject, comprising administering to the subject an effective amount of at least
25 one compound of Formula I.

The details of the invention are set forth in the accompanying detailed description below.

Although any methods and materials similar to those described herein may be used in the practice or testing of the present invention, illustrative methods and materials are now
30 described. Other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention includes to inhibitors of histone deacetylase, compositions comprising at least one inhibitor of histone deacetylase, and methods of using the inhibitors of histone deacetylase for treating or preventing HIV infection in a subject.

5 Definitions and Abbreviations

The terms used herein have their ordinary meaning and the meaning of such terms is independent at each occurrence thereof. That notwithstanding and except where stated otherwise, the following definitions apply throughout the specification and claims. Chemical names, common names, and chemical structures may be used interchangeably to describe the
10 same structure. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence, the definition of "alkyl" applies to "alkyl" as well as the "alkyl" portions of "hydroxyalkyl," "haloalkyl," "-O-alkyl," etc.

As used herein, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

15 A "subject" is a human or non-human mammal. In one embodiment, a subject is a human. In another embodiment, a subject is a primate. In another embodiment, a subject is a monkey. In another embodiment, a subject is a chimpanzee. In still another embodiment, a subject is a rhesus monkey.

The term "effective amount" as used herein, refers to an amount of Tricyclic
20 Heterocycle Compound and/or an additional therapeutic agent, or a composition thereof that is effective in inhibiting HIV replication and in producing the desired therapeutic, ameliorative, inhibitory or preventative effect when administered to a subject suffering from HIV infection or AIDS. In the combination therapies of the present invention, an effective amount can refer to each individual agent or to the combination as a whole, wherein the amounts of all agents
25 administered are together effective, but wherein the component agent of the combination may not be present individually in an effective amount.

The terms "treating" or "treatment" as used herein with respect to an HIV viral infection or AIDS, includes inhibiting the severity of HIV infection or AIDS, i.e., arresting or reducing the development of the HIV infection or AIDS or its clinical symptoms; or relieving the
30 HIV infection or AIDS, i.e., causing regression of the severity of HIV infection or AIDS or its clinical symptoms.

The terms "preventing," or "prophylaxis," as used herein with respect to an HIV viral infection or AIDS, refers to reducing the likelihood or severity of HIV infection or AIDS.

The term "alkyl," as used herein, refers to an aliphatic hydrocarbon group having one of its hydrogen atoms replaced with a bond. An alkyl group may be straight or branched and contain from about 1 to about 20 carbon atoms. In one embodiment, an alkyl group contains from about 1 to about 12 carbon atoms. In different embodiments, an alkyl group contains from about 1 to about 6 carbon atoms (C₁-C₆ alkyl) or from about 1 to about 4 carbon atoms (C₁-C₄ alkyl). Non-limiting examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl, isopentyl, n-hexyl, isohexyl and neoheptyl. In one embodiment, an alkyl group is linear. In another embodiment, an alkyl group is branched. Unless otherwise indicated, an alkyl group is unsubstituted.

The term "alkenyl," as used herein, refers to an aliphatic hydrocarbon group having at least one carbon to carbon double bond. An alkenyl group may be straight or branched and contain from about 2 to about 10 carbon atoms. In one embodiment, an alkenyl group contains from about 2 to about 6 carbon atoms. In different embodiments, an alkenyl group contains from 2 to 3 carbon atoms (C₂₋₃ alkyl). Non-limiting examples of alkenyl groups include ethenyl, propenyl, butenyl, pentenyl and hexenyl. In one embodiment, an alkenyl group is linear. In another embodiment, an alkenyl group is branched. Unless otherwise indicated, an alkenyl group is unsubstituted.

The term "halo," as used herein, means -F, -Cl, -Br or -I.

The term "haloalkyl," as used herein, refers to an alkyl group as defined above, wherein one or more of the alkyl group's hydrogen atoms has been replaced with a halogen. In one embodiment, a haloalkyl group has from 1 to 6 carbon atoms. In another embodiment, a haloalkyl group is substituted with from 1 to 3 F atoms. Non-limiting examples of haloalkyl groups include -CH₂F, -CHF₂, -CF₃, -CH₂Cl and -CCl₃. The term "C₁-C₆ haloalkyl" refers to a haloalkyl group having from 1 to 6 carbon atoms.

The term "cycloalkyl" means a monocyclic or bicyclic saturated aliphatic hydrocarbon group having the specified number of carbon atoms. For example, "cycloalkyl" includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and so on. Bicyclic cycloalkyl ring systems include fused ring systems, where two rings share two atoms, and spiro ring systems, where two rings share one atom.

The term "aryl," as used herein, represents a stable bicyclic or tricyclic ring system of up to 10 atoms in each ring, wherein at least one ring is aromatic, and all of the ring atoms are carbon. Bicyclic and tricyclic ring systems include fused ring systems, where two rings share two atoms, and spiro ring systems, where two rings share one atom.

The term "heteroaryl", as used herein, represents a stable monocyclic or bicyclic ring system of up to 10 atoms in each ring, wherein at least one ring is aromatic, and at least one ring contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Bicyclic heteroaryl ring systems include fused ring systems, where two rings share two atoms, and spiro ring systems, where two rings share one atom. Heteroaryl groups within the scope of this definition include but are not limited to: azaindolyl, benzoimidazolyl, benzisoxazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, indolinyl, indolyl, indolaziny, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, pyran, pyrazinyl, pyrazolyl, pyrazolopyrimidinyl, pyridazinyl, pyridopyridinyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydroindolyl, dihydroquinolinyl, dihydrobenzodioxinyl, dihydropyrazoloxazinyl, dihydropyrazolythiazinedioxidyl, methylenedioxybenzene, benzothiazolyl, benzothienyl, quinolinyl, isoquinolinyl, oxazolyl, tetra-hydroquinoline and 3-oxo-3,4-dihydro-2N-benzo[b][1,4]thiazine. If the heteroaryl contains nitrogen atoms, it is understood that the corresponding N-oxides thereof are also encompassed by this definition.

The term "heterocycle" or "heterocycl" as used herein is intended to mean a stable nonaromatic monocyclic or bicyclic ring system of up to 10 atoms in each ring, unless otherwise specified, containing from 1 to 4 heteroatoms selected from the group consisting of O, N, S, SO, or SO₂. Bicyclic heterocyclic ring systems include fused ring systems, where two rings share two atoms, and spiro ring systems, where two rings share one atom. "Heterocycl" therefore includes, but is not limited to the following: azaspiro-nonan, azaspiro-octan, azetidyl, dioxan, oxadiazaspirodecenyl, oxaspiro-octan, oxazolidinon, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, tetrahydrofuran, tetrahydropyran, dihydropiperidinyl, tetrahydrothiophenyl and the like. If the heterocycle contains a nitrogen, it is understood that the corresponding N-oxides thereof are also encompassed by this definition.

"Celite®" (Fluka) diatomite is diatomaceous earth, and can be referred to as "celite".

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such

combinations result in stable compounds. By “stable compound” or “stable structure” is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term “in substantially purified form,” as used herein, refers to the physical state of a compound after the compound is isolated from a synthetic process (*e.g.*, from a reaction mixture), a natural source, or a combination thereof. The term “in substantially purified form,” also refers to the physical state of a compound after the compound is obtained from a purification process or processes described herein or well-known to the skilled artisan (*e.g.*, chromatography, recrystallization and the like), in sufficient purity to be characterizable by standard analytical techniques described herein or well-known to the skilled artisan.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed “protected”, this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in Organic Synthesis* (1991), Wiley, New York.

When any substituent or variable (*e.g.*, R⁴) occurs more than one time in any constituent or in Formula I, its definition on each occurrence is independent of its definition at every other occurrence, unless otherwise indicated.

As used herein, the term “composition” is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term “prodrug” means a compound (*e.g.*, a drug precursor) that is transformed *in vivo* to provide a compound of Formula I or a pharmaceutically acceptable salt of the compound. The transformation may occur by various mechanisms (*e.g.*, by metabolic or chemical processes), such as, for example, through hydrolysis in blood. For example, if a compound of Formula I or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed

by the replacement of the hydrogen atom of the acid group with a group such as, for example, (C₁-C₈)alkyl, (C₂-C₁₂)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxy-carbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxy-carbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxy-carbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxy-carbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxy-carbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C₁-C₂)alkylamino(C₂-C₃)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C₁-C₂)alkyl, N,N-di (C₁-C₂)alkylcarbamoyl-(C₁-C₂)alkyl and piperidino-, pyrrolidino- or morpholino(C₂-C₃)alkyl, and the like.

Similarly, if a compound of Formula I contains an alcohol functional group, a prodrug can be formed by the replacement of one or more of the hydrogen atoms of the alcohol groups with a group such as, for example, (C₁-C₆)alkanoyloxymethyl, 1-((C₁-C₆)alkanoyloxy)ethyl, 1-methyl-1-((C₁-C₆)alkanoyloxy)ethyl, (C₁-C₆)alkoxy-carbonyloxymethyl, N-(C₁-C₆)alkoxy-carbonylaminomethyl, succinoyl, (C₁-C₆)alkanoyl, α-amino(C₁-C₄)alkyl, α-amino(C₁-C₄)alkylene-aryl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

If a compound of Formula I incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl-, RO-carbonyl-, NRR'-carbonyl- wherein R and R' are each independently (C₁-C₁₀)alkyl, (C₃-C₇) cycloalkyl, benzyl, a natural α-aminoacyl, -C(OH)C(O)OY¹ wherein Y¹ is H, (C₁-C₆)alkyl or benzyl, -C(OY²)Y³ wherein Y² is (C₁-C₄) alkyl and Y³ is (C₁-C₆)alkyl; carboxy (C₁-C₆)alkyl; amino(C₁-C₄)alkyl or mono-N- or di-N,N-(C₁-C₆)alkylaminoalkyl; -C(Y⁴)Y⁵ wherein Y⁴ is H or methyl and Y⁵ is mono-N- or di-N,N-(C₁-C₆)alkylamino morpholino; piperidin-1-yl or pyrrolidin-1-yl, and the like.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy group of a hydroxyl compound, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (e.g., methyl, ethyl, n-propyl, isopropyl, t-butyl, sec-butyl or n-butyl), alkoxyalkyl (e.g., methoxymethyl), aralkyl (e.g., benzyl), aryloxyalkyl (for example, phenoxy-methyl), aryl (e.g., phenyl optionally substituted with, for example, halogen, C₁₋₄alkyl, -O-(C₁₋₄alkyl) or amino); (2) sulfonate esters, such as

alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters, including those corresponding to both natural and non-natural amino acids (*e.g.*, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C₁₋₂₀ alcohol or reactive derivative thereof, or by a 2,3-di
5 (C₆₋₂₄)acyl glycerol.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent
10 molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of solvates include ethanولات, methanولات, and the like. A "hydrate" is a
15 solvate wherein the solvent molecule is water.

One or more compounds of the invention may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates,
20 hemisolvates, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than room temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated
25 by standard methods. Analytical techniques such as, for example IR spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

The compound of Formula I can form salts which are also within the scope of this invention. Reference to a compound of Formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic
30 salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula I contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. In one embodiment, the salt is a pharmaceutically acceptable (*i.e.*, non-

toxic, physiologically acceptable) salt. In another embodiment, the salt is other than a pharmaceutically acceptable salt. Salts of the Compounds of Formula I may be formed, for example, by reacting a compound of Formula I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use*. (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamine, t-butyl amine, choline, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (*e.g.*, methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.*, dimethyl, diethyl, and dibutyl sulfates), long chain halides (*e.g.*, decyl, lauryl, and stearyl chlorides, bromides and iodides), arylalkyl halides (*e.g.*, benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

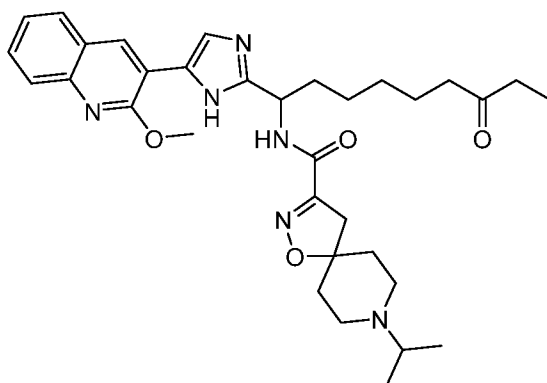
Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well-known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (*e.g.*, chiral auxiliary such as a chiral alcohol or

Mosher's acid chloride), separating the diastereomers and converting (*e.g.*, hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Stereochemically pure compounds may also be prepared by using chiral starting materials or by employing salt resolution techniques. Also, some of the compound of Formula I may be atropisomers (*e.g.*, substituted biaryls) and are considered as part of this invention. Enantiomers can also be directly separated using chiral chromatographic techniques.

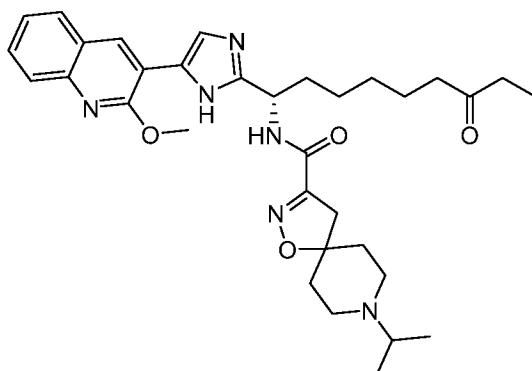
It is also possible that the compound of Formula I may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. For example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

Unless otherwise indicated, all stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, hydrates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention. If a compound of Formula I incorporates a double bond or a fused ring, both the *cis*- and *trans*-forms, as well as mixtures, are embraced within the scope of the invention.

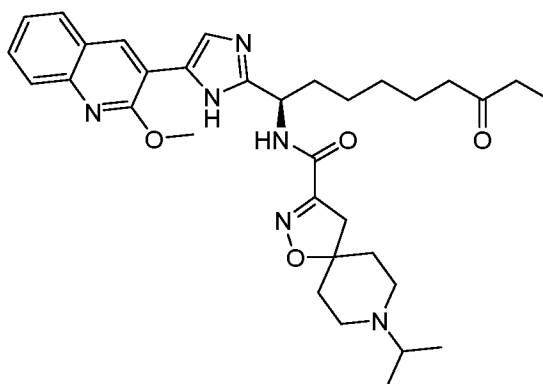
When a substituent on a chiral carbon atom is depicted without specific stereochemistry (by using a straight line bond to a chiral center), it is to be understood that both the α and β configurations of said substituent group are to be considered part of the present invention. For example, the compound of the present invention, which is drawn as follows:



is understood to encompass both stereoisomers at the indicated chiral center, the structures of which are as follows:



and



In the Examples section below, compounds of the present invention that have been purified as individual stereoisomers are sometimes depicted in non-stereospecific form but identified using one or more of the terms: “diastereomer 1,” “diastereomer 2,” “isomer 1,” “isomer 2,” “enantiomer A” and “enantiomer B.” In this instance, the absolute stereochemistry of each isolated diastereomer and enantiomeric center has not been determined and the terms used above are used to represent each individual purified stereochemically pure compound.

Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate", "ester", "prodrug" and the like, is intended to apply equally to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrugs of the inventive compounds.

In the Compounds of Formula I, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of generic Formula I. For example, different

isotopic forms of hydrogen (H) include protium (^1H) and deuterium (^2H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may provide certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples.

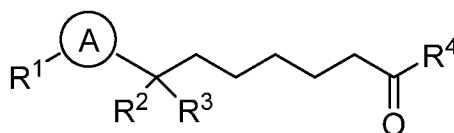
5 Isotopically-enriched Compounds of Formula I can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates. In one embodiment, a Compound of Formula I has one or more of its hydrogen atoms replaced with deuterium.

10 The compounds of Formula I may be useful in human and veterinary medicine for treating or preventing HIV infection in a subject. In one embodiment, the compounds of Formula I can be inhibitors of HIV viral replication. In a specific embodiment, the compound of Formula I are inhibitors of HIV-1. Accordingly, the compounds of Formula I may be useful for treating HIV infections and AIDS. In accordance with the invention, the compounds of Formula
15 I can be administered to a subject in need of treatment or prevention of HIV infection.

Accordingly, in one embodiment, the invention provides methods for treating HIV infection in a subject comprising administering to the subject an effective amount of at least one compound of Formula I or a pharmaceutically acceptable salt thereof. In a specific embodiment, the present invention provides methods for treating AIDS in a subject comprising
20 administering to the subject an effective amount of at least one compound of Formula I or a pharmaceutically acceptable salt thereof.

The Compounds of Formula I

The present invention provides Compounds of Formula I:



25 wherein (A) is a five-membered heteroaryl ring which is optionally substituted with halo, cyano, R^5 , R^6 , $(\text{C}=\text{O})\text{N}(\text{R}^5)_2$, $\text{NR}^5(\text{C}=\text{O})\text{N}(\text{R}^5)_2$, $(\text{C}=\text{O})\text{R}^6$ or $(\text{C}_{1-3} \text{ alkyl})\text{O}(\text{C}=\text{O})\text{R}^5$;
 R^1 is phenyl, bicyclic aryl, tricyclic aryl or heteroaryl, which may be monocyclic, bicyclic or tricyclic, wherein said phenyl and heteroaryl groups are optionally substituted with one to four groups independently selected from the group consisting of halo, oxo, cyano, C_{2-3} alkenyl, R^5 ,
 30 R^6 , OR^5 , $\text{N}(\text{R}^5)_2$, $(\text{C}=\text{O})\text{NHR}^6$, $\text{NR}^5(\text{C}=\text{O})\text{N}(\text{R}^5)_2$, $\text{NR}^5(\text{C}=\text{NR}^5)\text{N}(\text{R}^5)_2$, SO_2R^5 , $\text{SO}_2\text{N}(\text{R}^5)_2$, $\text{NR}^5\text{SO}_2\text{R}^5$, and $\text{NR}^5\text{SO}_2\text{N}(\text{R}^5)_2$;

R^2 is selected from the group consisting of hydrogen, $N(R^5)_2$, $NR^5(C=O)R^5$, $NR^5(C=O)N(R^5)_2$, $NR^5(C=NR^5)N(R^5)_2$, $NR^5(C=O)R^6$, $NR^5(C_{1-3}alkyl)R^6$ and $NR^5(C=O)(C_{1-3}alkyl)R^6$;

R^3 is selected from hydrogen, C_{1-6} alkyl or CH_2OR^5 ;

R^4 is C_{1-6} alkyl, or C_{3-6} cycloalkyl, which is optionally substituted with one to three substituents

5 independently selected from the group consisting of halo and hydroxyl, or C_{3-6} cycloalkyl; each R^5 is independently hydrogen, cyano, or C_{1-6} alkyl, which is optionally substituted with NH_2 , $N(CH_3)_2$, $NH(CH_3)_2$, $N(CH_2CH_3)_2$, or one to three halo;

R^6 is

- (a) heterocyclyl, which may be monocyclic, bicyclic or tricyclic,
- 10 (b) C_{3-6} cycloalkyl,
- (c) phenyl, or
- (d) heteroaryl, which may be monocyclic, bicyclic or tricyclic,

wherein said heterocyclyl, cycloalkyl, phenyl and heteroaryl groups are optionally substituted with one to four groups independently selected from the group consisting of halo, cyano, oxo,

15 R^5 , OR^5 , $(C=O)R^5$, $(C=O)OR^5$, $N(R^5)_2$, $(C=O)N(R^5)_2$, $NR^5(C=O)R^5$, $NR^5(C=O)N(R^5)_2$, $NR^5(C=NR^5)N(R^5)_2$, SO_2R^5 , $SO_2N(R^5)_2$, $NR^5SO_2R^5$, $NR^5SO_2N(R^5)_2$, C_{2-3} alkenyl, benzyl, benzyl- OR^5 , $CH_2(C_{3-6}$ cycloalkyl), CH_2 (heteroaryl), heteroaryl, heterocyclyl and C_{3-6} cycloalkyl; or a pharmaceutically acceptable salt thereof.

In an embodiment of the invention, $\textcircled{A}$ is selected from imidazolyl, oxazolyl, 20 oxadiazolyl or triazolyl, wherein said groups are optionally substituted with halo, cyano or C_{1-3} alkyl. In a class of the embodiment, $\textcircled{A}$ is selected from imidazolyl. In another embodiment of the invention, $\textcircled{A}$ is oxazolyl. In another class of the embodiment, $\textcircled{A}$ is oxadiazolyl. In another class of the embodiment, $\textcircled{A}$ is triazolyl.

In an embodiment of the invention, R^1 is azaindazolyl, benzoxazolyl, 25 benzothiazolyl, carbazolyl, chromenyl, cinnolinyl, dihydroisoquinolinyl, imidazolyl, imidazopyridinyl, indazolyl, isoquinolinyl, naphthalenyl, naphthyridinyl, phenyl, pyridinyl, pyrimidinyl, quinolinyl, quinoxalinyl, or tetrahydroepaminonaphthalenyl, tetrahydromethanonaphthalenyl, wherein said groups are optionally substituted with one to three groups optionally selected from the group consisting of halo, oxo, cyano, C_{2-3} alkenyl, R^5 , R^6 , 30 OR^5 , $N(R^5)_2$, $(C=O)NHR^6$ and SO_2R^5 .

In an embodiment of the invention, R^2 is $NH(C=O)R^6$ or $NH(C=O)(C_{1-3}alkyl)R^6$, and R^6 is selected from the group consisting of azaspirobicyclooctanecyclopropanyl, azetidiny,

azaspirohepatnyl, azaspirohexanyl, azaspirononanyl, azaspirooctanyl, diazaspirooctanyl, dihydropyrroloindolyl, dihydroethanoquinolyl, isoxazolyl, oxadiazaspirodecenyl, oxaspirooctanyl, quinuclidine, spirooctanyl, spirocyclohexanefuropyridinyl, tetrahydrocyclopentaindolyl, tetrahydropyranyl and thiazolyl, wherein said groups are optionally substituted with one or two groups independently selected from the group consisting of halo, oxo, R^5 , OR^5 , $(C=O)N(R^5)_2$, C_{2-3} alkenyl, benzyl, benzyl- OR^5 , $CH_2(C_{3-6}$ cycloalkyl), CH_2 (heteroaryl), heteroaryl and C_{3-6} cycloalkyl.

In an embodiment of the invention, R^3 is hydrogen.

In an embodiment of the invention, R^4 is ethyl.

In another embodiment, the Compounds of Formula I are in substantially purified form.

It is to be understood that any of the aforementioned embodiments may be combined with one or more separate embodiments.

Other embodiments of the present invention include the following:

(a) A pharmaceutical composition comprising an effective amount of a Compound of Formula I, and a pharmaceutically acceptable carrier.

(b) The pharmaceutical composition of (a), further comprising a second therapeutic agent selected from the group consisting of HIV antiviral agents, immunomodulators, anti-infective agents, vaccines, and antibodies.

(c) The pharmaceutical composition of (b), wherein the HIV antiviral agent is an antiviral selected from the group consisting of HIV protease inhibitors, HIV integrase inhibitors and HIV NNRTI inhibitors.

(d) A pharmaceutical combination that is (i) a Compound of Formula I and (ii) a second therapeutic agent selected from the group consisting of HIV antiviral agents, immunomodulators, and anti-infective agents, vaccines, and antibodies; wherein the Compound of Formula I and the second therapeutic agent are each employed in an amount that renders the combination effective for inhibiting HIV replication, or for treating HIV infection and/or reducing the likelihood or severity of symptoms of HIV infection, and eradicates HIV infection.

(e) The combination of (d), wherein the HIV antiviral agent is an antiviral selected from the group consisting of HIV protease inhibitors, HIV integrase inhibitors and HIV NNRTI inhibitors.

(f) A method of inhibiting HIV replication in a subject in need thereof which comprises administering to the subject an effective amount of a Compound of Formula I.

(g) A method of treating HIV infection and/or reducing the likelihood or severity of symptoms of HIV infection in a subject in need thereof which comprises administering to the subject an effective amount of a Compound of Formula I.

5 (h) The method of (g), wherein the Compound of Formula I is administered in combination with an effective amount of at least one second therapeutic agent selected from the group consisting of HIV antiviral agents, immunomodulators, and anti-infective agents.

(i) The method of (h), wherein the HIV antiviral agent is an antiviral selected from the group consisting of HIV protease inhibitors, HIV integrase inhibitors and HIV NNRTI inhibitors.

10 (j) A method of inhibiting HIV replication in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b) or (c) or the combination of (d) or (e).

(k) A method of treating HIV infection and/or reducing the likelihood or severity of symptoms of HIV infection in a subject in need thereof which comprises
15 administering to the subject the pharmaceutical composition of (a), (b) or (c) or the combination of (d) or (e).

Additional embodiments of the present invention include the following:

(l) A pharmaceutical composition comprising an effective amount of a pharmaceutically acceptable salt of a Compound of Formula I, and a pharmaceutically
20 acceptable carrier.

(m) The pharmaceutical composition of (l), further comprising a second therapeutic agent selected from the group consisting of HIV antiviral agents, immunomodulators, anti-infective agents, vaccines and antibodies.

25 (n) The pharmaceutical composition of (m), wherein the HIV antiviral agent is an antiviral selected from the group consisting of HIV protease inhibitors and HIV NNRTI inhibitors.

(o) A pharmaceutical combination that is (i) a pharmaceutically acceptable salt of a Compound of Formula I and (ii) a second therapeutic agent selected from the group consisting of HIV antiviral agents, immunomodulators, and anti-infective agents; wherein the
30 pharmaceutically acceptable salt of the Compound of Formula I and the second therapeutic agent are each employed in an amount that renders the combination effective for inhibiting HIV replication, or for treating HIV infection and/or reducing the likelihood or severity of symptoms of HIV infection.

(p) The combination of (o), wherein the HIV antiviral agent is an antiviral selected from the group consisting of HIV protease inhibitors and HIV NNRTI inhibitors.

(q) A method of inhibiting HIV replication in a subject in need thereof which comprises administering to the subject an effective amount of a pharmaceutically acceptable salt of a Compound of Formula I.

(r) A method of treating HIV infection and/or reducing the likelihood or severity of symptoms of HIV infection in a subject in need thereof which comprises administering to the subject an effective amount of a pharmaceutically acceptable salt of a Compound of Formula I.

(s) The method of (r), wherein the pharmaceutically acceptable salt of the Compound of Formula I is administered in combination with an effective amount of at least one second therapeutic agent selected from the group consisting of HIV antiviral agents, immunomodulators, and anti-infective agents.

(t) The method of (s), wherein the HIV antiviral agent is an antiviral selected from the group consisting of HIV protease inhibitors and HIV NS5B polymerase inhibitors.

(u) A method of inhibiting HIV replication in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (l), (m) or (n) or the combination of (o) or (p).

(v) A method of treating HIV infection and/or reducing the likelihood or severity of symptoms of HIV infection in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (l), (m) or (n) or the combination of (o) or (p).

Further embodiments of the present invention include the following:

(w) A pharmaceutical composition comprising an effective amount of a Compound of Formula I or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

(x) The pharmaceutical composition of (w), further comprising a second therapeutic agent selected from the group consisting of HIV antiviral agents, immunomodulators, and anti-infective agents.

(y) The pharmaceutical composition of (x), wherein the HIV antiviral agent is an antiviral selected from the group consisting of HIV protease inhibitors and HIV NNRTI inhibitors.

(z) A pharmaceutical combination that is (i) a Compound of Formula I and (ii) or a pharmaceutically acceptable salt thereof, a second therapeutic agent selected from the

group consisting of HIV antiviral agents, immunomodulators, and anti-infective agents; wherein the Compound of Formula I and the second therapeutic agent are each employed in an amount that renders the combination effective for inhibiting HIV replication, or for treating HIV infection and/or reducing the likelihood or severity of symptoms of HIV infection.

5 (aa) The combination of (z), wherein the HIV antiviral agent is an antiviral selected from the group consisting of HIV protease inhibitors and HIV NNRTI inhibitors.

(bb) A method of inhibiting HIV replication in a subject in need thereof which comprises administering to the subject an effective amount of a Compound of Formula I or a pharmaceutically acceptable salt thereof.

10 (cc) A method of treating HIV infection and/or reducing the likelihood or severity of symptoms of HIV infection in a subject in need thereof which comprises administering to the subject an effective amount of a Compound of Formula I or a pharmaceutically acceptable salt thereof.

(dd) The method of (cc), wherein the Compound of Formula I or
15 pharmaceutically acceptable salt thereof, is administered in combination with an effective amount of at least one second therapeutic agent selected from the group consisting of HIV antiviral agents, immunomodulators, and anti-infective agents.

(ee) The method of (dd), wherein the HIV antiviral agent is an antiviral selected from the group consisting of HIV protease inhibitors and HIV NNRTI inhibitors.

20 (ff) A method of inhibiting HIV replication in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (w), (x) or (y) or the combination of (z) or (aa).

(gg) A method of treating HIV infection and/or reducing the likelihood or severity of symptoms of HIV infection in a subject in need thereof which comprises
25 administering to the subject the pharmaceutical composition of (w), (x) or (y) or the combination of (z) or (aa).

The present invention also includes a compound of the present invention for use I in, (ii) as a medicament for, or (iii) in the preparation of a medicament for: (a) medicine; (b) inhibiting HIV replication or (c) treating HIV infection and/or reducing the likelihood or severity
30 of symptoms of HIV infection. In these uses, the compounds of the present invention can optionally be employed in combination with one or more second therapeutic agents selected from HIV antiviral agents, anti-infective agents, and immunomodulators.

Additional embodiments of the invention include the pharmaceutical compositions, combinations and methods set forth in (a)-(gg) above and the uses set forth in the

preceding paragraph, wherein the compound of the present invention employed therein is a compound of one of the embodiments, aspects, classes, sub-classes, or features of the compounds described above. In all of these embodiments, the compound may optionally be used in the form of a pharmaceutically acceptable salt or hydrate as appropriate.

5 It is further to be understood that the embodiments of compositions and methods provided as (a) through (gg) above are understood to include all embodiments of the compounds, including such embodiments as result from combinations of embodiments.

Non-limiting examples of the Compounds of Formula I include compounds **1-196** as set forth in the Examples below, and pharmaceutically acceptable salts thereof.

10 **Methods For Making the Compounds of Formula I**

The Compounds of Formula I may be prepared from known or readily prepared starting materials, following methods known to one skilled in the art of organic synthesis. Methods useful for making the Compounds of Formula I are set forth in the Examples below and generalized in the Schemes below. Alternative synthetic pathways and analogous structures will
15 be apparent to those skilled in the art of organic synthesis.

General List of Abbreviations

Abbreviations and acronyms employed herein include the following:

Ac	Acetyl
Aq	Aqueous
ACN	Acetonitrile
AIBN	Azobisisobutyronitrile
AUC	Area under the curve
BAST	Bis(2-methoxyethyl)aminosulfur trifluoride
BOC	<i>tert</i> -butoxycarbonyl
BPD	3-(1,3-Benzodioxol-5-yl)-4-phenyl-2,5-furandione
Brettphos	2-(Dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl
Bu	Butyl
Burgess reagent	Methyl <i>N</i> -(triethylammoniosulfonyl)carbamate
Bz	Benzoyl
CDI	Carbonyldiimidazole
DBDMH	1,3-Dibromo-5,5-dimethylhydantoin
DBU	2,3,4,6,7,8,9,10-Octahydropyrimidol[1,2- <i>a</i>]azepine
DCM	Dichloromethane
DCE	1,2-Dichloroethane
DEAD	1,2-Ethoxycarbonyl diazene solution
DHP	3,4-dihydro-2H-pyran
DIBAL-H	Diisobutylaluminium hydride
DIEA, DIPEA or Hünig's base	<i>N,N</i> -diisopropylethylamine
DMA	<i>N,N</i> -Dimethylacetamide
DMAP	4-dimethylaminopyridine

DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess–Martin periodinane
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
DMSO	dimethyl sulfoxide
DTBPF	1,1'-bis(di-tert-butylphosphino)ferrocene
EA	Ethyl Acetate
EDCI	<i>N</i> -ethyl- <i>N'</i> -(3-dimethylaminopropyl)carbodiimide hydrochloride
Et	Ethyl
EtOH	Ethanol
EtOAc	ethyl acetate
G	Grams
GI	Gastrointestinal
H	Hour
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HCHO	Formaldehyde
HIV	human immunodeficiency virus
HOBT, HOBt	1-Hydroxybenzotriazole hydrate
HPBCD	hydroxypropyl β -cyclodextrin
HPLC	high-performance liquid chromatography
mCPBA, CPBA	<i>meta</i> -Chloroperoxybenzoic
Hz	Hertz
IPA	Isopropanol
IV	Intravenous
iPr	Isopropyl
Ir[dF(CF ₃)ppy] ₂ (dtbpy)PF ₆	[4,4'- <i>Bis</i> (1,1-dimethylethyl)-2,2'-bipyridine- <i>N</i> 1, <i>N</i> 1'] <i>bis</i> [3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl- <i>N</i>]phenyl-C]Iridium(III) hexafluorophosphate
L	Liter
LC	liquid chromatography
LC/MS	liquid chromatography mass spectrometry
LDA	Lithium diisopropylamide
LED	light-emitting diode
LiHMDS	lithium bis(trimethylsilyl)amide
Me	Methyl
MeOH	Methanol
Mg	Milligrams
MHz	Megahertz
Min	Minute
μ L	Microliters
mL	Milliliters
Mmol	Millimoles
MOM-Cl	chloromethyl methyl ether
MPLC	medium pressure liquid chromatography
MS	mass spectrometry
NBS	<i>N</i> -Bromosuccinimide
NCS	<i>N</i> -Chlorosuccinimide

NHS	normal human serum
NIS	N-Iodosuccinimide
NMO	4-methylmorpholine N-oxide
NMR	nuclear magnetic resonance spectroscopy
PBMC	peripheral blood mononuclear cell
Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)dipalladium(0)
Ph	Phenyl
P.O.	Oral
PPTS	Pyridinium <i>p</i> -toluenesulfonate
PTSA	para-toluenesulfonic acid
Pr	Propyl
Rpm	revolutions per minute
RT or rt	room temperature (ambient, about 25 °C)
sat or sat'd	Saturated
SelectFluor	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
SEMCl	2-Chloromethoxyethyl)trimethylsilane
SFC	supercritical fluid chromatography
T3P, T ₃ P	1-Propanephosphonic anhydride solution
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TBDPSCI	<i>tert</i> -Butyldiphenylchlorosilane
TBSCl	<i>tert</i> -Butyldimethylsilyl chloride
tBu	<i>tert</i> -butyl
TCP	2,3,5-Trichloro-6-hydroxypyridine
TEA	triethylamine (Et ₃ N)
TEMED	Tetramethylethylenediamine
TFA	trifluoroacetic acid
TFV	Tenofovir
TFV-MP	Tenofovir monophosphate
TFV-DP	Tenofovir diphosphate
THF	Tetrahydrofuran
TMS	Tetramethylsilane
TosMIC	Toluenesulfonylmethyl isocyanide
TPAP	Tetrapropylammonium perruthenate
Ts	Tosyl
UPLC	ultrahigh pressure liquid chromatography
UV	Ultraviolet
UV/VIS	ultraviolet/visible
W	Watt
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
XPhos-Pd-G2	Chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)

General Procedures

Starting materials and intermediates are purchased or are made using known procedures, or as otherwise illustrated. The general route applied to the synthesis of compounds of Formula I is described in the Schemes that follows. In some cases the order of carrying out the reaction

5

steps in the schemes may be varied to facilitate the reaction or to avoid unwanted reaction products.

Reactions sensitive to moisture or air were performed under nitrogen or argon using anhydrous solvents and reagents. The progress of reactions was determined by either analytical
5 thin layer chromatography (TLC) usually performed with E. Merck pre-coated TLC plates, silica gel 60F-254, layer thickness 0.25 mm or liquid chromatography-mass spectrometry (LC/MS).

Typically the analytical LC-MS system used consisted of a Waters ZQ™ platform with electrospray ionization in positive ion detection mode with an Agilent 1100 series HPLC with
10 autosampler. The column was commonly a Waters Xterra MS C18, 3.0 × 50 mm, 5 μm or a Waters Acquity UPLC® BEH C18 1.0 x 50 mm, 1.7 μm. The flow rate was 1 mL/min, and the injection volume was 10 μL. UV detection was in the range 210–400 nm. The mobile phase consisted of solvent A (water plus 0.05% TFA) and solvent B (MeCN plus 0.05% TFA) with a gradient of 100% solvent A for 0.7 min changing to 100% solvent B over 3.75 min, maintained
15 for 1.1 min, then reverting to 100% solvent A over 0.2 min. Alternatively, the column was commonly a Waters Acquity UPLC® BEH C18 1.0 X 50 mm, 1.7 μm. The flow rate was 0.3 mL/min, and the injection volume was 0.5 μL. UV detection was 215 or 254 nm. Either the mobile phase consisted of solvent A (water plus 0.05% TFA) and solvent B (MeCN plus 0.05% TFA) with a gradient of 90% solvent A changing to 99% solvent B over 1.6 min, maintained for
20 0.4 min, then reverting to 90% solvent A over 0.1 min or the mobile phase consisted of solvent A (water plus 0.05% TFA) and solvent B (MeCN plus 0.05% TFA) with a gradient of 97% solvent A changing to 4% then 50% solvent B over 0.5 min and 0.9 min, 50%-99% solvent B over 0.2 min, maintained for 0.4 min, then reverting to 90% solvent A over 0.1 min.

Preparative HPLC purifications were usually performed using either a mass spectrometry
25 directed system or a non-mass guided system. Usually they were performed on a Waters Chromatography Workstation configured with LC-MS System consisting of: Waters ZQ™ single quad MS system with Electrospray Ionization, Waters 2525 Gradient Pump, Waters 2767 Injecto/Collector, Waters 996 PDA Detector, the MS Conditions of: 150-750 amu, Positive Electrospray, Collection Triggered by MS, and a Waters SUNFIRE® C-18 5 micron, 30 mm (id)
30 × 100 mm column. The mobile phases consisted of mixtures of acetonitrile (10-100%) in water containing 0.1% TFA. Flow rates were maintained at 50 mL/min, the injection volume was 1800 μL, and the UV detection range was 210–400 nm. An alternate preparative HPLC system used was a Gilson Workstation consisting of: Gilson GX-281 Injector/Collector, Gilson UV/VIS-155 Detector, Gilson 322, 333, and 334 Pumps, and a Phenomenex Gemini-NX C-18 5

micron, 50 mm (id) × 250 mm column, a Waters XBridge™ C-18 5 micron OBD™, 30 mm (id) × 250 mm column, or a Waters SUNFIRE™ C-18 OBD™ 10 micron, 30 mm (id) × 150 mm column. The mobile phases consisted of mixtures of acetonitrile (0-90%) in water containing 0.1% or 0.05% TFA. Flow rates were maintained at 50 mL/min for the Waters Xbridge™

5 column, 90 mL / min for the Phenomenex Gemini column, and 30 mL/min for the Waters SUNFIRE™ column. The injection volume ranged from 1000-8000 μ L, and the UV detection range was 210–400 nm. Mobile phase gradients were optimized for the individual compounds.

Reactions performed using microwave irradiation were normally carried out using an Emrys Optimizer manufactured by Personal Chemistry, or an Initiator manufactured by Biotage.

10 Reactions performed using photon irradiation were normally carried out using either a second generation Merck photoreactor or a Kessil 34 W blue LED lamp. Concentration of solutions was carried out on a rotary evaporator under reduced pressure. Flash chromatography was usually performed using either a Biotage® Flash Chromatography apparatus (Dyax Corp.), an ISCO CombiFlash® Rf apparatus, or an ISCO CombiFlash® Companion XL on silica gel (32-63

15 microns, 60 Å pore size) in pre-packed cartridges of the size noted. ¹H NMR spectra were acquired at 500 MHz spectrometers in CDCl₃ solutions unless otherwise noted. Chemical shifts were reported in parts per million (ppm). Tetramethylsilane (TMS) was used as internal reference in CDCl₃ solutions, and residual CH₃OH peak or TMS was used as internal reference in CD₃OD solutions. Coupling constants (J) were reported in hertz (Hz). Chiral analytical

20 chromatography was most commonly performed on one of CHIRALPAK® AS, CHIRALPAK® AD, CHIRALCEL® OD, CHIRALCEL® IA, or CHIRALCEL® OJ columns (250 × 4.6 mm) (Daicel Chemical Industries, Ltd.) with noted percentage of ethanol in hexane (%EtOH/Hex), isopropanol in heptane (%IPA/Hep), ethanol in carbon dioxide (% EtOH/CO₂), or isopropanol in carbon dioxide (%IPA/CO₂) as isocratic solvent systems. Chiral preparative

25 chromatography was conducted on one of CHIRALPAK AS, of CHIRALPAK AD, CHIRALCEL® OD, CHIRALCEL® IA, CHIRALCEL® OJ columns (20 × 250 mm) (Daicel Chemical Industries, Ltd.) with desired isocratic solvent systems identified on chiral analytical chromatography or by supercritical fluid (SFC) conditions.

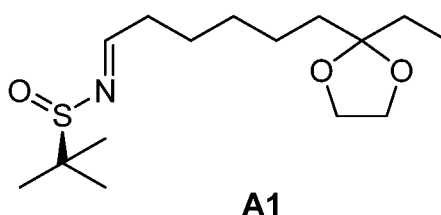
Several catalysts are used in the following procedures. “UMICORE M71 SIPR” is also

30 known as Umicore Hoveyda Grubbs Catalyst M71 SIPr” and [1,3-Bis(2,6-diisopropylphenyl)-2-imidazolidinylidene]dichloro[(2-isopropoxy)(5-trifluoroacetamido)benzylidene]ruthenium(II). It is available from Umicore Precious Metals Chemistry USA, LLC, 1305 Main Parkway Catoosa, OK 74015. “Zhan’s catalyst” is available from Sigma Aldrich.

Several methods for preparing the compounds of this invention are also described in the Examples. Starting materials and intermediates were purchased commercially from common catalog sources or were made using known procedures, or as otherwise illustrated.

Example 1

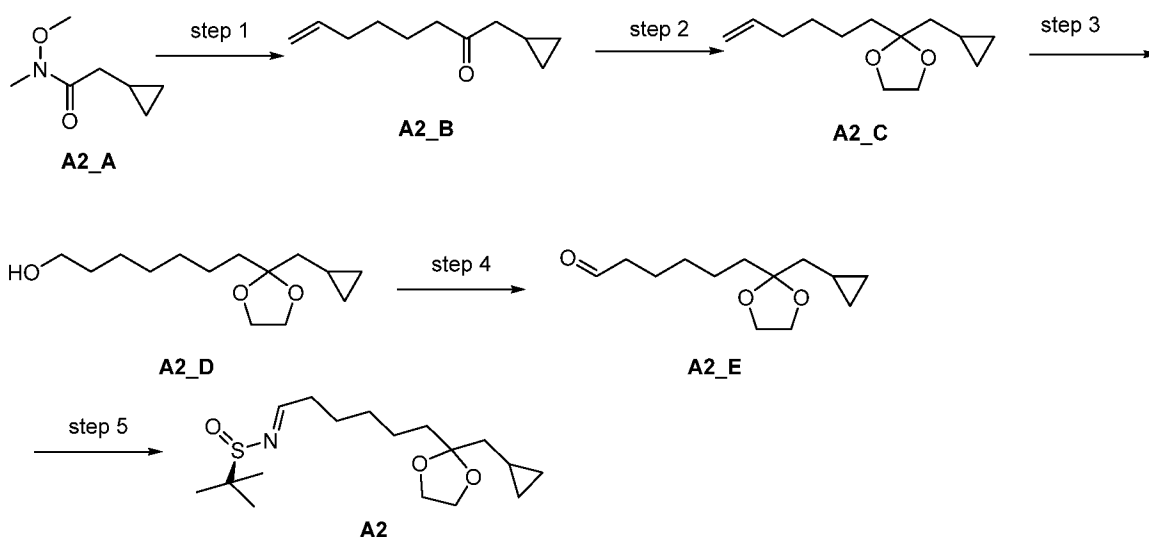
Preparation of Intermediate A1



Intermediate **A1** was prepared by the procedures described in Tetrahedron, **2009**, 65 (45) ,9487 – 9493.

Example 2

Preparation of Intermediate A2



Step 1: Preparation of 1-cyclopropyloct-7-en-2-one (A2_B): Hex-5-en-1-ylmagnesium bromide (37.9 g, 202 mmol) in anhydrous THF (150 mL) was added to a stirred mixture of 2-cyclopropyl-N-methoxy-N-methylacetamide (**A2_A**, 20 g, 140 mmol) in THF (100 mL) at 0°C and the mixture was stirred at room temperature for 2 h. The mixture was cooled to 0°C, hydrochloric acid (1 M, 30 mL) was added and the mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic fractions were washed with brine (saturated, 2 x 50 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with EtOAc/petroleum ether = 0 - 10% to give 1-cyclopropyloct-7-en-2-one (**A2_B**). ¹H NMR (400 MHz, CDCl₃) δ 5.76-5.83 (m,

1H), 4.88-5.08 (m, 2H), 2.46 (t, $J = 7.4$ Hz, 2H), 2.28 (d, $J = 7.0$ Hz, 2H), 2.05-2.12 (m, 2H), 1.56-1.64 (m, 2H), 1.34-1.45 (m, 2H), 0.93-1.04 (m, 1H), 0.50-0.60 (m, 2H), 0.06-0.17 (m, 2H).

Step 2: Preparation of 2-(cyclopropylmethyl)-2-(hex-5-en-1-yl)-1,3-dioxolane (A2_C): Ts-OH

(1.4 g, 7.36 mmol) was added to a stirred mixture of ethane-1,2-diol (32 mL, 575 mmol), and 1-cyclopropyloct-7-en-2-one (A2_B, 31.7 g, 191 mmol) in toluene (100 mL) at room temperature and the mixture was stirred at 135°C for 12 h. The mixture was cooled to room temperature, aqueous sodium hydrogen carbonate (saturated, 50 mL) was added and the mixture was

extracted with ethyl acetate (3 x 50 mL). The combined organic fractions were washed with brine (saturated, 2 x 100 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under

reduced pressure to afford 2-(cyclopropylmethyl)-2-(hex-5-en-1-yl)-1,3-dioxolane (A2_C)

which was used to the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 5.86-5.94 (m, 1H), 4.98-5.13 (m, 2H), 4.04 (s, 4H), 2.12-2.17 (m, 2H), 1.78-1.83 (m, 2H), 1.60 (d, $J = 6.8$ Hz, 2H), 1.48-1.49 (m, 4H), 0.77-0.91 (m, 1H), 0.51-0.59 (m, 2H), 0.16-0.20 (m, 2H).

Step 3: Preparation of 6-(2-(cyclopropylmethyl)-1,3-dioxolan-2-yl)hexan-1-ol (A2_D): BH₃

·THF (1.0 M, 160 mL, 160 mmol) was added to a stirred mixture of 2-(cyclopropylmethyl)-2-(hex-5-en-1-yl)-1,3-dioxolane (A2_C, 15 g, 71.3 mmol) in THF (50 mL) at room temperature and the mixture was stirred at room temperature for 2 h. NaOH (3 g, 75 mmol) in H₂O₂ (30%, 60 mL, 685 mmol) was drop-wise added in the mixture at 0°C carefully, then aq Na₂SO₃ (saturated, 50 mL) was added and the mixture was extracted with ethyl acetate (3 x 100 mL). The

combined organic fractions were washed with brine (saturated, 2 x 100 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with EtOAc/petroleum ether = 0-40% to give 6-(2-(cyclopropylmethyl)-1,3-dioxolan-2-yl)hexan-1-ol (A2_D). ¹H NMR (400 MHz, CDCl₃) δ 3.92-4.01 (m, 4H), 3.65 (t, $J = 6.6$ Hz, 2H), 1.68-1.78 (m, 2H), 1.47-1.63 (m, 5H), 1.32-1.43 (m, 7H), 0.71-0.81 (m, 1H), 0.44-0.50 (m, 2H), 0.08-0.13 (m, 2H).

Step 4: Preparation of 6-(2-(cyclopropylmethyl)-1,3-dioxolan-2-yl)hexanal (A2_E): Pyridine sulfur trioxide (105 mg, 0.657 mmol), and DIEA (0.153 mL, 0.876 mmol) was added to a stirred mixture of 6-(2-(cyclopropylmethyl)-1,3-dioxolan-2-yl)hexan-1-ol (A2_D, 100 mg, 0.438 mmol) in DCM (5 mL) / DMSO (1 mL) at room temperature and the mixture was stirred at room

temperature for 12 h. The mixture was then stirred at 40°C for 12 h. The mixture was cooled, diluted with ethyl acetate (10 mL), washed with brine (saturated, 3 x 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with EtOAc / petroleum ether = 0 - 30% to give 6-(2-(cyclopropylmethyl)-1,3-dioxolan-2-yl)hexanal (A2_E). ¹H NMR (400 MHz, CDCl₃) δ

9.76 (s, 1H), 3.87-4.04 (m, 4H), 2.36-2.49 (m, 2H), 1.69-1.76 (m, 2H), 1.61-1.66 (m, 2H), 1.51 (d, $J = 6.7$ Hz, 2H), 1.31-1.44 (m, 4H), 0.68-0.79 (m, 1H), 0.42-0.50 (m, 2H), 0.09 (d, $J = 4.7$ Hz, 2H).

Step 5: Preparation of (*R,E*)-*N*-(6-(2-(cyclopropylmethyl)-1,3-dioxolan-2-yl)hexylidene)-2-

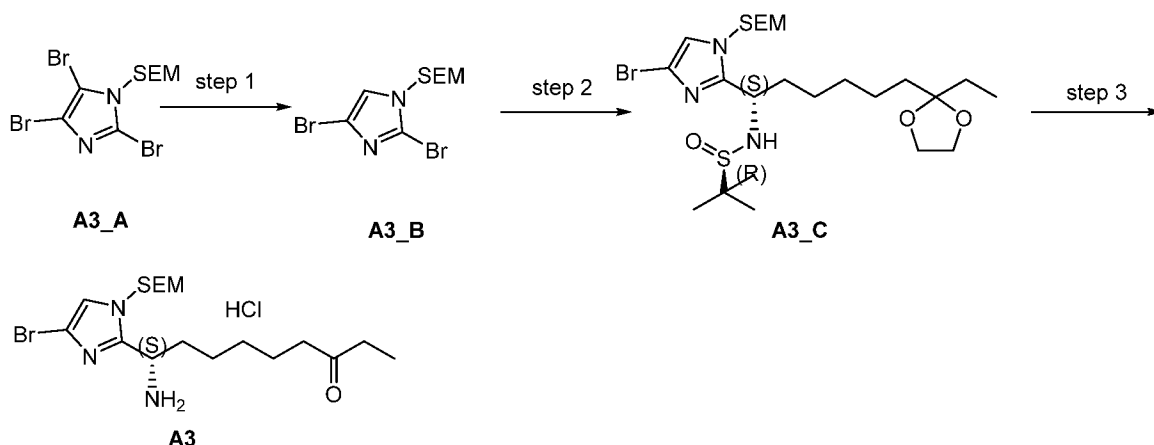
methylpropane-2-sulfinamide (A2): Copper(II) sulfate (30 g, 188 mmol), and (*R*)-2-methylpropane-2-sulfinamide (3.00 g, 24.79 mmol) were added to a stirred mixture of 6-(2-(cyclopropylmethyl)-1,3-dioxolan-2-yl)hexanal (A2_E, 5.1 g, 22.54 mmol) in DCM (50 mL) at room temperature and the mixture was stirred at room temperature for 48 h. The mixture was filtered, washed with ethyl acetate, the residue was purified by silica gel column flash

chromatography, eluting with EtOAc / petroleum ether = 0 - 40% to give (*R,E*)-*N*-(6-(2-(cyclopropylmethyl)-1,3-dioxolan-2-yl)hexylidene)-2-methylpropane-2-sulfinamide (A2).

¹HNMR (400 MHz, CDCl₃) δ 8.07 (t, $J = 4.8$ Hz, 1H), 3.94-4.00 (m, 4H), 2.50-2.55 (m, 2H), 1.69-1.76 (m, 2H), 1.62-1.67 (m, 2H), 1.52 (d, $J = 6.8$ Hz, 2H), 1.35-1.42 (m, 4H), 1.20 (s, 9H), 0.70-0.79 (m, 1H), 0.41-0.50 (m, 2H), 0.07-0.14 (m, 2H).

Example 3

Preparation of Intermediate A3



Step 1: Preparation of 2,4-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (A3 B):

Into a 10-L 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 2,4,5-tribromo-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-imidazole (A3_A, 420 g, 965.46 mmol) in tetrahydrofuran (4000 mL). This was followed by the addition of *n*-BuLi (783 mL, 2.02 equiv) dropwise with stirring at -78°C. The mixture was stirred at -78°C for 10 min. To this was added water (17.4 g, 966.67 mmol) at -78°C. The mixture was slowly warmed to -50°C over 1 h. To the mixture was added Br₂ (170 g, 1.06 mol, 1.20 equiv) at -78°C. The mixture was stirred at -78°C for 30 min. The reaction was then quenched by the addition of 2 L of water. The resulting solution was extracted with 3x2 L of

ethyl acetate and the organic layers combined. The resulting mixture was washed with 1x1 L of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:30) to afford 2,4-dibromo-1-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-imidazole (**A3_B**).

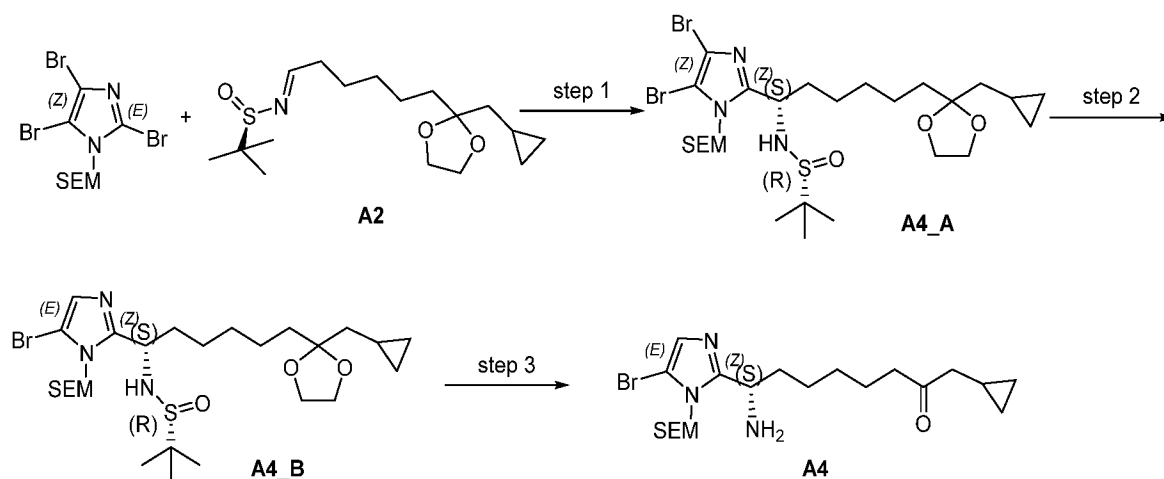
- 5 Step 2: Preparation of (*R*)-*N*-[(*S*)-1-(4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl]-2-methylpropane-2-sulfinamide (**A3_C**): Into a 5-L 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 2,4-dibromo-1-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-imidazole (**A3_B**, 120 g, 336.96 mmol) in tetrahydrofuran (1200 mL). This was followed by the addition of *n*-BuLi (138 g, 2.15 mol, 1.02 equiv) dropwise with stirring at -78°C. To this was added (*R*)-*N*-[(1*E*)-6-(2-ethyl-1,3-dioxolan-2-yl)hexylidene]-2-methylpropane-2-sulfinamide (**A1**, 102 g, 336.12 mmol) at -78°C. The resulting solution was stirred for 30 min at -30°C in a liquid nitrogen bath. The reaction was then quenched by the addition of 1 L of water. The resulting solution was extracted with 3x1 L of ethyl acetate and the organic layers combined. The resulting mixture was washed with 1x500 mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product (200 g) was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, silica gel; mobile phase, ACN/water NH₄HCO₃=50% increasing to ACN/water NH₄HCO₃=70% within 20 min; Detector, UV 254 nm. 130 g product was obtained. The crude product was purified by Chiral-Prep-HPLC with the following conditions (Prep SFC 350): Column, CHIRALPAK IA-SFC-025cm*25cmChiral-P(IA)011S90IA0SCY-SL-001; mobile phase, CO₂:80, MeOH; Detector, uv 220nm. This resulted in (*R*)-*N*-[(1*S*)-1-(4-bromo-1-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-imidazol-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl]-2-methylpropane-2-sulfinamide (**A3_C**).

- 25 Step 3: Preparation of (*S*)-9-amino-9-(4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)nonan-3-one (**A3**): Into a 3-L 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of (*R*)-*N*-[(1*S*)-1-(4-bromo-1-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-imidazol-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl]-2-methylpropane-2-sulfinamide (**A3_C**, 130 g, 223.87 mmol) in tetrahydrofuran (1300 mL). This was followed by the addition of hydrogen chloride (24 g, 1.10 equiv) dropwise with stirring at 0-5°C. The resulting solution was stirred at room temperature for 8 h. The resulting solution was diluted with 1000 mL of ice-water. The resulting solution was extracted with 3x500 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 1x500 mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with DCM/EtOH (30/1). The

product was diluted with DCM 500 mL and washed with Na₂CO₃, followed by brine, and mixed with HCl conc. (16 g in EtOAc 100 mL). The mixture was washed with brine, dried over Na₂SO₄, and concentrated to afford (9*S*)-9-amino-9-(4-bromo-1-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-imidazol-2-yl]nonan-3-one hydro chloride (**A3**). LCMS (ESI) calc'd for C₁₈H₃₄BrN₃O₂Si [M+H]⁺: 432.2, found: 434.0. ¹H NMR (300 MHz, DMSO) δ 8.29 (brs, 3H), 7.51 (s, 1H), 5.54 (d, *J* = 11.1 Hz, 1H), 5.23 (d, *J* = 11.2 Hz, 1H), 4.40 (t, *J* = 6.9 Hz, 1H), 3.44 (m, 2H), 2.41- 2.26 (m, 4H), 1.84 (brs, 2H), 1.36 (m, 2H), 1.11 (m, 5H), 0.94- 0.68 (m, 5H), -0.06 (s, 9H).

Example 4

Preparation of Intermediate **A4**



Step 1: Preparation of (S)-N-((S)-6-(2-(cyclopropylmethyl)-1,3-dioxolan-2-yl)-1-(4,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)hexyl)-2-methylpropane-2-sulfinamide

(A4_A): *n*BuLi (1.8 mL, 4.50 mmol) was added to a stirred mixture of 2,4,5-tribromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole (1.954 g, 4.49 mmol) in THF (20 mL) at -78°C and the mixture was stirred at -78°C for 30 min. (R,*E*)-*N*-(6-(2-(cyclopropylmethyl)-1,3-dioxolan-2-yl)hexylidene)-2-methylpropane-2-sulfinamide (**A2**, 1 g, 3.03 mmol) in THF (2 mL) was added dropwise. Then the mixture was stirred at -78°C for 2 h. Aqueous ammonium chloride (saturated, 15 mL), water (20 mL) was added at -78°C and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were washed with brine (saturated, 2 x 20 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with EtOAc / petroleum ether = 0 - 50% to give (S)-*N*-((S)-6-(2-(cyclopropylmethyl)-1,3-dioxolan-2-yl)-1-(4,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**A4_A**). LCMS (ESI) calc'd for C₂₆H₄₇Br₂N₃O₄SSi [M+H]⁺: 684.1, found: 686.2. ¹H NMR (400

MHz, CDCl₃) δ 5.48 (d, J = 11.2 Hz, 1H), 5.27 (d, J = 11.3 Hz, 1H), 4.51-4.59 (m, 1H), 3.89-4.00 (m, 4H), 3.68-3.77 (m, 1H), 3.56 (t, J = 8.3 Hz, 2H), 2.08-2.18 (m, 1H), 1.94-2.04 (m, 1H), 1.59-1.71 (m, 3H), 1.50 (d, J = 6.8 Hz, 2H), 1.33 (brs, 3H), 1.17 (s, 9H), 0.88-0.97 (m, 2H), 0.74 (m, 1H), 0.42-0.49 (m, 2H), 0.07-0.12 (m, 2H), 0.02 (s, 9H).

5 Step 2: Preparation of (S)-N-((S)-1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-6-(2-(cyclopropylmethyl)-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide

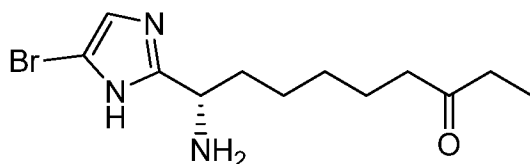
(A4_B): *n*BuLi (2.5 M, 0.45 mL, 1.125 mmol) was added to a stirred mixture of (S)-N-((S)-6-(2-(cyclopropylmethyl)-1,3-dioxolan-2-yl)-1-(4,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**A4_A**, 500 mg, 0.729 mmol) in THF
 10 (5 mL) at -78°C and the mixture was stirred at -78°C for 30 min. *i*-PrOH (0.3 mL, 3.89 mmol) was added, and the mixture was stirred at -78°C for 20 min. Aqueous ammonium chloride (saturated, 10 mL) was added and the mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic fractions were washed with brine (saturated, 2 x 15 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by
 15 silica gel column flash chromatography, eluting with EtOAc / petroleum ether = 0 - 50% to give (S)-N-((S)-1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-6-(2-(cyclopropylmethyl)-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**A4_B**). LCMS (ESI) calc'd for C₂₆H₄₈BrN₃O₄SSi [M+H]⁺: 606.2, found: 606.3. ¹H NMR (400 MHz, CDCl₃) δ 6.89 (s, 1H), 5.40 (d, J = 11.0 Hz, 1H), 5.14 (d, J = 10.8 Hz, 1H), 4.47-4.54 (m, 1H), 3.90-3.98
 20 (m, 4H), 3.50 (t, J = 8.3 Hz, 2H), 2.13 (d, J = 9.0 Hz, 1H), 1.97-2.04 (m, 1H), 1.59-1.72 (m, 4H), 1.49 (d, J = 6.8 Hz, 2H), 1.33 (brs, 4H), 1.16 (s, 9H), 0.88-0.95 (m, 2H), 0.68-0.78 (m, 1H), 0.42-0.49 (m, 2H), 0.07-0.11 (m, 2H), 0.01 (s, 9H).

Step 3: Preparation of (S)-8-amino-8-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-1-cyclopropyloctan-2-one hydrochloride (A4): HCl/MeOH (0.25 mL, 1.000

25 mmol) was added to a stirred mixture of (S)-N-((S)-1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-6-(2-(cyclopropylmethyl)-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**A4_B**, 150 mg, 0.247 mmol) in MeOH (2 mL) at room temperature and the mixture was stirred at room temperature for 2 h. Most of the MeOH was removed, and it was concentrated to give (S)-8-amino-8-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-1-cyclopropyloctan-2-one hydrochloride (**A4**)
 30 which was used to the next step without further purification. LCMS (ESI) calc'd for C₂₀H₃₆BrN₃O₂Si [M+H]⁺: 458.2, found: 460.1.

Example 5

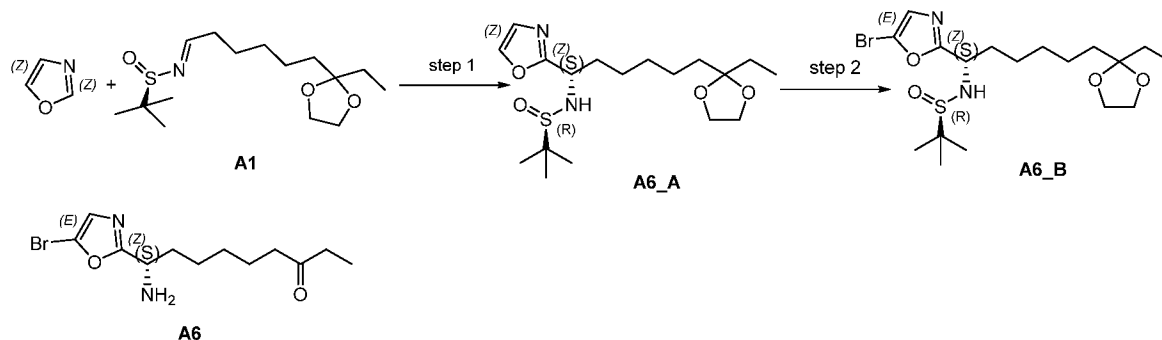
Preparation of Intermediate A5



Hydrogen chloride in EtOAc (4 M, 20.0 mL, 80.0 mmol) was added to a stirred mixture of (*S*)-9-amino-9-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)nonan-3-one hydrochloride (**A2**, 2.50 g, 5.33 mmol) in ethyl acetate (20 mL) at room temperature and the mixture was stirred at room temperature for 12 h. The mixture was quenched with aqueous NaHCO₃ (saturated, 30 mL) and the mixture was extracted with DCM (3x30 mL). The combined organic fractions were washed with brine (30 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with DCM / MeOH = 10:1 to give (*S*)-9-amino-9-(5-bromo-1*H*-imidazol-2-yl)nonan-3-one (**A3**). LCMS (ESI) calc'd for C₁₂H₂₀BrN₃O [M+H]⁺: 302.1, found: 304.0.

Example 6

Preparation of Intermediate A6



Step 1: (*R*)-*N*-((*S*)-6-(2-ethyl-1,3-dioxolan-2-yl)-1-(oxazol-2-yl)hexyl)-2-methylpropane-2-

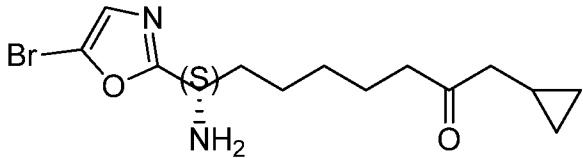
sulfonamide (**A6_A**): BH₃·THF (1.0 M, 1.8 mL, 1.800 mmol) was added to a stirred mixture of oxazole (148 mg, 2.142 mmol) in THF (5 mL) at rt and the mixture was stirred at rt for 1 h under N₂. The reaction mixture was cooled to -78°C, and then *n*-butyllithium (2.5 M, 0.7 mL, 1.750 mmol) was added to the mixture slowly under N₂. The mixture was stirred at -78°C for 1 h. (*R,E*)-*N*-(6-(2-ethyl-1,3-dioxolan-2-yl)hexylidene)-2-methylpropane-2-sulfinamide (**A1**, 500 mg, 1.648 mmol) in THF (1 mL) was added to the mixture slowly at -78°C and the mixture was stirred at -78°C for 2 h. Aqueous NH₄Cl (saturated, 0.2 mL) was added to the mixture. The mixture was extracted with ethyl acetate (3x10 mL). The combined organic fractions were washed with brine (5 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (ISCORF75; Sepa flash column), eluting with DCM / MeOH = 10/1 to give (*R*)-*N*-((*S*)-6-(2-ethyl-1,3-dioxolan-2-

yl)-1-(oxazol-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**A6_A**). LCMS (ESI) calc'd for $C_{18}H_{32}N_2O_4S$ $[M+H]^+$: 373.2, found: 373.1.

Step 2: Preparation of (R)-N-((S)-1-(5-bromooxazol-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (A6_B): Tert-butyllithium (1.3 M, 3.3 mL, 4.29 mmol) was added to a stirred mixture of (R)-N-((S)-6-(2-ethyl-1,3-dioxolan-2-yl)-1-(oxazol-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**A6_A**, 400 mg, 1.074 mmol) in THF (4 mL) at -78°C and the mixture was stirred at -78°C for 1 h under N_2 . Then CBr_4 (1068 mg, 3.22 mmol) in THF (0.5 mL) was added to the mixture slowly at -78°C and the mixture was stirred at -78°C for 1 h. Aqueous NH_4Cl (saturated, 2 mL) was added and the mixture was extracted with DCM (3x6 mL). The combined organic fractions were washed with brine (5 mL), dried (Na_2SO_4), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (ISCORF75; Sepa flash column), eluting with petroleum ether / EtOAc = 1/1~0/1 to give (R)-N-((S)-1-(5-bromooxazol-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**A6_B**). LCMS (ESI) calc'd for $C_{18}H_{31}BrN_2O_4S$ $[M+H]^+$: 451.1, found: 453.1.

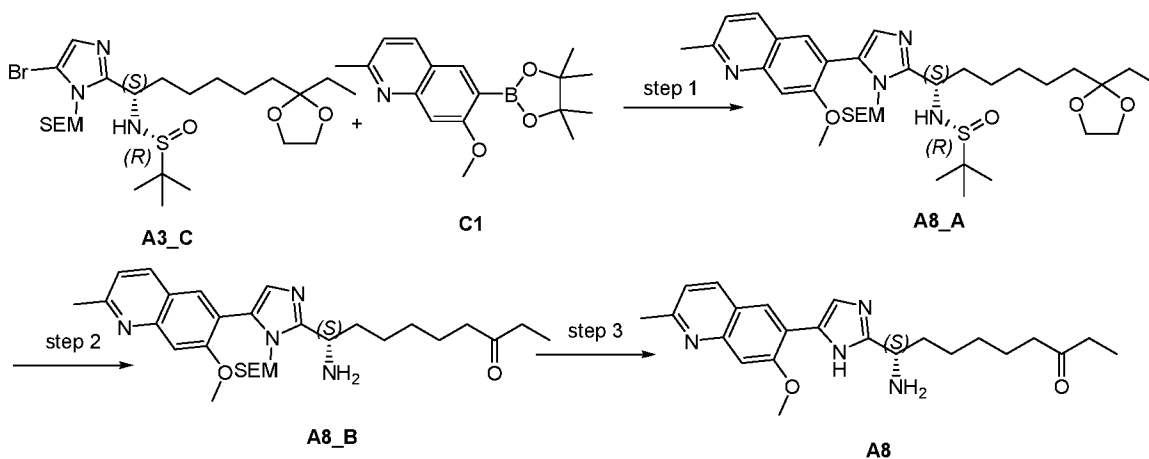
Step 3: Preparation of (S)-9-amino-9-(5-bromooxazol-2-yl)nonan-3-one (A6): HCl (~4 M in MeOH, 0.1 mL, 0.400 mmol) was added to a stirred mixture of (R)-N-((S)-1-(5-bromooxazol-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**A6_B**, 91 mg, 0.202 mmol) in MeOH (1 mL) at rt and the mixture was stirred at rt for 5 min. Aqueous $NaHCO_3$ (saturated, 1 mL) was added and the mixture was extracted with ethyl acetate (3 x 3 mL). The combined organic fractions were washed with brine (saturated, 2 mL), dried (Na_2SO_4), filtered and the filtrate was concentrated to give (S)-9-amino-9-(5-bromooxazol-2-yl)nonan-3-one (**A6**) which was used without further purification. LCMS (ESI) calc'd for $C_{12}H_{19}BrN_2O_2$ $[M+H]^+$: 303.1, found: 303.0.

The following intermediate was prepared using similar procedures as described for intermediate **A6**

Intermediate ID	Structures	Observed $[M+H]^+$
A7		329.1

Example 7

Preparation of Intermediate **A8** (209)



Step 1: (R)-N-((S)-6-(2-ethyl-1,3-dioxolan-2-yl)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)hexyl)-2-methylpropane-2-sulfinamide

(A8_A): PdCl₂(DTBPF) (20 mg, 0.031 mmol) was added to a mixture of (R)-N-((S)-1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**A3_C**, 152 mg, 0.262 mmol), 7-methoxy-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (**C1**, 90 mg, 0.301 mmol) and K₃PO₄ (220 mg, 1.036 mmol) in co-solvents of THF (2 mL) and water (0.2 mL) and the mixture was stirred at 80°C for 3 h. The mixture was diluted with water (15 mL), extracted with DCM (3 x 10 mL). The combined organic fractions were washed with brine (saturated, 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with DCM / MeOH = 0~6% to give (R)-N-((S)-6-(2-ethyl-1,3-dioxolan-2-yl)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**A8_A**). LCMS (ESI) calc'd for C₃₅H₅₆N₄O₅SSi [M+H]⁺: 673.4, found: 673.4.

Step 2: (S)-9-amino-9-(5-(7-methoxy-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)nonan-3-one (**A8_B**): HCl (3 mL, 12.00 mmol) (MeOH solution) was added to (R)-N-((S)-6-(2-ethyl-1,3-dioxolan-2-yl)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**A8_A**, 146 mg, 0.217 mmol) and the mixture was stirred at 26°C for 30 mins. The solvent was evaporated under reduced pressure to give (S)-9-amino-9-(5-(7-methoxy-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)nonan-3-one (**A8_B**), which was used to the next step without further purification. LCMS (ESI) calc'd for C₂₉H₄₄N₄O₃Si [M+H]⁺: 525.3, found: 525.3.

Step 3: (S)-9-amino-9-(5-(7-methoxy-2-methylquinolin-6-yl)-1H-imidazol-2-yl)nonan-3-one (**A8**): TFA (2 mL, 26.0 mmol) was added to (S)-9-amino-9-(5-(7-methoxy-2-methylquinolin-6-

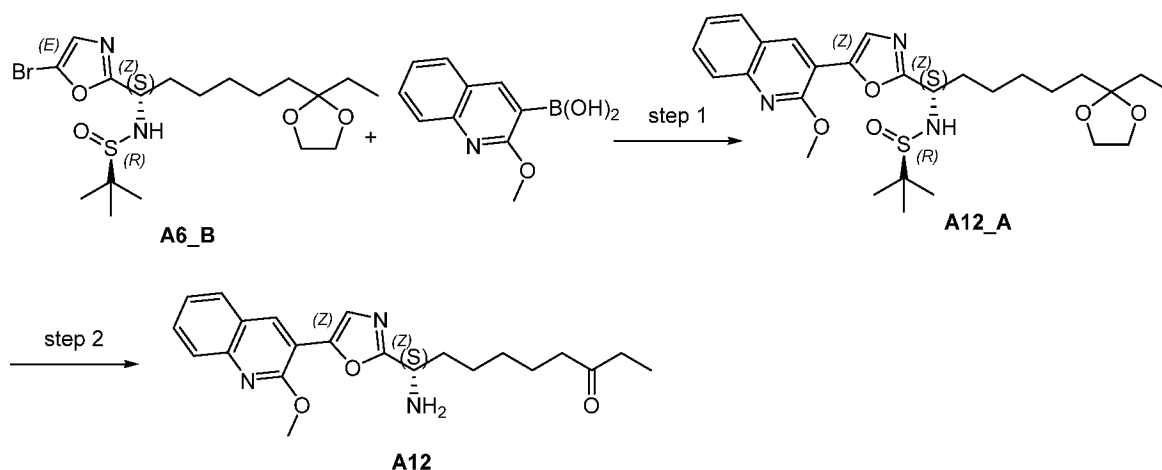
yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)nonan-3-one (**A8_B**, 152 mg, 0.290 mmol) and the mixture was stirred at 26°C for 3 h. The solvent was evaporated under reduced pressure and pH was adjusted to 7 with Et₃N (0.2 mL). The residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.05% NH₃·H₂O, to give
 5 (*S*)-9-amino-9-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)nonan-3-one (**A8**).
 LCMS (ESI) calc'd for C₂₃H₃₀N₄O₂ [M+H]⁺: 395.2, found: 395.2.

The following intermediates were prepared using similar procedures as described for intermediate **A8**

Intermediate ID	Structures	Observed [M+H] ⁺
A9		381.2
A10 (178)		365.2
A11		354.1

Example 8

Preparation of Intermediate **A12**

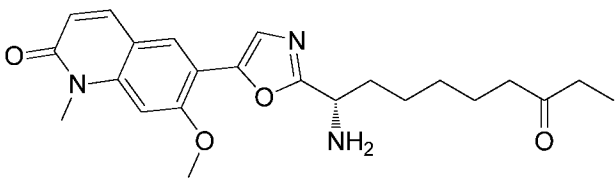
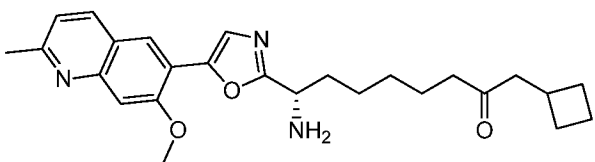


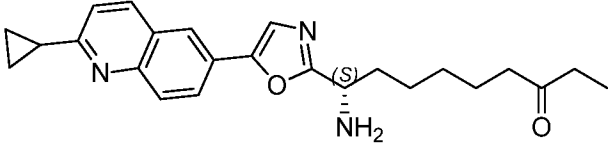
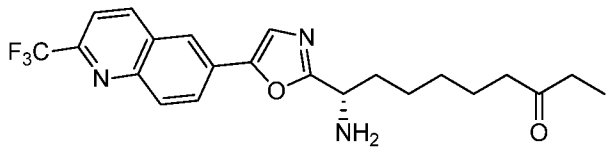
Step 1: Preparation of (R)-N-((S)-6-(2-ethyl-1,3-dioxolan-2-yl)-1-(5-(2-methoxyquinolin-3-yl)oxazol-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**A12_A**): PdCl₂(DTBPF) (0.144 g, 0.222

mmol) was added to a stirred mixture of K_2CO_3 (0.918 g, 6.65 mmol), (2-methoxyquinolin-3-yl)boronic acid (0.450 g, 2.215 mmol) and (*R*)-*N*-((*S*)-1-(5-bromooxazol-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**A6_B**, 1.0 g, 2.215 mmol) in THF (10 mL) and Water (1 mL) at room temperature and the mixture was heated with stirring at 80°C for 18 h under N_2 protection. The mixture was cooled to room temperature, water (10 mL) was added and the mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic fractions were washed with brine (saturated, 15 mL), dried (Na_2SO_4), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (ISCORF75; Sepa flash column), eluting with petroleum ether / EtOAc = 1/1~0/1 to give (*R*)-*N*-((*S*)-6-(2-ethyl-1,3-dioxolan-2-yl)-1-(5-(2-methoxyquinolin-3-yl)oxazol-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**A12_A**). LCMS (ESI) calc'd for $C_{28}H_{39}N_3O_5S$ $[M+H]^+$: 530.3, found: 530.3

Step 2: Preparation of (*S*)-9-amino-9-(5-(2-methoxyquinolin-3-yl)oxazol-2-yl)nonan-3-one (A12**):** HCl/MeOH (0.2 mL, 0.800 mmol) was added to a stirred mixture of (*R*)-*N*-((*S*)-6-(2-ethyl-1,3-dioxolan-2-yl)-1-(5-(2-methoxyquinolin-3-yl)oxazol-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**A12_A**, 247 mg, 0.466 mmol) in MeOH (2 mL) at room temperature and the mixture was stirred at room temperature for 30 min. The mixture was cooled to room temperature, aqueous $NaHCO_3$ (saturated, 5 mL) was added and the mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic fractions were washed with brine (saturated, 5 mL), dried (Na_2SO_4), filtered and concentrated to give (*S*)-9-amino-9-(5-(2-methoxyquinolin-3-yl)oxazol-2-yl)nonan-3-one (**A12**), which was used to next step without further purification. LCMS (ESI) calc'd for $C_{22}H_{27}N_3O_3$ $[M+H]^+$: 382.2, found: 382.2

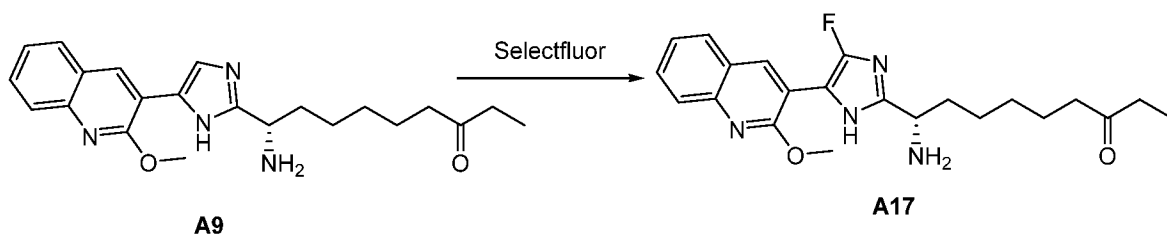
The following intermediates were prepared using similar procedures as described for intermediate **A12**

Intermediate ID	Structures	Observed $[M+H]^+$
A13 (224)		412.1
A14		436.3

A15		392.2
A16		420.2

Example 9

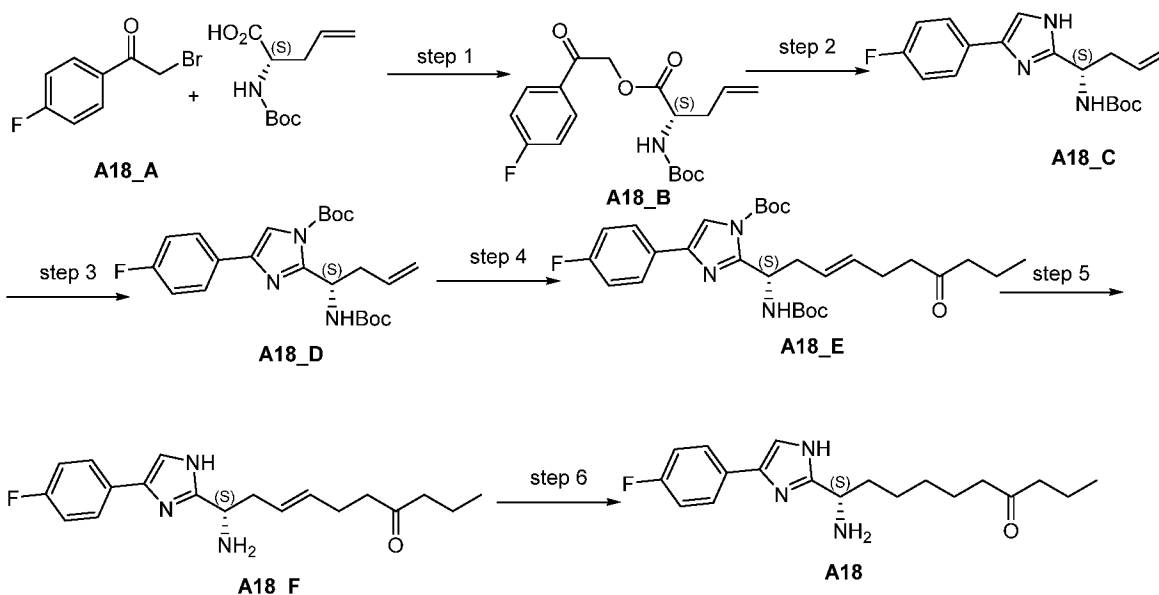
Preparation of Intermediate A17



To the solution of (S)-9-amino-9-(5-(2-methoxyquinolin-3-yl)-1H-imidazol-2-yl)nonan-3-one (**A9**, 0.5 g, 1.04 mmol) in 5.0 mL DMF and 0.5 mL H₂O, SelectFluor (0.55 g, 1.56 mmol) was added. The mixture was stirred at rt for 16 h. 10 mL water was added, the mixture was extracted with ethyl acetate. The organic phase was washed with brine and dried with anhydrous Na₂SO₄. After concentration it was purified by silica gel chromatography (10% MeOH in DCM) to give the title compound mixed with chloride. ¹H NMR (400 MHz, CDCl₃) δ 0.95 (t, *J* = 7.43 Hz, 3H), 1.16-1.39 (m, 5H), 1.40-1.54 (m, 2H), 1.78-1.91 (m, 1H), 1.91-2.01 (m, 1H), 2.22-2.38 (m, 4H), 4.05-4.24 (m, 3H), 4.36 (q, *J* = 7.30 Hz, 1H), 7.27-7.36 (m, 1H), 7.47-7.67 (m, 2H), 7.68-7.78 (m, 1H), 8.15-8.23 (m, 0.5H), 8.50-8.59 (m, 0.5H). LCMS (ESI) calc'd for C₃₅H₄₆FN₅O₅ [M+K]⁺: 437.2, found: 437.0.

Example 10

Preparation of Intermediate A18



Step 1: Preparation of (S)-2-(4-fluorophenyl)-2-oxoethyl 2-((tert-butoxycarbonyl) amino)pent-4-enoate (A18_B): To the solution of (S)-2-((tert-butoxycarbonyl)amino)pent-4-enoic acid (0.5 g, 2.32 mmol) in 5.0 mL DMF, 2-bromo-1-(4-fluorophenyl)ethanone (A18_A, 0.48 g, 2.21 mmol) was added. DIEA (0.57 g, 4.42 mmol) was then added dropwise. The mixture was stirred at rt for 1 h. 10 mL water was added and it was extracted with EtOAc three times. The combined organic phase was washed with brine and dried with anhydrous Na₂SO₄. It was concentrated to give the title compound (A18_B). ¹H NMR (400 MHz, CDCl₃) δ 1.44 (s, 9H), 2.68 (brs, 2H), 4.46-4.58 (m, 1H), 4.95-5.09 (m, 1H), 5.12-5.29 (m, 3H), 5.43-5.58 (m, 1H), 5.77-5.95 (m, 1H), 7.10-7.22 (m, 2H), 7.84-8.00 (m, 2H); LCMS (ESI) calc'd for C₁₈H₂₂FN₂O₅ [M+H]⁺: 352.1, found: 352.1

Step 2: Preparation of (S)-tert-butyl (1-(4-(4-fluorophenyl)-1H-imidazol-2-yl) but-3-en-1-yl)carbamate (A18_C): To the solution of (S)-2-(4-fluorophenyl)-2-oxoethyl 2-((tert-butoxycarbonyl)amino) pent-4-enoate (A18_B, 0.6 g, 1.7 mmol) in 15 mL toluene, NH₄OAc (1.3 g, 17.0 mmol) was added. The mixture was heated to 130°C (to make toluene flux) with stirring at 130°C for 16 h. The crude product, after evaporation, was purified by silica gel chromatography to give the target compound (A18_C). ¹H NMR (400 MHz, CDCl₃) δ 1.43 (s, 9H), 2.01-2.07 (m, 1H), 2.71-2.84 (m, 2H), 4.77 (d, J = 6.3 Hz, 1H), 5.05-5.20 (m, 2H), 5.53 (brs, 1H), 5.74-5.91 (m, 1H), 7.02 (s, 2H), 7.07-7.16 (m, 1H), 7.40-7.76 (m, 2H); LCMS (ESI) calc'd for C₁₈H₂₂FN₃O₂ [M+H]⁺: 332.2, found: 332.2

Step 3: Preparation of (S)-tert-butyl 2-(1-((tert-butoxycarbonyl)amino) but-3-en-1-yl)-4-(4-fluorophenyl)-1H-imidazole-1-carboxylate (A18_D): (S)-tert-butyl (1-(4-(4-fluorophenyl)-1H-imidazol-2-yl)but-3-en-1-yl)carbamate (A18_C, 0.5 g, 1.51 mmol) was dissolved in 8.0 mL

DCM, then the solution was cooled down to 0°C, then the solution of (Boc)₂O (0.35 mL, 1.51 mmol) in 2.0 DCM was dropwise added. Subsequently DMAP (20 mg, 0.16 mmol) was added. The mixture was stirred at 0°C for 1 h. 5 ml water was added, and it was extracted with EtOAc. The organic phase was washed with brine and dried with anhydrous Na₂SO₄. The crude product
5 obtained after concentration was purified by silica gel chromatography (10% EtOAc in petroleum ether) to give the target compound (**A18_D**). ¹H NMR (400 MHz, CDCl₃) δ 1.21 (s, 9H), 1.41 (s, 9H), 2.19-2.32 (m, 1H), 2.37-2.50 (m, 1H), 4.81 (s, 2H) 5.26-5.36 (m, 1H) 5.41-5.60 (m, 2H), 6.77-6.89 (m, 2H), 7.02 (s, 1H), 7.43-7.57 (m, 2H); LCMS (ESI) calc'd for C₂₃H₃₀FN₃O₄ [M+H]⁺: 432.1, found: 432.1

10 Step 4: Preparation of (S, E)-tert-butyl 2-(1-((tert-butoxycarbonyl)amino)-7-oxodec-3-en-1-yl)-4-(4-fluorophenyl)-1H-imidazole-1-carboxylate (**A18_E**): (S)-tert-butyl 2-(1-((tert-butoxycarbonyl)amino)but-3-en-1-yl)-4-(4-fluorophenyl)-1H-imidazole-1-carboxylate (**A18_D**, 300 mg, 0.7 mmol) and oct-7-en-4-one (175 mg, 1.39 mmol) were dissolved in 7 mL degassed toluene, then Zhan's catalyst (25.5 mg, 34.76 μmol) was added under N₂. The mixture was
15 stirred at 60°C for 16 h. The solvent was removed by evaporator and the crude product was purified by silica gel chromatography (5% EtOAc in petroleum ether) to afford a mixture of mono-Boc and di-Boc product (**A18_E**) which was used directly for the next step without further purification. LCMS (ESI) calc'd for C₂₉H₄₀FN₃O₅ [M+H]⁺: 530.3, found: 530.2

Step 5: Preparation of (S, E)-10-amino-10-(4-(4-fluorophenyl)-1H-imidazol-2-yl)dec-7-en-4-one (**A18_F**): (S, E)-tert-butyl 2-(1-((tert-butoxycarbonyl)amino)-7-oxodec-3-en-1-yl)-4-(4-fluorophenyl)-1H-imidazole-1-carboxylate and its de-Boc product (mixture, 150 mg) were
20 dissolved in 3.0 mL DCM, then 0.3 mL TFA was added dropwise. The mixture was stirred at 25°C for 5 h. Afterwards it was quenched with saturated NaHCO₃ at 0°C, and extracted with DCM three times. The combined organic phase was washed with brine and dried with
25 anhydrous Na₂SO₄. The solvent was removed by evaporator to give the crude product (**A18_F**). LCMS (ESI) calc'd for C₁₉H₂₄FN₃O [M+H]⁺: 330.2, found: 330.1

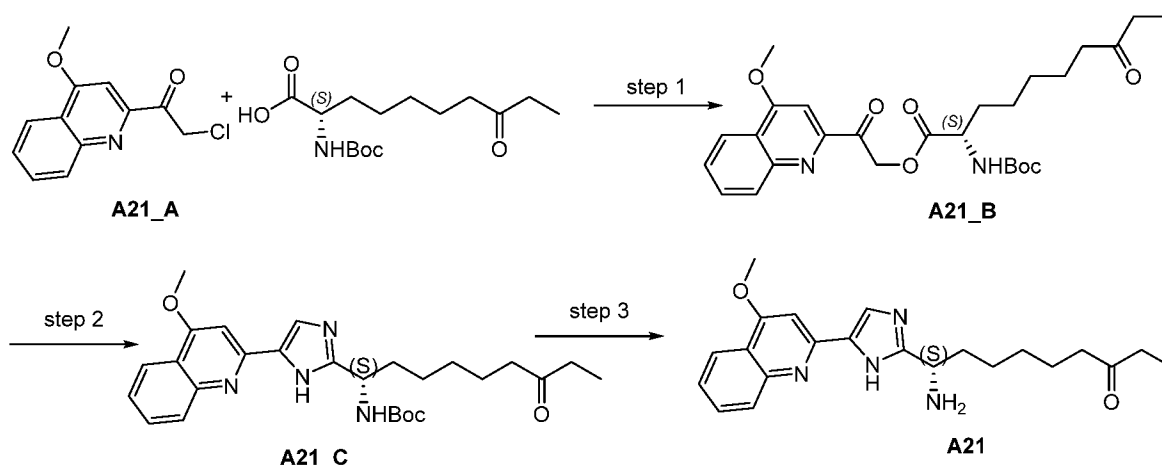
Step 6: Preparation of (S)-10-amino-10-(4-(4-fluorophenyl)-1H-imidazol-2-yl)decan-4-one (**A18**): The crude (S, E)-10-amino-10-(4-(4-fluorophenyl)-1H-imidazol-2-yl)dec-7-en-4-one (**A18_F**, 100 mg) was dissolved in 3.0 mL MeOH, then 10% Pd/C (10 mg) was added. The
30 mixture was stirred under H₂ at 25°C for 16 h. Afterwards it was filtered on diatomite and the filtrate was concentrated to give the target product (**A18**) which was directly used for the next step without further purification. LCMS (ESI) calc'd for C₁₉H₂₆FN₃O [M+H]⁺: 332.2, found: 332.2

The following intermediates were prepared using similar procedures as described for intermediate **A16**

Intermediate ID	Structures	Observed [M+H] ⁺
A19		372.2
A20		344.1
A30		409.2

Example 11

Preparation of Intermediate **A21**



Step 1: Preparation of (S)-2-(4-methoxyquinolin-2-yl)-2-oxoethyl 2-((tert-

butoxycarbonyl)amino)-8-oxodecanoate (**A21_B**): 2-chloro-1-(4-methoxyquinolin-2-

yl)ethanone (**A21_A**, 496 mg, 2.105 mmol) was added to a stirred mixture of (S)-2-((tert-

butoxycarbonyl)amino)-8-oxodecanoic acid (Synthesis, **2006**, 12, 2069-2073, 692 mg, 2.296

mmol) and DIPEA (1.2 mL, 6.87 mmol) in DMF (5 mL) at rt and the mixture was stirred at 60°C

for 3 h. The mixture was diluted with water (20 mL), extracted with ethyl acetate (3 x 20 mL).

The combined organic fractions were washed with water (3 x 8 mL) and brine (saturated, 10 mL),

dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by preparative TLC on silica gel, eluting with petroleum ether / EtOAc = 3: 1 to give (S)-2-(4-methoxyquinolin-2-yl)-2-oxoethyl 2-((tert-butoxycarbonyl)amino)-8-oxodecanoate (**A21_B**). LCMS (ESI) calc'd for C₂₇H₃₆N₂O₇ [M+H]⁺: 501.5, found: 501.3

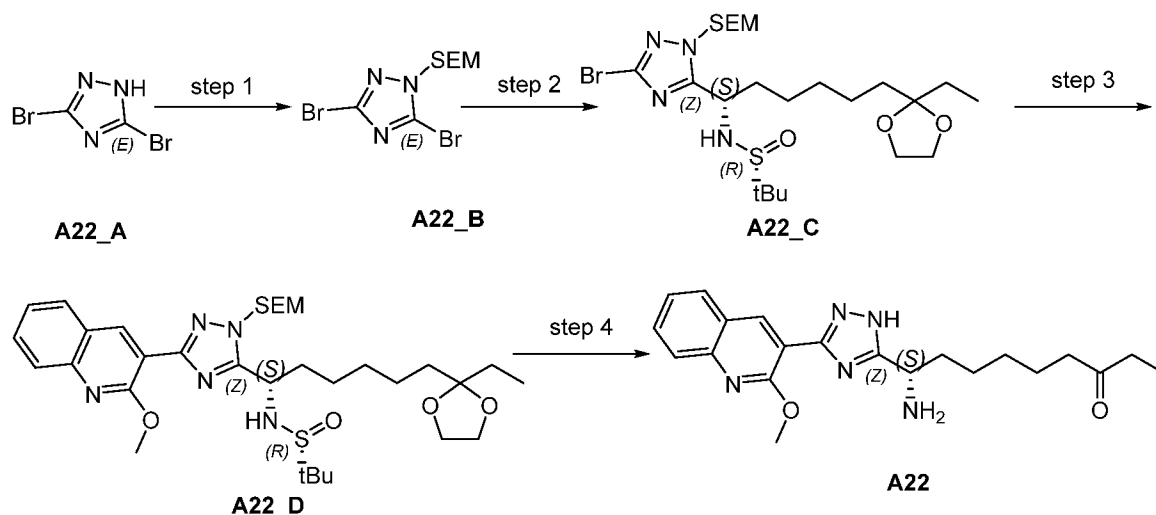
- 5 Step 2: Preparation of (S)-tert-butyl (1-(5-(4-methoxyquinolin-2-yl)-1H-imidazol-2-yl)-7-oxononyl)carbamate (**A21_C**): A mixture of (S)-2-(4-methoxyquinolin-2-yl)-2-oxoethyl 2-((tert-butoxycarbonyl)amino)-8-oxodecanoate (**A21_B**, 330 mg, 0.659 mmol) and ammonium acetate (780 mg, 10.12 mmol) in xylene (18 mL) was stirred at 140°C for 2 h. The mixture was concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel, eluting with
10 DCM / MeOH = 10: 1 to give (S)-tert-butyl (1-(5-(4-methoxyquinolin-2-yl)-1H-imidazol-2-yl)-7-oxononyl)carbamate (**A21_C**). LCMS (ESI) calc'd for C₂₇H₃₆N₄O₄ [M+H]⁺: 481.5, found: 481.3.

¹H NMR (400 MHz, CDCl₃) δ 8.07 (d, *J* = 8.22 Hz, 1H), 7.88 (brs, 1H), 7.55-7.64 (m, 1H), 7.37 (d, *J* = 7.43 Hz, 1H), 6.92 (d, *J* = 10.56 Hz, 1H), 5.05 (brs, 1H), 4.05 (brs, 2H), 2.28-2.39 (m,
15 3H), 1.75-1.91 (m, 2H), 1.53 (d, *J* = 8.61 Hz, 4H), 1.29-1.44 (m, 12H), 0.97 (t, *J* = 7.24 Hz, 2H).

- Step 3: Preparaton of (S)-9-amino-9-(5-(4-methoxyquinolin-2-yl)-1H-imidazol-2-yl)nonan-3-one (**A21**): TFA (0.5 ml, 6.49 mmol) was added to a mixture of (S)-tert-butyl (1-(5-(4-methoxyquinolin-2-yl)-1H-imidazol-2-yl)-7-oxononyl)carbamate (**A21_C**, 180 mg, 0.375 mmol) in DCM (5 ml) at rt and the mixture was stirred at rt for 3 h. The solvent was evaporated under
20 reduced pressure to give (S)-9-amino-9-(5-(4-methoxyquinolin-2-yl)-1H-imidazol-2-yl)nonan-3-one, TFA salt (**A21**) which was used to the next step without further purification. LCMS (ESI) calc'd for C₂₂H₂₈N₄O₂ [M+H]⁺: 381.4, found: 381.2

Example 12

Preparation of Intermediate **A22**



Step 1: Preparation of 3,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazole

(A22_B): NaH (1.058 g, 26.4 mmol) was added to a stirred mixture of 3,5-dibromo-1H-1,2,4-triazole (**A22_A**, 5.0 g, 22.04 mmol) in DMF (30.0 mL) at 0 - 5°C and the mixture was stirred at 0 - 5°C for 30 min. SEM-Cl (4.10 mL, 23.14 mmol) was added. The mixture was stirred at 0°C - rt for 12 h. The mixture was cooled to 0 - 5°C, aqueous NH₄Cl (saturated, 60 mL) was added and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic fractions were washed with water (3 x 50 mL), brine (saturated, 60 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 100 : 1 - 5 : 1 to give 3,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazole (**A22_B**). LCMS (ESI) calc'd for C₈H₁₅Br₂N₃OSi [M+H]⁺: 355.9, found: 357.9. ¹H NMR (400 MHz, CDCl₃) δ 5.46 (s, 2H), 3.62-3.74 (m, 2H), 0.88-1.00 (m, 2H), 0.01 (s, 9H).

Step 2: Preparation of (R)-N-((S)-1-(3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazol-5-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfonamide (A22_C):

*n*Butyllithium (1.1 mL, 2.75 mmol) was added to a stirred mixture of 3,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazole (**A22_B**, 900 mg, 2.52 mmol) in THF (10 mL) at -78°C and the mixture was stirred at -78°C for 1 h under N₂. Then (*R,E*)-*N*-(6-(2-ethyl-1,3-dioxolan-2-yl) hexylidene)-2-methylpropane-2-sulfonamide (**A1**, 700 mg, 2.307 mmol) in THF (1 mL) was added to the mixture and the mixture was stirred at -78°C for 2 h. The mixture was concentrated. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 100:1 - 2 : 1 to give (*R*)-*N*-((*S*)-1-(3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazol-5-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfonamide (**A22_C**), and (*R*)-*N*-((*R*)-1-(3-bromo-1-((2-

(trimethylsilyl)ethoxy)methyl)-1*H*-1,2,4-triazol-5-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide. LCMS (ESI) calc'd for C₂₃H₄₅BrN₄O₄SSi [M+H]⁺: 581.2, found: 583.1

Step 3: Preparation of (R)-N-((S)-6-(2-ethyl-1,3-dioxolan-2-yl)-1-(3-(2-methoxyquinolin-3-yl)-

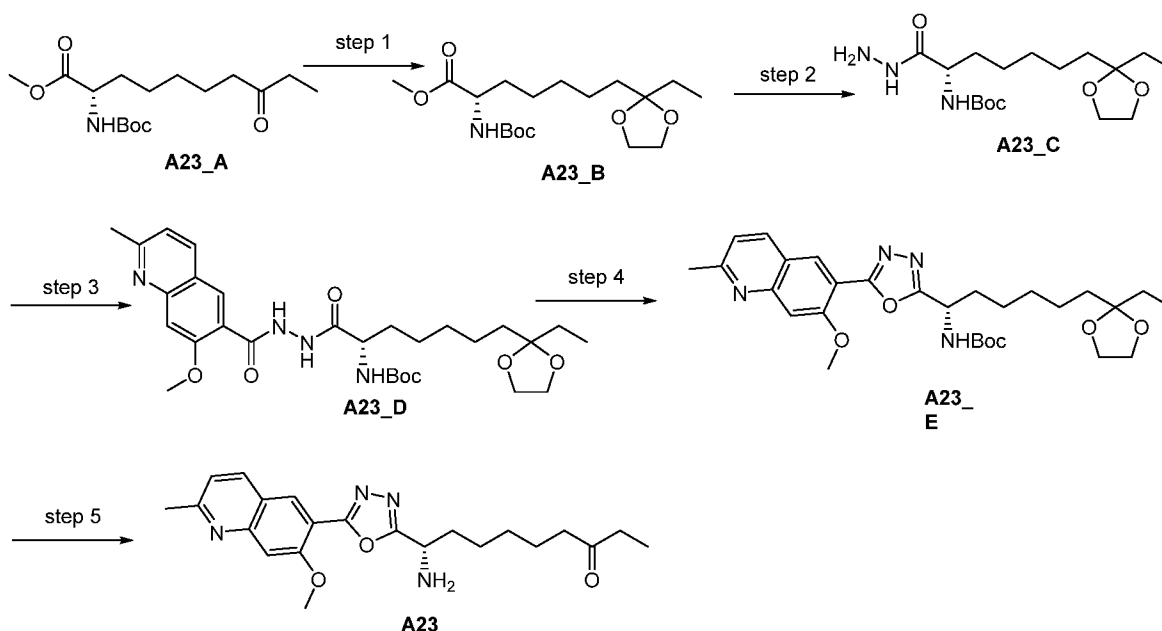
5 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-1,2,4-triazol-5-yl)hexyl)-2-methylpropane-2-sulfinamide (A22_D): PdCl₂(DTBPF) (16 mg, 0.025 mmol) was added to a stirred mixture of (2-methoxyquinolin-3-yl)boronic acid (100 mg, 0.493 mmol), (R)-N-((S)-1-(3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-1,2,4-triazol-5-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (A22_C, 300 mg, 0.516 mmol) and K₃PO₄ (314 mg, 1.478 mmol)
10 in THF (6.0 mL) and water (0.5 mL) at room temperature. The mixture was stirred at 65°C for 12 h under N₂. The mixture was concentrated, the residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 1:1 to give (R)-N-((S)-6-(2-ethyl-1,3-dioxolan-2-yl)-1-(3-(2-methoxyquinolin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-1,2,4-triazol-5-yl)hexyl)-2-methylpropane-2-sulfinamide (A22_D). LCMS (ESI) calc'd for
15 C₃₃H₅₃N₅O₅SSi [M+H]⁺: 660.4, found: 660.1

Step 4: Preparation of (S)-9-amino-9-(3-(2-methoxyquinolin-3-yl)-1*H*-1,2,4-triazol-5-yl)

nonan-3-one (A22): HCl/MeOH (4 M, 0.7 mL, 2.80 mmol) was added to a stirred mixture of (R)-N-((S)-6-(2-ethyl-1,3-dioxolan-2-yl)-1-(3-(2-methoxyquinolin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-1,2,4-triazol-5-yl)hexyl)-2-methylpropane-2-sulfinamide
20 (A22_D, 300 mg, 0.455 mmol) in MeOH (10.0 mL) at room temperature and the mixture was stirred at room temperature for 2 h. The mixture was stirred at room temperature for another 3 h. The mixture was quenched with aqueous NaHCO₃ (saturated, 20 mL) and the mixture was extracted with ethyl acetate (3x25 mL). The combined organic fractions were washed with brine (saturated, 25 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced
25 pressure to give crude (S)-9-amino-9-(3-(2-methoxyquinolin-3-yl)-1*H*-1,2,4-triazol-5-yl) nonan-3-one (A22) which was used to the next step without further purification. LCMS (ESI) calc'd for C₂₁H₂₇N₅O₂ [M+H]⁺: 382.2, found: 382.2

Example 13

Preparation of Intermediate A23



Step 1: Preparation of (S)-methyl 2-((tert-butoxycarbonyl)amino)-7-(2-ethyl-1,3-dioxolan-2-yl)heptanoate (A23_B): TsOH (0.055 g, 0.317 mmol) and ethane-1,2-diol (3.94 g, 63.4 mmol)

were added to a stirred mixture of (S)-methyl 2-((tert-butoxycarbonyl)amino)-8-oxodecanoate (A23_A, 2 g, 6.34 mmol) in toluene (50 mL) at room temperature and the mixture was heated with stirring at 130°C for 18 h. The mixture was cooled to room temperature, aqueous NaHCO₃ (saturated, 20 mL) was added, and the mixture was extracted with ethyl acetate (2x 20 mL). The combined organic fractions were washed with brine (saturated, 2x20 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 80:20 to give (S)-methyl 2-((tert-butoxycarbonyl)amino)-7-(2-ethyl-1,3-dioxolan-2-yl)heptanoate (A23-B). ¹H NMR (400 MHz, CDCl₃) δ 4.99 (d, *J* = 7.7 Hz, 1H), 4.29 (d, *J* = 5.1 Hz, 1H), 3.93 (s, 4H), 3.74 (s, 3H), 2.45-2.38 (m, 1H), 1.84-1.73 (m, 0.5H), 1.66-1.55 (m, 6H), 1.45 (s, 9H), 1.42-1.25 (m, 7H), 1.05 (t, *J* = 7.4 Hz, 0.5H), 0.90 (t, *J* = 7.5 Hz, 3H).

Step 2: Preparation of (S)-tert-butyl (7-(2-ethyl-1,3-dioxolan-2-yl)-1-hydrazinyl-1-oxoheptan-2-yl)carbamate (A23_C): Hydrazine (1.468 g, 38.9 mmol) was added to a stirred mixture of (S)-methyl 2-((tert-butoxycarbonyl)amino)-7-(2-ethyl-1,3-dioxolan-2-yl)heptanoate (A23_B, 1.4 g, 3.89 mmol) in MeOH (15 mL) at room temperature and the mixture was heated with stirring at 60°C overnight. The mixture was cooled to room temperature. Water (50 mL) was added and the mixture was extracted with ethyl acetate (2 x 50 mL). The combined organic fractions were washed with water (2 x 50 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting

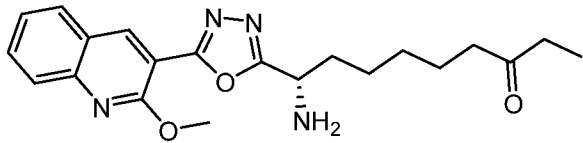
with DCM / MeOH = 40:1 to give (*S*)-tert-butyl (7-(2-ethyl-1,3-dioxolan-2-yl)-1-hydrazinyl-1-oxoheptan-2-yl)carbamate (**A23_C**). ¹H NMR (400 MHz, CDCl₃) δ 7.40 (brs, 1H), 5.29 (s, 1H), 4.80 (s, 1H), 3.92 (s, 4H), 1.80 (m, 1H), 1.55-1.63 (m, 5H), 1.43 (s, 9H), 1.32 (brs, 5H), 0.88 (t, *J* = 7.2 Hz, 3H).

- 5 Step 3: Preparation of (*S*)-tert-butyl (7-(2-ethyl-1,3-dioxolan-2-yl)-1-(2-(7-methoxy-2-methylquinoline-6-carbonyl)hydrazinyl)-1-oxoheptan-2-yl)carbamate (**A23_D**): HATU (473 mg, 1.243 mmol) and DIEA (0.434 ml, 2.486 mmol) were added to a stirred mixture of 7-methoxy-2-methylquinoline-6-carboxylic acid (180 mg, 0.829 mmol) in DMF (4 mL) at room temperature and the mixture was stirred at rt for 10 min. Then (*S*)-tert-butyl (7-(2-ethyl-1,3-dioxolan-2-yl)-1-hydrazinyl-1-oxoheptan-2-yl)carbamate (**A21_C**, 298 mg, 0.829 mmol) was added and the mixture was stirred at rt for 1 h. The mixture was added to water (20 mL) and was extracted with ethyl acetate (40 mL). The combined organic fractions were washed with brine (2 x 20 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 1:3 to give (*S*)-tert-butyl (7-(2-ethyl-1,3-dioxolan-2-yl)-1-(2-(7-methoxy-2-methylquinoline-6-carbonyl)hydrazinyl)-1-oxoheptan-2-yl)carbamate (**A23_D**). LCMS (ESI) calc'd for C₂₉H₄₂N₄O₇ [M+H]⁺: 559.3, found: 559.3
- 10
- 15

- Step 4: Preparation of (*S*)-tert-butyl (6-(2-ethyl-1,3-dioxolan-2-yl)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1,3,4-oxadiazol-2-yl)hexyl)carbamate (**A23_E**): Burgess reagent (308 mg, 1.289 mmol) was added to a stirred mixture of (*S*)-tert-butyl (7-(2-ethyl-1,3-dioxolan-2-yl)-1-(2-(7-methoxy-2-methylquinoline-6-carbonyl)hydrazinyl)-1-oxoheptan-2-yl)carbamate (**A23_D**, 360 mg, 0.644 mmol) in THF (5 mL). The mixture was heated at 50°C for 2 h, and the mixture was stirred overnight at room temperature. The mixture was filtered and the filter cake was washed with DCM (20 mL). The filtrate was concentrated to dryness. The residue was purified by silica gel column flash chromatography, eluting with DCM: EtOAc = 3:1 to give (*S*)-tert-butyl (6-(2-ethyl-1,3-dioxolan-2-yl)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1,3,4-oxadiazol-2-yl)hexyl)carbamate (**A23_E**). LCMS (ESI) calc'd for C₂₉H₄₀N₄O₆ [M+H]⁺: 541.3, found: 541.3
- 20
- 25

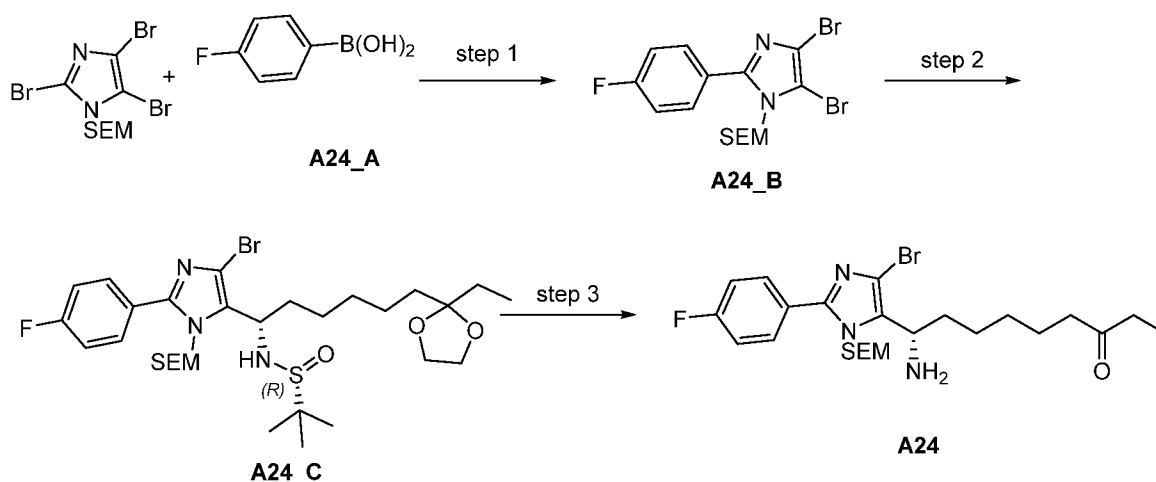
- Step 5: Preparation of (*S*)-9-amino-9-(5-(7-methoxy-2-methylquinolin-6-yl)-1,3,4-oxadiazol-2-yl)nonan-3-one (**A23**): HCl / MeOH (4 M, 0.139 mL, 0.555 mmol) was added to a stirred mixture of (*S*)-tert-butyl (6-(2-ethyl-1,3-dioxolan-2-yl)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1,3,4-oxadiazol-2-yl)hexyl)carbamate (**A23_E**, 50 mg, 0.092 mmol) in MeOH (1 mL) and the mixture was stirred at rt for 0.5 h. The solution was concentrated to give crude compound which was used to the next step without further purification. LCMS (ESI) calc'd for C₂₂H₂₈N₄O₃ [M+H]⁺: 397.2, found: 397.2
- 30

The following intermediate was prepared using similar procedures as described for intermediate **A23**.

Intermediate ID	Structures	Observed [M+H] ⁺
A29		383.3

Example 14

Preparation of Intermediate A24



Step 1: Preparation of 4,5-dibromo-2-(4-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (**A24_B**): Pd(PPh₃)₄ (0.133 g, 0.115 mmol) was added to a stirred mixture of potassium carbonate (0.635 g, 4.60 mmol), (4-fluorophenyl)boronic acid (0.354 g, 2.53 mmol), 2,4,5-tribromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (**A24_A**, 1.00 g, 2.299 mmol) in toluene (10 mL) and MeOH (2 mL) at room temperature and the mixture was stirred at 65°C for 24 h under N₂. The mixture was cooled to room temperature, water (50 mL) was added and the mixture was extracted with ethyl acetate (3x40 mL). The combined organic fractions were washed with brine (saturated, 3 x 20 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with pet.ether/ EtOAc = 1/0~10/1 to give 4,5-dibromo-2-(4-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (**A24_B**). ¹H NMR (400 MHz, CDCl₃) δ 7.81 (dd, *J* = 5.40, 8.49 Hz, 2H), 7.15 (t, *J* = 8.60 Hz, 2H), 5.28 (s, 2H), 3.70 (t, *J* = 8.16 Hz, 2H), 0.97 (t, *J* = 8.27 Hz, 2H), 0.02 (s, 9H).

Step 2: Preparation of (R)-N-((S)-1-(4-bromo-2-(4-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-((trimethylsilyl)ethoxy)methyl-1H-imidazole (**A24_C**):

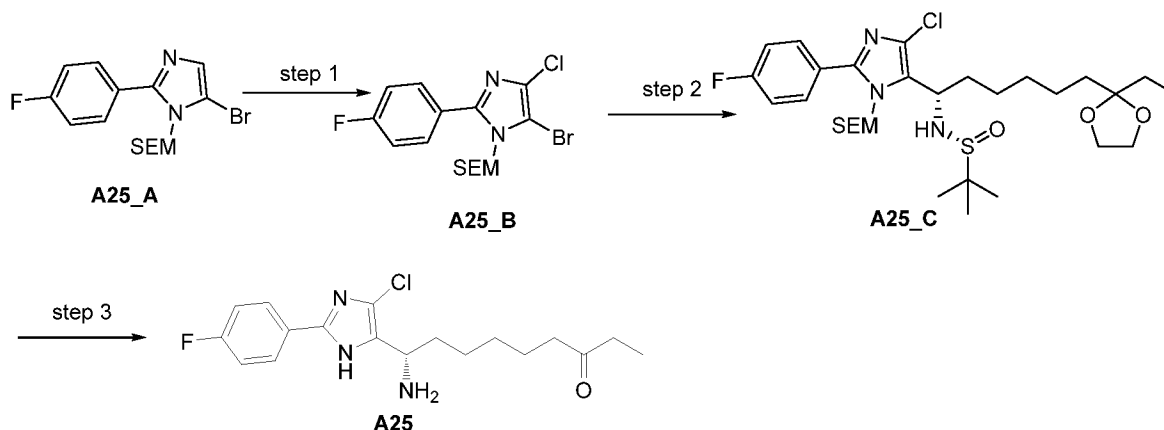
methylpropane-2-sulfinamide(A24_C): $\text{BF}_3 \cdot \text{OEt}_2$ (3.10 mL, 24.43 mmol) was added to a stirred mixture of 4,5-dibromo-2-(4-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole (A24_B, 10.0 g, 22.21 mmol) in THF (100 mL) at -78°C and *n*butyllithium (11.55 mL, 28.9 mmol) was added to the mixture slowly under N_2 . The mixture was stirred at -78°C for 1 h.

Then (*R,E*)-*N*-(6-(2-ethyl-1,3-dioxolan-2-yl)hexylidene)-2-methyl propane-2- sulfinamide (A1, 7.41 g, 24.43 mmol) in THF(10 mL) was added to the mixture slowly and the mixture was stirred at -78°C for 2 h. Aqueous NH_4Cl (saturated, 50 mL) and water (50 mL) was added and the mixture was extracted with ethyl acetate (3x75 mL). The combined organic fractions were washed with brine (saturated, 50 mL), dried (Na_2SO_4), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (ISCORF75; Sepa flash column), eluting with petroleum ether / EtOAc = 10/1~3/1 to give and (*R*)-*N*-((*S*)-1-(4-bromo-2-(4-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (7.0 g, crude). The crude product was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile /water, to give (*R*)-*N*-((*S*)-1-(4-bromo- 2-(4-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (A24_C). LCMS (ESI) calc'd for $\text{C}_{30}\text{H}_{49}\text{BrFN}_3\text{O}_4\text{SSi}$ $[\text{M}+\text{H}]^+$: 674.2, found: 676.3

Step 3: Preparation of (*S*)-9-amino-9-(4-bromo-2-(4-fluorophenyl)-1- ((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)nonan-3-one (A24): HCl / MeOH (0.608 mL,

7.41 mmol) was added to a stirred mixture of (*R*)-*N*-((*S*)-1-(4-bromo-2-(4-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (A24_C, 5.0 g, 7.41 mmol) in MeOH (50 mL) at 30°C and the mixture was stirred at 30°C for 10 min. Aqueous NaHCO_3 (saturated, 10 mL) was added and the mixture was extracted with DCM (3 x50 mL). The combined organic fractions were washed with brine (50 mL), dried (Na_2SO_4), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (ISCORF75; Sepa flash column), eluting with petroleum ether / EtOAc =3/1~1/1 to give (*S*)-9-amino-9-(4- bromo-2-(4-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)nonan-3-one (A24). LCMS (ESI) calc'd for $\text{C}_{24}\text{H}_{37}\text{BrFN}_3\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$: 526.3, found: 528.3. ^1H NMR (400 MHz, CDCl_3) δ 7.62-7.67 (m, 2H), 7.11-7.17 (m, 2H), 5.14-5.50 (m, 2H), 4.09-4.19 (m, 1H), 3.42-3.48 (m, 2H), 2.36-2.44 (m, 4H), 1.80-2.03 (m, 2H), 1.55-1.60 (m, 2H), 1.23-1.38 (m, 5H), 1.01-1.06 (m, 3H), 0.87-0.92 (m, 2H), -0.02-0.00 (m, 9H).

Example 15

Preparation of Intermediate **A25**

Step 1: Preparation of 5-bromo-4-chloro-2-(4-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)

5 methyl)-1H-imidazole (**A25_B**): NCS (281 mg, 2.101 mmol) was added to a stirred mixture of 5-bromo-2-(4-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (**A25_A**, 600 mg, 1.616 mmol) in THF (15 mL) at rt and the resulting mixture was stirred at rt for 4 h. The solvent was evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (ISCORF75; Sepa flash column), eluting with petroleum ether / EtOAc = 0~10% to give the title compound (**A25_B**). LCMS (ESI) calc'd for $C_{15}H_{19}BrClFN_2OSi$ $[M+H]^+$: 405.0, found: 407.0

Step 2: Preparation of (R)-N-((S)-1-(4-chloro-2-(4-fluorophenyl)-1-((2-(trimethylsilyl)

ethoxy)methyl)-1H-imidazol-5-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-

sulfonamide (**A25_C**): *n*-BuLi (0.71 mL, 1.775 mmol) was added dropwise to a stirred mixture

15 of 5-bromo-4-chloro-2-(4-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (**A25_B**, 550 mg, 1.355 mmol) in THF (10 mL) at -78°C under N_2 . The mixture was stirred at -

78°C for 1 h. Then a solution of (*R,E*)-*N*-(6-(2-ethyl-1,3-dioxolan-2-yl)hexylidene)-2-

methylpropane-2-sulfinamide (**A1**, 452 mg, 1.491 mmol) in THF (5 mL) was added slowly and

the mixture was stirred at -78°C for 2 h. Aqueous NH_4Cl (saturated, 20 mL) was added and the

20 mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic fractions were

washed with brine (saturated, 30 mL), dried (Na_2SO_4), filtered and the solvent was evaporated

under reduced pressure. The residue was purified by silica gel flash chromatography

(ISCORF75; Sepa flash column), eluting with petroleum ether / EtOAc = 10/1~1/1 to give the

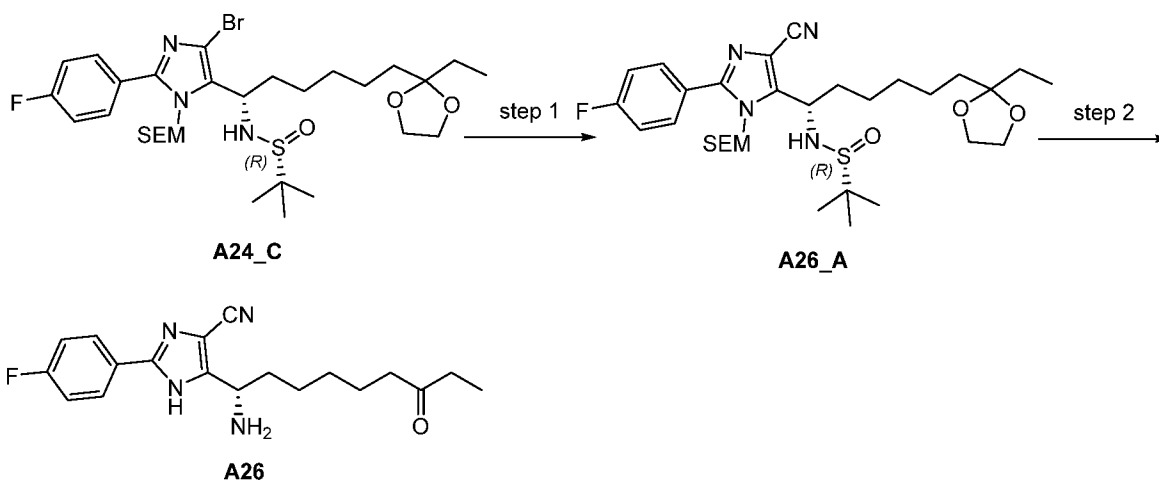
title compound (**A25_C**). LCMS (ESI) calc'd for $C_{30}H_{49}ClFN_3O_4SSi$ $[M+H]^+$: 630.3, found:

25 630.3.

Step 3: Preparation of (S)-9-amino-9-(4-chloro-2-(4-fluorophenyl)-1H-imidazol-5-yl)nonan-3-one hydrochloride (A25): The mixture of (R)-N-((S)-1-(4-chloro-2-(4-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (A25_C, 350 mg, 0.555 mmol) and HCl/MeOH (10 mL, 40.0 mmol) was stirred at rt for 4 h. The mixture was concentrated under reduced pressure to give HCl salt of the title compound (A25) which was used to the next step without further purification. LCMS (ESI) calc'd for C₁₈H₂₃ClFN₃O [M+H]⁺: 352.2, found: 352.1

Example 16

Preparation of Intermediate A26



Step 1: Preparation of (R)-N-((S)-1-(4-cyano-2-(4-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (A26_A): Brettphos (16 mg, 0.030 mmol) was added to a stirred mixture of potassium ferrocyanide trihydrate (69 mg, 0.163 mmol), allylpalladium chloride dimer (5 mg, 0.014 mmol), (R)-N-((S)-1-(4-bromo-2-(4-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (A24_C, 200 mg, 0.296 mmol) in DMA (2 mL) and water (1 mL), the mixture was stirred at 100°C for 18 h under N₂. The mixture was cooled to room temperature, water (5 mL) was added and the mixture was extracted with DCM (3 x 5 mL). The combined organic fractions were washed with brine (saturated, 5 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (ISCORF75; Sepa flash column), eluting with petroleum ether / EtOAc = 1/2 to give (R)-N-((S)-1-(4-cyano-2-(4-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (A26_A). LCMS (ESI) calc'd for C₃₁H₄₉FN₄O₄SSi [M+H]⁺: 621.3, found: 621.3. ¹H NMR (400 MHz,

CDCl₃) δ 7.66 (dd, *J* = 5.28, 8.41 Hz, 2H), 7.19 (t, *J* = 8.61 Hz, 2H), 5.11-5.38 (m, 2H), 4.62 (d, *J* = 3.13 Hz, 1H), 3.92 (s, 4H), 3.72 (d, *J* = 2.74 Hz, 1H), 3.49 (t, *J* = 8.41 Hz, 2H), 2.16 (d, *J* = 6.65 Hz, 1H), 2.04 (brs, 1H), 1.36 (brs, 6H), 1.19-1.28 (m, 10H), 0.85-1.00 (m, 5H), 0.00 (s, 9H).

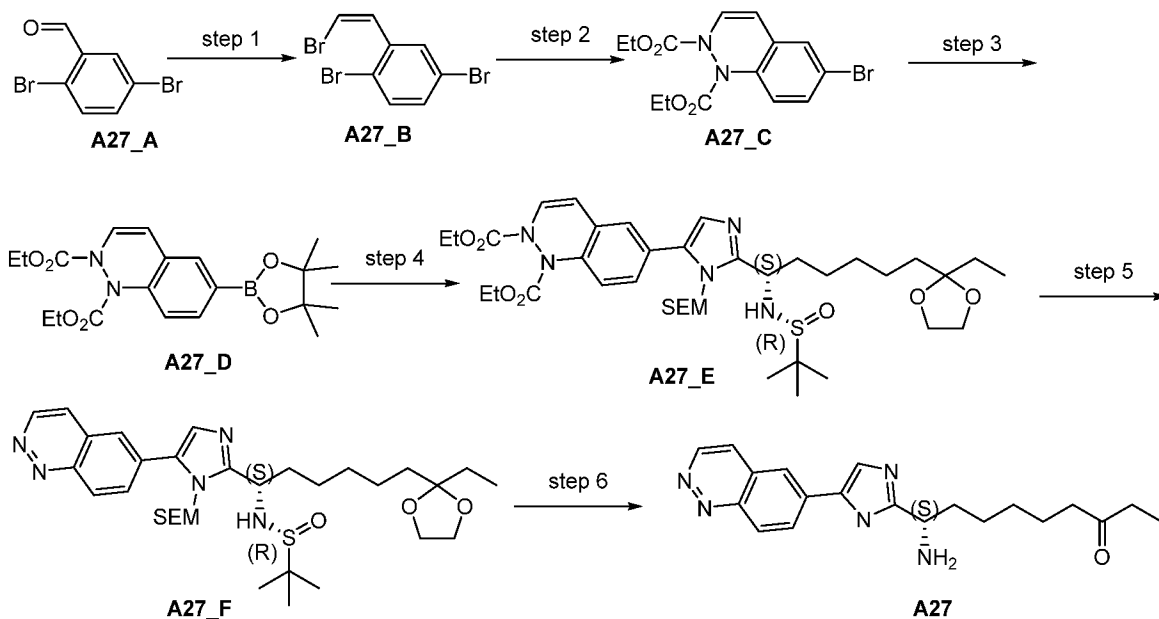
Step 2: Preparation of (S)-5-(1-amino-7-oxononyl)-2-(4-fluorophenyl)-1-((2-

- 5 (trimethylsilyl)ethoxy)methyl)-1*H*-imidazole-4-carbonitrile (A26): Hydrogen chloride in MeOH (0.05 mL, 0.200 mmol) was added to a stirred mixture of (R)-*N*-((S)-1-(4-cyano-2-(4-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfonamide (A26_A, 132 mg, 0.213 mmol) in MeOH (1 mL) at room temperature and the mixture was stirred at 30°C for 3 h. The reaction mixture was concentrated and another batch of hydrogen chloride / MeOH (0.05 mL, 0.200 mmol) was added, and the mixture was stirred at 30°C for 3 h. The reaction mixture was concentrated to give crude (S)-5-(1-amino-7-oxononyl)-2-(4-fluorophenyl)-1*H*-imidazole-4-carbonitrile which was used to next step without further purification. LCMS (ESI) calc'd for C₁₉H₂₃FN₄O [M+H]⁺: 343.2, found: 343.2

15

Example 17

Preparation of Intermediate A27



Step 1: (Z)-1,4-dibromo-2-(2-bromovinyl)benzene (A27_B): *t*-BuOK (0.510 g, 4.55 mmol) was added to a solution of (bromomethyl)triphenylphosphonium bromide (1.983 g, 4.55 mmol) in THF (30 mL) at -78°C. The mixture was stirred for 1 h. Then 2,5-dibromobenzaldehyde (A27_A, 1 g, 3.79 mmol) was added at -78°C and the reaction was stirred at rt for another 12 h. Aqueous NH₄Cl (saturated, 10 mL) was added and the mixture was extracted with ethyl acetate (20 x 3

mL). The combined organic fractions were washed with brine (saturated, 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, eluent of 0% EtOAc/Petro. Ether gradient @ 40 mL/min) to give (Z)-1,4-dibromo-2-(2-bromovinyl)benzene (**A27_B**). ¹H NMR (400 MHz, CDCl₃) δ 7.90 (d, *J* = 1.8 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 1H), 7.34 - 7.28 (m, 1H), 7.12 (s, 1H), 6.64 (d, *J* = 8.2 Hz, 1H).

Step 2: diethyl 6-bromocinnoline-1,2-dicarboxylate (**A27_C**): Diethyl hydrazine-1,2-dicarboxylate (0.517 g, 2.93 mmol) was added to a stirred mixture of copper(I) iodide (0.028 g, 0.147 mmol), K₂CO₃ (0.507 g, 3.67 mmol), *N1,N2*-dimethylethane-1,2-diamine (0.026 g, 0.293 mmol) and (Z)-1,4-dibromo-2-(2-bromovinyl)benzene (**A27_B**, 0.5 g, 1.467 mmol) in dioxane (5 mL) and water (1 mL), the mixture was degassed and backfilled with N₂ three times. The mixture was heated to 90°C for 10 h. The mixture was cooled and filtered, the filter cake was washed with ethyl acetate (50 mL). The filtrate was concentrated to dryness. The crude product was purified by silica gel column flash chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, eluent of 0~20% EtOAc/Petro. Ether gradient @ 40 mL/min) to give diethyl 6-bromocinnoline-1,2-dicarboxylate (**A27_C**). LCMS (ESI) calc'd for C₁₄H₁₅BrN₂O₄ [M+H]⁺: 355.0, 357.0, found: 354.9, 356.9

Step 3: diethyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cinnoline-1,2-dicarboxylate (**A27_D**): Diethyl 6-bromocinnoline-1,2-dicarboxylate (**A27_C**, 150 mg, 0.422 mmol) was added to a stirred mixture of Pd(DPPF)Cl₂ (30.9 mg, 0.042 mmol), potassium acetate (104 mg, 1.056 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (139 mg, 0.549 mmol) in dioxane (5 mL) and water (1 mL), the mixture was degassed and backfilled with N₂ three times. The mixture was heated to 90°C for 10 h. The mixture was cooled and filtered, the filter cake was washed with ethyl acetate (50 mL). The filtrate was concentrated to dryness. The crude product was purified by silica gel column flash chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, eluent of 0~50% EtOAc/Petro. Ether gradient @ 40 mL/min) to give diethyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cinnoline-1,2-dicarboxylate (**A27_D**). LCMS (ESI) calc'd for C₂₀H₂₇BN₂O₆ [M+H]⁺: 403.2, found: 403.2. ¹H NMR (400 MHz, CDCl₃) δ 7.74-7.66 (m, 1H), 7.59-7.52 (m, 1H), 7.47-7.37 (m, 1H), 7.29-7.20 (m, 1H), 6.22-6.01 (m, 1H), 4.39-4.06 (m, 4H), 1.32 (s, 12H), 1.26-1.21 (m, 9H).

Step 4: diethyl 6-(2-((*S*)-1-((*R*)-1,1-dimethylethylsulfonamido)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)cinnoline-1,2-dicarboxylate (**A27_E**): A mixture of diethyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cinnoline-1,2-dicarboxylate (**A27_D**, 130 mg, 0.323 mmol), (*R*)-*N*-((*S*)-1-(5-bromo-1-((2-

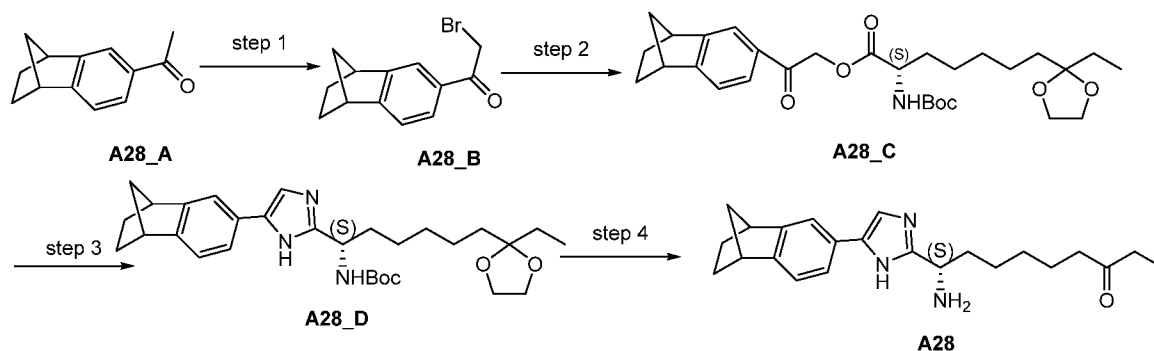
(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**A3_C**, 225 mg, 0.388 mmol), K₃PO₄ (206 mg, 0.970 mmol) and Pd(DTBPF)Cl₂ (21 mg, 0.032 mmol) in THF (10 mL) and water (1 mL) was degassed and backfilled with N₂ (three times). The mixture was heated to 80°C for 12 h. The mixture was concentrated to dryness. The crude product was purified by silica gel column flash chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, eluent of 0~100% EtOAc/Petro. Ether gradient @ 40 mL/min) to give diethyl 6-(2-((*S*)-1-((*R*)-1,1-dimethylethylsulfinamido)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)cinnoline-1,2-dicarboxylate (**A27_E**). LCMS (ESI) calc'd for C₃₈H₆₁N₅O₈SSi [M+H]⁺: 776.4, found: 776.3.

Step 5: (*R*)-*N*-((*S*)-1-(5-(cinnolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**A27_F**): A open mixture of diethyl 6-(2-((*S*)-1-((*R*)-1,1-dimethylethylsulfinamido)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)cinnoline-1,2-dicarboxylate (**A27_E**, 120 mg, 0.155 mmol), NaOH (0.2 mL, 1.000 mmol) in EtOH (2 mL) was heated at 70°C for 12 h. After cooling to rt, the mixture was cooled, diluted with DCM (20 mL), washed with water (10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure to give (*R*)-*N*-((*S*)-1-(5-(cinnolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**A27_F**) which used directly in next step. LCMS (ESI) calc'd for C₃₂H₅₁N₅O₄SSi [M+H]⁺: 630.3, found: 630.3.

Step 6: (*S*)-9-amino-9-(5-(cinnolin-6-yl)-1*H*-imidazol-2-yl)nonan-3-one (**A27**): TFA (2 mL, 26.0 mmol) was added to a stirred mixture of (*R*)-*N*-((*S*)-1-(5-(cinnolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**A27_F**, 100 mg, 0.159 mmol) in DCM (2 mL) at rt and the mixture was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure to give (*S*)-9-amino-9-(5-(cinnolin-6-yl)-1*H*-imidazol-2-yl)nonan-3-one (**A27**) which was used directly in next step. LCMS (ESI) calc'd for C₂₀H₂₅N₅O [M+H]⁺: 352.2, found: 352.1.

Example 18

Preparation of Intermediate **A28**



Step 1: Preparation of 2-bromo-1-((1*S*,4*R*)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)ethanone (A28_B): The mixture of 1-((1*S*,4*R*)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)ethanone (prepared according to Journal of Medicinal Chemistry, 1984, 27, 1516-1531)

5 (A28_A, 420 mg, 2.255 mmol) and phenyltrimethylammonium tribromide (1.30 g, 3.46 mmol) in THF (15 mL) was stirred at rt for 2 h under nitrogen atmosphere. The mixture was diluted with EtOAc (20 mL), washed with brine (2 x 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure to give the title compound (A28_B) which was used to the next step without further purification.

10 **Step 2: Preparation of (2*S*)-2-oxo-2-(1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)ethyl 2-((tert-butoxycarbonyl)amino)-7-(2-ethyl-1,3-dioxolan-2-yl)heptanoate (A28_C):** The mixture of 2-bromo-1-((1*S*,4*R*)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)ethanone (A28_B, 600 mg, 2.263 mmol), (2*S*)-2-((tert-butoxycarbonyl)amino)-7-(2-ethyl-1,3-dioxolan-2-yl)heptanoic acid (782 mg, 2.263 mmol) and DIPEA (1.2 mL, 6.87 mmol) in THF (10 mL) was stirred at rt for 16

15 h under nitrogen atmosphere. The mixture was concentrated to dryness and the residue was purified by silica gel column flash chromatography, eluting with EtOAc in petroleum ether = 0~35% to give the title compound (A28_C). LCMS (ESI) calc'd for C₃₀H₄₃NO₇ [M+H]⁺: 530.3, found: 552.1 (M+23).

Step 3: Preparation of tert-butyl ((*S*)-6-(2-ethyl-1,3-dioxolan-2-yl)-1-(5-((1*R*,4*S*)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)-1*H*-imidazol-2-yl)hexyl)carbamate (A28_D): The mixture of (2*S*)-2-oxo-2-(1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)ethyl 2-((tert-butoxycarbonyl)amino)-7-(2-ethyl-1,3-dioxolan-2-yl)heptanoate (A28_C, 760 mg, 1.435 mmol) and ammonium acetate (1.10 g, 14.27 mmol) in xylene (15 mL) was stirred at 120°C for 4 h

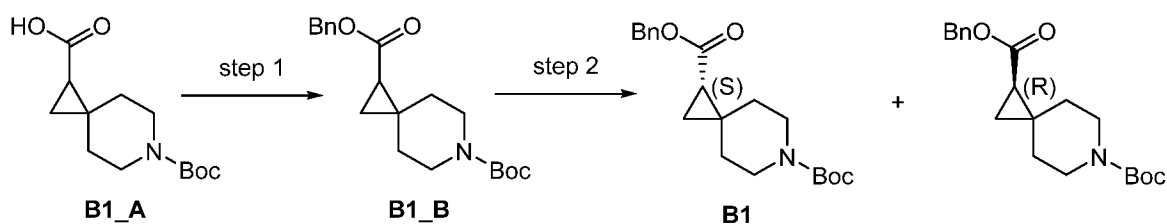
20 under nitrogen atmosphere. The mixture was concentrated to remove xylene and the residue was triturated with EtOAc (30 mL), washed with brine (2 x 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with EtOAc in petroleum ether = 0~35% to give the mixture of tert-butyl ((*S*)-6-(2-ethyl-1,3-dioxolan-2-yl)-1-(5-((1*R*,4*S*)-1,2,3,4-tetrahydro-1,4-

methanonaphthalen-6-yl)-1*H*-imidazol-2-yl)hexyl)carbamate (**73D**) and tert-butyl ((*S*)-7-oxo-1-(5-((1*R*,4*S*)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)-1*H*-imidazol-2-yl)nonyl)carbamate. LCMS (ESI) calc'd for C₃₀H₄₃N₃O₄ [M+H]⁺: 509.3, found: 510.2. LCMS (ESI) calc'd for C₂₈H₃₉N₃O₃ [M+H]⁺: 465.3, found: 466.2.

- 5 Step 4: Preparation of (*S*)-9-amino-9-(5-((1*R*,4*S*)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)-1*H*-imidazol-2-yl)nonan-3-one hydrochloride (**A28**): The mixture of tert-butyl ((*S*)-7-oxo-1-(5-((1*R*,4*S*)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)-1*H*-imidazol-2-yl)nonyl)carbamate (**A28_D**) and tert-butyl ((*S*)-6-(2-ethyl-1,3-dioxolan-2-yl)-1-(5-((1*R*,4*S*)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)-1*H*-imidazol-2-yl)hexyl)carbamate (400 mg mixture) in HCl (5 mL, 4 M)/EtOAc (10 mL) was stirred at rt for 4 h. The mixture was concentrated *in vacuo* to give the title compound (**A28**) which was used to the next step without further purification. LCMS (ESI) calc'd for C₂₃H₃₁N₃O [M+H]⁺: 366.2, found: 366.1.

Example 19

Preparation of Intermediate **B1**



Step 1: 1-benzyl 6-tert-butyl 6-azaspiro[2.5]octane-1,6-dicarboxylate (**B1_A**): Two reactions were carried out in parallel.

- DBU (235 g, 1.55 mol, 233 mL) was added in one portion to a solution of 6-(tert-butoxycarbonyl)-6-azaspiro[2.5]octane-1-carboxylic acid (**B1_A**, 330 g, 1.29 mol) in CH₃CN (3.3 L) at 20°C. Benzyl bromide (242 g, 1.42 mol, 168 mL) was added to the suspension in one portion at 20°C. The suspension was stirred at 20°C for 4 h. The two reactions were combined and concentrated. Ethyl acetate (5.5 L) was added to dissolve the residual, and precipitate appeared. The precipitate was filtered and then washed with ethyl acetate (300 mL * 3). The organic phase was washed with citric acid (10% w/w, 3 L * 2), sat. NaHCO₃ aqueous (3 L * 2), water (2 L) and brine (2 L) in sequence. The organic phase was dried over Na₂SO₄. It was filtered and the filtrate was concentrated to give the crude product.

- The crude product was dissolved with petroleum ether (7 L) and it was put in a dry ice-acetone bath for 12 h. A solid appeared; the solution was removed and the solid was grinded with petroleum ether (600 mL) for 1 hour. The suspension was filtered, and the filter cake was washed with petroleum ether (30 mL * 2).

The mother solutions were concentrated *in vacuo* to yield 1-benzyl 6-tert-butyl 6-azaspiro[2.5]octane-1,6-dicarboxylate (**B1_B**). ¹H NMR (400 MHz, CDCl₃) δ 7.41-7.31 (m, 5H), 5.19-5.07 (m, 2H), 3.55-3.36 (m, 3H), 3.28-3.17 (m, 1H), 1.77-1.61 (m, 3H), 1.49-1.37 (m, 1H), 1.21 (t, *J* = 4.9 Hz, 1H), 0.96 (dd, *J* = 4.5, 7.6 Hz, 1H).

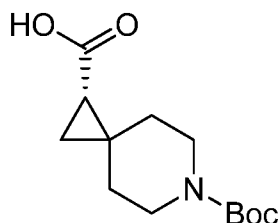
- 5 Step 2: (S)-1-benzyl 6-tert-butyl 6-azaspiro[2.5]octane-1,6-dicarboxylate (**B1**): Racemic 1-benzyl 6-tert-butyl 6-azaspiro[2.5]octane-1,6-dicarboxylate (**B1_B**) was resolved on a ChiralPak AD column (300x50 mm) under supercritical fluid chromatography (SFC) conditions on a Thar 200 preparative SFC instrument. The racemate was dissolved isopropanol/DCM. The separation was accomplished using 20% MeOH/CO₂, flow rate 200 mL/min, 100 bar, 38 °C. The 2nd peak
10 is the *S* one.

Alternatively, the resolution could also be achieved using a mobile phase of 20% 1:1 heptane: ethanol/CO₂ on ChiralPak AY column (300x50 mm) with a flow rate of 200 mL/min. In that case the sample was prepared by dissolving in MeCN/ethanol. After separation, the fractions were dried off via rotary evaporator at bath temperature 40°C.

- 15 ¹H NMR-P1 (400 MHz, CDCl₃) δ 7.42-7.29 (m, 5H), 5.19-5.06 (m, 2H), 3.55-3.35 (m, 3H), 3.26-3.16 (m, 1H), 1.75-1.59 (m, 3H), 1.53-1.33 (m, 11H), 1.21 (t, *J* = 4.9 Hz, 1H), 0.96 (dd, *J* = 4.6, 7.7 Hz, 1H).
¹H NMR-P2 (400 MHz, CDCl₃) δ 7.43-7.29 (m, 5H), 5.18-5.07 (m, 2H), 3.54-3.36 (m, 3H), 3.26-3.16 (m, 1H), 1.73-1.60 (m, 3H), 1.53-1.34 (m, 11H), 1.21 (t, *J* = 5.1 Hz, 1H), 0.96 (dd, *J* =
20 4.4, 7.9 Hz, 1H).

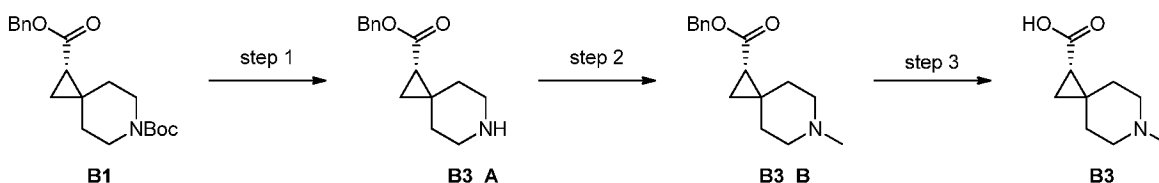
Example 20

Preparation of Intermediate **B2**



B2

- A mixture of (S)-1-benzyl 6-tert-butyl 6-azaspiro[2.5]octane-1,6-dicarboxylate (**B1**, 5 g, 14.47 mmol), 10% Pd/C (0.154 g, 1.447 mmol) in MeOH (30 mL) was hydrogenated under H₂
25 (20 psi) at room temperature for 18 h. The mixture was filtered and the filter cake was washed with MeOH (30x3 mL). The filtrate was concentrated to dryness to give (S)-6-(tert-butoxycarbonyl)-6-azaspiro[2.5]octane-1-carboxylic acid (**B2**) which was used without further purification. LCMS (ESI) calc'd for C₁₃H₂₁NO₄ [M+H]⁺: 256.2, found: 200.1 (M-55).

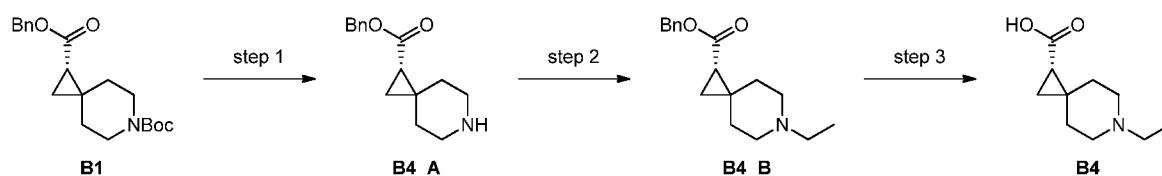
Example 21**Preparation of Intermediate B3**

Step 1: (S)-benzyl 6-azaspiro[2.5]octane-1-carboxylate (B3_A): TFA (15 mL, 202 mmol) was added to a stirred mixture of (S)-1-benzyl 6-tert-butyl 6-azaspiro[2.5]octane-1,6-dicarboxylate (**B1**, 10.02 g, 29.0 mmol) in DCM (100 mL) at 0 - 5°C and the mixture was stirred at room temperature for 4 h. All the volatiles were removed by evaporator to give crude (S)-benzyl 6-azaspiro[2.5]octane-1-carboxylate (**B3_A**) which was used without further purification. LCMS (ESI) calc'd for C₁₅H₁₉NO₂ [M+H]⁺: 246.3, found: 246.1

Step 2: (S)-benzyl 6-methyl-6-azaspiro[2.5]octane-1-carboxylate (B3_B): Formaldehyde (18.77 g, 231 mmol) was added to a stirred mixture of (S)-benzyl 6-azaspiro[2.5]octane-1-carboxylate (**B3_A**, 9.9 g, 28.9 mmol) in MeOH (100 mL) at room temperature and the mixture was stirred at room temperature for 2 h. Sodium triacetoxhydroborate (18.39 g, 87 mmol) was added to the stirred mixture and the mixture was stirred at room temperature for 1 h. The solvent was removed by evaporator, then water (100 mL) was added and the mixture was extracted with ethyl acetate (50 mL) three times. The combined organic fractions were washed with aqueous NaHCO₃ (saturated, 50 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with DCM / MeOH = 10 / 1 to give (S)-benzyl 6-methyl-6-azaspiro[2.5]octane-1-carboxylate (**B3_B**). LCMS (ESI) calc'd for C₁₆H₂₁NO₂ [M+H]⁺: 260.3, found: 260.1

Step 3: (S)-6-methyl-6-azaspiro[2.5]octane-1-carboxylic acid (B3): A solution of (S)-benzyl 6-methyl-6-azaspiro[2.5]octane-1-carboxylate (**B3_B**, 7.5 g, 28.9 mmol) in MeOH (75 mL) was added to 100 mL three-necked bottle and then Pd/C (520 mg, 0.489 mmol) (10%, wet) was added under Ar. The suspension was degassed under vacuum and purged with N₂ several times. The mixture was then stirred under H₂ (15 psi) at 24°C for 90 min. The mixture was filtered and the filter cake was washed with MeOH (20 mL x 2). The filtrate was concentrated to dryness to give as (S)-6-methyl-6-azaspiro[2.5]octane-1-carboxylic acid (**B3**). ¹H NMR (400 MHz, DMSO-d₆) δ 2.95 (brs, 2H), 2.60 (s, 3H), 1.77-1.89 (m, 2H), 1.58 (t, J = 6.6 Hz, 1H), 0.91-0.99 (m, 2H).

Example 22**Preparation of Intermediate B4**



Step 1: Preparation of (*S*)-benzyl 6-azaspiro[2.5]octane-1-carboxylate 2,2,2-trifluoroacetate

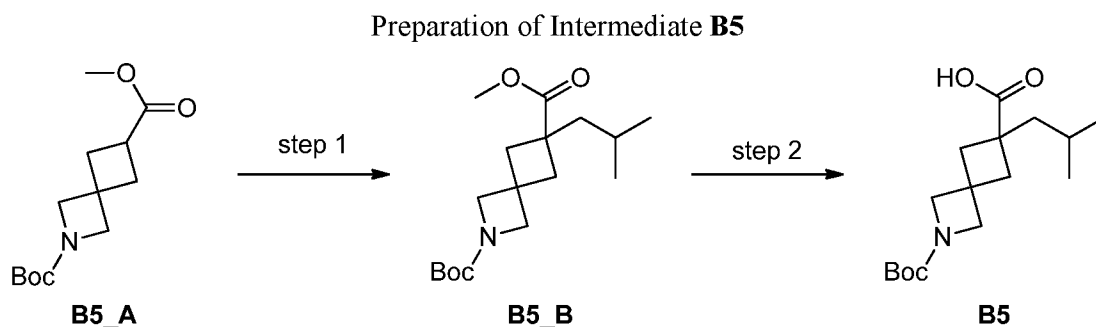
(B4_A): TFA (4.5 ml, 60.6 mmol) was added to a stirred mixture of (*S*)-1-benzyl 6-tert-butyl 6-azaspiro[2.5]octane-1,6-dicarboxylate (**B1**, 3.0 g, 8.68 mmol) in DCM (30 mL) at rt and the mixture was stirred at room temperature for 4 h. All the volatiles were removed by evaporator to give crude (*S*)-benzyl 6-azaspiro[2.5]octane-1-carboxylate (**B4_A**, 3.1 g) which was used directly for the next step without further purification treatment. LCMS (ESI) calc'd for $C_{15}H_{19}NO_2$ $[M+H]^+$: 246.1, found: 246.1

Step 2: Preparation of (*S*)-benzyl 6-ethyl-6-azaspiro[2.5]octane-1-carboxylate (B4_B):

Acetaldehyde (21 ml, 149 mmol) was added to a stirred mixture of (*S*)-benzyl 6-azaspiro[2.5]octane-1-carboxylate (**B4_A**, 6.2 g, 18.11 mmol) in MeOH (60 mL) at room temperature and the mixture was stirred at 30°C for 16 h. Then another batch of acetaldehyde (4.0 mL) was added and it was stirred at 30°C for further 16 h. Sodium triacetoxyhydroborate (11.52 g, 54.3 mmol) was added then the mixture was stirred at 30°C for 16 h. Most of the MeOH was removed by evaporator. Water (50 mL) was added and the mixture was extracted with ethyl acetate (3 x 35 mL). The combined organic fractions were washed with aqueous $NaHCO_3$ (saturated, 2 x 35 mL) then brine (2 x 35 mL), dried (Na_2SO_4), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (ISCORF75; Sepa flash column), eluting with DCM / MeOH = 0~ 10 / 1 to give (*S*)-benzyl 6-ethyl-6-azaspiro[2.5]octane-1-carboxylate (**B4_B**). LCMS (ESI) calc'd for $C_{17}H_{23}NO_2$ $[M+H]^+$: 274.2, found: 274.1

Step 3: Preparation of (*S*)-6-ethyl-6-azaspiro[2.5]octane-1-carboxylic acid (B4): To a solution of (*S*)-benzyl 6-ethyl-6-azaspiro[2.5]octane-1-carboxylate (**B4_B**, 4.5 g, 16.46 mmol) in MeOH (45 mL) was added Pd/C (300 mg, 0.282 mmol) (10%, wet) under Ar. The suspension was degassed under vacuum and purged with N_2 several times. The mixture was then stirred under H_2 (15 psi) at 18°C for 2 h. The mixture was filtered and the filter cake was washed with MeOH (3 x 15 mL). The filtrate was concentrated to dryness to give (*S*)-6-ethyl-6-azaspiro[2.5]octane-1-carboxylic acid (**B4**) which was used as crude. ^1H NMR (400 MHz, $DMSO-d_6$) δ 2.60-2.71 (m, 2H), 2.54-2.60 (m, 2H), 2.50 (brs, 2H), 1.65-1.78 (m, 2H), 1.48 (dd, $J = 5.6, 7.4$ Hz, 3H), 1.06 (t, $J = 7.2$ Hz, 3H), 0.87-0.92 (m, 1H), 0.81-0.87 (m, 1H).

Example 23



Step 2: preparation of 2-tert-butyl 6-methyl 6-isobutyl-2-azaspiro[3.3]heptane-2,6-dicarboxylate

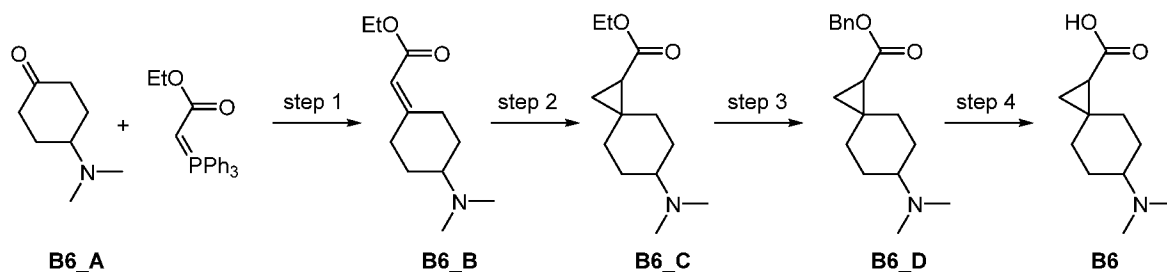
(**B5_B**): LDA (0.58 mL, 1.160 mmol) was added to a stirred mixture of 1-iodo-2-methylpropane (360 mg, 1.958 mmol) and 2-tert-butyl 6-methyl 2-azaspiro[3.3]heptane-2,6-dicarboxylate (**B5_A**, 100 mg, 0.392 mmol) in THF (3 mL) at -78°C, and the mixture was stirred at -78°C for 3 h, then at rt for 10 h. The mixture was quenched with NH₄Cl (10 mL), extracted with EtOAc (10 mL*3), the combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO[®], 4 g SepaFlash[®] Silica Flash Column, Eluent of 0~10% EtOAc/Petro. Ether gradient @ 40 mL/min) to give 2-tert-butyl 6-methyl 6-isobutyl-2-azaspiro[3.3]heptane-2,6-dicarboxylate (**B5_B**). ¹H NMR (400 MHz, CDCl₃) δ 3.87 (d, *J* = 3.1 Hz, 4H), 3.69 (s, 3H), 2.68-2.58 (m, 1H), 2.18-2.09 (m, 1H), 1.67-1.61 (m, 3H), 1.59-1.48 (m, 1H), 1.42 (s, 9H), 0.83 (d, *J* = 6.7 Hz, 6H).

Step 3: preparation of 2-(tert-butoxycarbonyl)-6-isobutyl-2-azaspiro[3.3]heptane-6-carboxylic acid (**B5**): NaOH aq (2 M, 2 mL, 4.00 mmol) was added to a stirred mixture of 2-tert-butyl 6-methyl 6-isobutyl-2-azaspiro[3.3]heptane-2,6-dicarboxylate (**B5_B**, 250 mg, 0.803 mmol) in MeOH (4 mL) at rt and the mixture was stirred at 50°C for 15 h. The mixture was cooled,

extracted with EtOAc (5 mL), the aqueous layers was adjusted to pH2 with HCl (2 M), and then extracted with EtOAc (5 mL*3), the combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated to get 2-(tert-butoxycarbonyl)-6-isobutyl-2-azaspiro[3.3]heptane-6-carboxylic acid (**B5**). ¹H NMR (400 MHz, CDCl₃) δ 3.99-3.78 (m, 4H), 2.74-2.59 (m, 1H), 2.22-2.08 (m, 1H), 1.64 (brs, 2H), 1.40 (s, 5H), 0.84 (brs, 3H).

Example 24

Preparation of Intermediate **B6**



Step 1: Preparation of ethyl 2-(4-(dimethylamino)cyclohexylidene)acetate (B6_B): Ethyl 2-(triphenylphosphoranylidene)acetate (4.934 g, 14.16 mmol) was added to the solution of 4-(dimethylamino)cyclohexanone (**B6_A**, 1.000 g, 7.08 mmol) in xylene (30 mL), and the resultant mixture was stirred at 135°C for 30 h. The mixture was concentrated to dryness. The residue was purified by silica gel flash chromatography (ISCORF75; Sepa flash column), eluting with DCM/ MeOH = 10:0-10:1 to give ethyl 2-(4-(dimethylamino)cyclohexylidene)acetate (**B6_B**). LCMS (ESI) calc'd for C₁₂H₂₁NO₂ [M+H]⁺: 212.1, found: 212.1

Step 2: Preparation of ethyl 6-(dimethylamino)spiro[2.5]octane-1-carboxylate (B6_C):

Pd(OAc)₂ (0.179 g, 0.795 mmol) and a solution of diazomethane (50.0 mL, 25.00 mmol) in ether was added sequentially in 5 portions to the solution of ethyl 2-(4-(dimethylamino)cyclohexylidene)acetate (**B6_B**, 1.68 g, 7.95 mmol) in DCM (5 mL) at 0°C with an interval of 20 min. The resultant mixture was stirred at 0°C for additional 1 h while the N₂ bubble stopped. The mixture was quenched with AcOH. The mixture was filtered and the filter cake was washed with MeOH (3 * 20 mL). The filtrate was concentrated to dryness to give ethyl 6-(dimethylamino)spiro[2.5]octane-1-carboxylate (**B6_C**) which is a mixture including starting material and used to the next step without purification. LCMS (ESI) calc'd for C₁₃H₂₃NO₂ [M+H]⁺: 226.2, found: 226.2

Step 3: Preparation of benzyl 6-(dimethylamino)spiro[2.5]octane-1-carboxylate (B6_D):

Titanium(IV) isopropoxide (3.51 mL, 11.98 mmol) and molecular sieve (4A, 3.0 g) was added to the solution of ethyl 6-(dimethylamino)spiro[2.5]octane-1-carboxylate (**B6_C**, 900 mg, 3.99 mmol) in BnOH (10.0 g, 92 mmol), and the resultant mixture was stirred at 120°C for 50 h. The reaction mixture was filtered and concentrated *in vacuo* to remove excess phenylmethanol. The residue was purified by silica gel column flash chromatography, eluting with DCM / MeOH = 10:0-4:1 to give benzyl 6-(dimethylamino)spiro[2.5]octane-1-carboxylate (**B6_D**). LCMS (ESI) calc'd for C₁₈H₂₅NO₂ [M+H]⁺: 288.2, found: 288.2

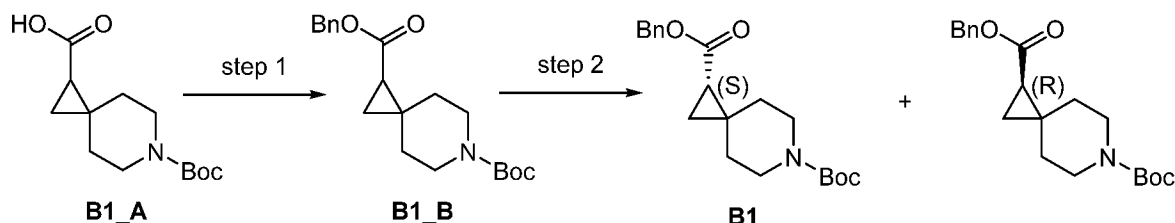
Step 4: Preparation of 6-(dimethylamino)spiro[2.5]octane-1-carboxylic acid (B6)

A solution of benzyl 6-(dimethylamino)spiro[2.5]octane-1-carboxylate (**B6_D**, 180 mg, 0.626 mmol) in MeOH (10 mL) was added to 100 mL bottle and then Pd-C (20 mg, 0.188 mmol)

(10%, wet) was added under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was then stirred under H₂ (Pressure: 1 atm) at 35°C for 18 h. The mixture was filtered through Celite and the filter cake was washed with THF (3 * 30 mL). The filtrate was concentrated to dryness to give 6-(dimethylamino)spiro[2.5]octane-1-carboxylic acid (B6) which was used without further purification. LCMS (ESI) calc'd for C₁₁H₁₉NO₂ [M+H]⁺: 198.1, found: 198.1

Example 25

Preparation of Intermediate B7



Step 1: Preparation of tert-butyl 3-methylene-8-azabicyclo[3.2.1]octane-8-carboxylate (B7_B)

Butyllithium (9 mL, 22.50 mmol) was added to a stirred mixture of methyltriphenylphosphonium bromide (8 g, 22.39 mmol) in THF (20 mL) at 0°C and the mixture was stirred at 0°C for 10 min under N₂ atmosphere. Tert-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (B7_A, 2 g, 8.88 mmol) in THF (30 mL) was then added dropwise. The mixture was stirred at 0-5°C for 45 min. The mixture was diluted with ethyl acetate (200 mL), washed with aqueous Na₂CO₃ (saturated, 1 x 50 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column (Petro. Ether: EtOAc = 20:1) to give tert-butyl 3-methylene-8-azabicyclo[3.2.1]octane-8-carboxylate (B7_B). LCMS (ESI) calc'd for C₁₇H₂₃BN₂O₂ [M+H]⁺: 224.2, found: 167.8 [M-55]⁺.

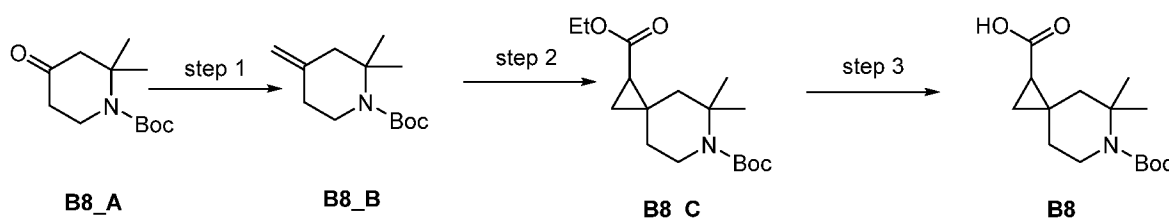
Step 2: Preparation of 8-tert-butyl 2'-ethyl 8-azaspiro[bicyclo[3.2.1]octane-3,1'-cyclopropane]-2',8-dicarboxylate (B7_C)

Ethyl 2-diazoacetate (1.022 g, 8.96 mmol) in DCM (5 mL) was added drop-wise carefully to a stirred mixture of diacetoxyrhodium (0.198 g, 0.448 mmol), and tert-butyl 3-methylene-8-azabicyclo[3.2.1]octane-8-carboxylate (B7_B, 1.0 g, 4.48 mmol) in DCM (5 mL) at room temperature and the mixture was stirred at room temperature for 12 h. AcOH (a drop) in water (10 mL) was added and the mixture was extracted with DCM (3 x 15 mL). The combined organic fractions were washed with brine (saturated, 3 x 15 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with EtOAc / petroleum ether = 0-10% to give 8-tert-butyl 2'-ethyl 8-azaspiro[bicyclo[3.2.1]octane-3,1'-cyclopropane]-2',8-dicarboxylate (B7_C). LCMS (ESI) calc'd for C₁₇H₂₇NO₄ [M+H]⁺: 310.2, found: 254.1 (M-55).

Step 3: Preparation of 8-(tert-butoxycarbonyl)-8-azaspiro[bicyclo[3.2.1]octane-3,1'-cyclopropane]-2'-carboxylic acid (**B7**): LiOH·H₂O (0.326 g, 7.76 mmol) was added to a stirred mixture of 8-tert-butyl 2'-ethyl 8-azaspiro[bicyclo[3.2.1]octane-3,1'-cyclopropane]-2',8-dicarboxylate (**B7_C**, 1.2 g, 3.88 mmol) in water (1 mL) / MeOH (10 mL) at room temperature and the mixture was stirred at 40°C for 12 h. The residue was concentrated to give 8-(tert-butoxycarbonyl)-8-azaspiro[bicyclo[3.2.1]octane-3,1'-cyclopropane]-2'-carboxylic acid (**B7**). LCMS (ESI) calc'd for C₁₅H₂₃NO₄ [M+H]⁺: 282.2, found: 226.1 (M-55).

Example 26

Preparation of Intermediate **B8**



Step 1: Preparation of tert-butyl 2,2-dimethyl-4-methylenepiperidine-1-carboxylate (**B8_B**):

nBuLi (1.214 mL, 3.04 mmol) was added to a stirred mixture of PPh₃MeBr (1.179 g, 3.30 mmol) in THF (6.0 mL) at 0 - 5°C and the mixture was stirred at 0 - 5°C for 10 min under N₂ atmosphere. Tert-butyl 2,2-dimethyl-4-oxopiperidine-1-carboxylate (**B8_A**, 300 mg, 1.320 mmol) in 1 mL of THF was then added dropwise. The mixture was stirred at rt for 16 h. The mixture was diluted with ethyl acetate (15 mL), washed with aqueous Na₂CO₃ (saturated, 1 x 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 10:1 to give tert-butyl 2,2-dimethyl-4-methylenepiperidine-1-carboxylate (**B8_B**). LCMS (ESI) calc'd for C₁₃H₂₃NO₂ [M+H]⁺: 226.2, found: 170.1 (M-55). ¹H NMR (400 MHz, CDCl₃) δ 4.82 (brs, 2H), 3.56 (t, *J* = 6.17 Hz, 2H), 2.38 (t, *J* = 5.95 Hz, 2H), 2.28 (s, 2H), 1.47 (s, 9H), 1.38 (s, 6H).

Step 2: Preparation of 6-tert-butyl 1-ethyl 5,5-dimethyl-6-azaspiro[2.5]octane-1,6-dicarboxylate (**B8_C**): Rh₂(OAc)₄ (29.4 mg, 0.067 mmol) was added to a stirred mixture of tert-butyl 2,2-

dimethyl-4-methylenepiperidine-1-carboxylate (150 mg, 0.666 mmol) in DCM (8.0 mL) at room temperature and ethyl diazoacetate (152 mg, 1.331 mmol) in 1 mL of DCM was added dropwise, and the mixture was stirred at rt for 5 h. Then, Rh₂(OAc)₄ (29.4 mg, 0.067 mmol) and ethyl diazoacetate (152 mg, 1.331 mmol) was added to above solution and stirred for another 5 h, then quenched with 1 M AcOH (3 mL), and the mixture was extracted with ethyl acetate (15 mL).

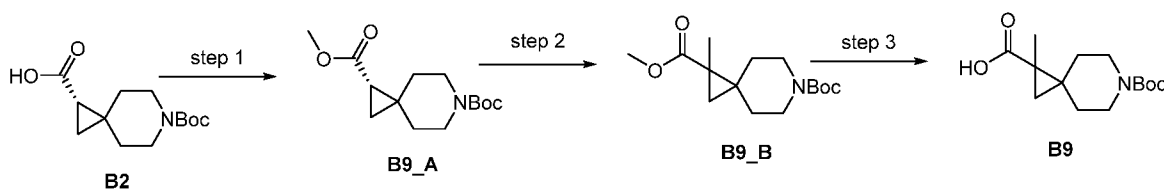
The combined organic fractions were washed with brine (saturated, 8 mL), dried (Na₂SO₄),

filtered and the solvent was evaporated under reduced pressure. The residue was purified by preparative TLC on silica gel, eluting with petroleum ether / EtOAc = 5:1 and further purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.225% HCOOH, to give 6-tert-butyl 1-ethyl 5,5-dimethyl-6-azaspiro[2.5]octane-1,6-dicarboxylate (**B8_C**). LCMS (ESI) calc'd for $C_{17}H_{29}NO_4$ $[M+H]^+$: 312.2, found: 312.1. ^1H NMR (400 MHz, $CDCl_3$) δ 4.04-4.17 (m, 2H), 3.37-3.57 (m, 2H), 1.70-1.77 (m, 2H), 1.56 (brs, 2H), 1.39-1.47 (m, 15H), 1.24 (t, $J = 7.04$ Hz, 3H), 1.11-1.18 (m, 1H), 0.87-0.97 (m, 1H).

Step 3: Preparation of 6-(tert-butoxycarbonyl)-5,5-dimethyl-6-azaspiro[2.5]octane-1-carboxylic acid (**B8**): LiOH·H₂O (27 mg, 0.643 mmol) was added to a stirred mixture of 6-tert-butyl 1-ethyl 5,5-dimethyl-6-azaspiro[2.5]octane-1,6-dicarboxylate (**B8_C**, 100 mg, 0.321 mmol) in MeOH (2.0 mL) and water (0.5 mL) at room temperature and the mixture was heated to 45°C and stirred for 16 h, concentrated, the mixture was adjusted to pH 7 with hydrochloric acid (0.2 M solution) and the mixture was extracted with ethyl acetate (10 mL). The combined organic fractions were washed with brine (saturated, 5 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure to afford 6-(tert-butoxycarbonyl)-5,5-dimethyl-6-azaspiro[2.5]octane-1-carboxylic acid (**B8**) without further purification. LCMS (ESI) calc'd for $C_{15}H_{25}NO_4$ $[M+H]^+$: 284.2, found: 228.1.

Example 27

Preparation of Intermediate **B9**



Step 1: Preparation of (R)-6-tert-butyl 1-methyl 6-azaspiro[2.5]octane-1,6-dicarboxylate (**B9_A**): (Diazomethyl)trimethylsilane (4.90 mL, 9.79 mmol) was added to a stirred mixture of 6-(tert-butoxycarbonyl)-6-azaspiro[2.5]octane-1-carboxylic acid (**B2**, 500 mg, 1.958 mmol) in MeOH (10 mL) at 0°C, and the mixture was stirred at 20°C for 15h. The solvent was removed under reduced pressure. The crude product was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% EtOAc/Petro.Ether gradient @ 30 mL/min) to give 6-tert-butyl 1-methyl 6-azaspiro[2.5]octane-1,6-dicarboxylate (**B9_A**). LCMS (ESI) calc'd for $C_{14}H_{23}NO_4$ $[M+H]^+$: 270.2, found: 213.9 (M-55).

Step 2: Preparation of (R)-6-tert-butyl 1-methyl 1-methyl-6-azaspiro[2.5]octane-1,6-

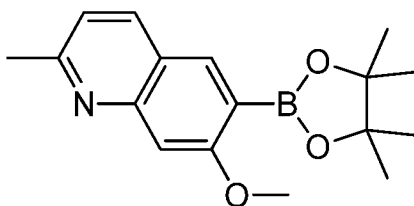
dicarboxylate (**B9_B**): LDA (0.557 mL, 1.114 mmol) was added to a stirred mixture of 6-tert-butyl 1-methyl 6-azaspiro[2.5]octane-1,6-dicarboxylate (**B9_A**, 100 mg, 0.371 mmol) and MeI

(0.116 mL, 1.856 mmol) in THF (2 mL) at -78°C and the mixture was stirred at -78°C for 3 h and then at rt for 15 h. The mixture was quenched with NH₄Cl (10 mL), extracted with EtOAc (10 mL*3), the combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated to get the crude. The residue was purified by prep-HPLC (TFA) to give
 5 6-tert-butyl 1-methyl 1-methyl-6-azaspiro[2.5]octane-1,6-dicarboxylate (**B9_B**). LCMS (ESI) calc'd for C₁₅H₂₅NO₄ [M+H]⁺: 284.2, found: 306.1 (M+Na⁺).

Step 3: Preparation of (R)-6-(tert-butoxycarbonyl)-1-methyl-6-azaspiro[2.5]octane-1-carboxylic acid (**B9**): Sodium hydroxide aq (2 M, 0.4 mL, 0.800 mmol) was added to a stirred mixture of 6-tert-butyl 1-methyl 1-methyl-6-azaspiro[2.5]octane-1,6-dicarboxylate (**B9_B**, 52 mg, 0.184
 10 mmol) in MeOH (3 mL) at 25°C, and the mixture was stirred at 50°C for 6 h. The mixture was concentrated and the aqueous layer was adjust to pH=2 with HCl aq (2 M), and extracted with EtOAc (10 mL*3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated to give 6-(tert-butoxycarbonyl)-1-methyl-6-azaspiro[2.5]octane-1-carboxylic acid (**B9**).

Example 28

Preparation of Intermediate C1



Step 1: 6-bromo-7-methoxy-2-methylquinoline (**C1_A**): A suspension of 4-bromo-3-methoxyaniline (15.00 g, 74.2 mmol) and HCl (52.5 mL, 639 mmol) in water (60 mL) was
 20 heated to 110°C. (E)-but-2-enal (8.23 g, 117 mmol) was added dropwise into the above mixture over 30 min. Then the reaction mixture was stirred at 110°C for another 2 h. The reaction mixture was combined with another reaction with the same scale. The combined mixture was cooled to rt, aqueous ammonia (28%, 300 mL) was added and the mixture was extracted with ethyl acetate (200 x 3 mL). The combined organic fractions were washed with brine (400 mL),
 25 dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 10%-40% to give 6-bromo-7-methoxy-2-methylquinoline (**C1_A**). LCMS (ESI) calc'd for C₁₁H₁₀BrNO [M+H]⁺: 252.0, found: 251.9.

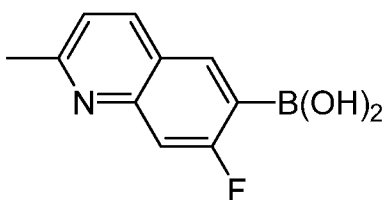
Step 2: 7-methoxy-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (**C1**):

30 PdCl₂(dppf) (85 mg, 0.116 mmol) was added to a stirred mixture of potassium acetate (405 mg, 4.13 mmol), BPD (786 mg, 3.09 mmol) and 6-bromo-7-methoxy-2-methylquinoline (**C1_A**, 520

mg, 2.063 mmol) in 1,4-dioxane (8 mL) at room temperature and the mixture was stirred at 80°C for 12 h under N₂ protection. The mixture was concentrated and the residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 1 : 1 to give 7-methoxy-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (**C1**). LCMS (ESI) calc'd for C₁₇H₂₂BNO₃ [M+H]⁺: 300.2, found: 300.2. ¹H NMR (400 MHz, CDCl₃) δ 8.12 (s, 1H), 7.98 (d, *J* = 8.22 Hz, 1H), 7.34 (s, 1H), 7.14 (d, *J* = 8.22 Hz, 1H), 3.97 (s, 3H), 2.72 (s, 3H), 1.41 (s, 12H).

Example 29

Preparation of Intermediate C2



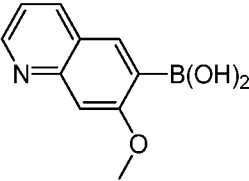
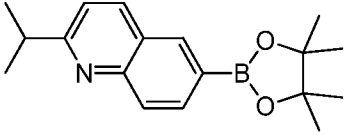
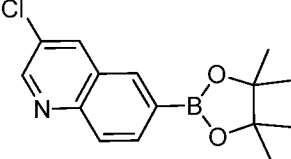
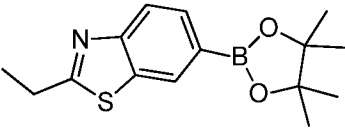
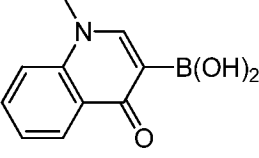
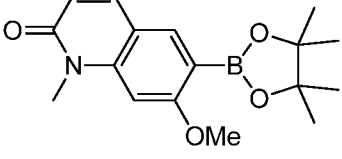
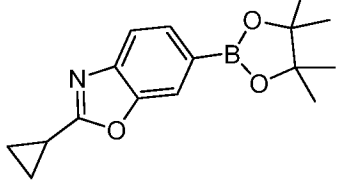
Step 1: 6-bromo-7-fluoro-2-methylquinoline (**C2_A**): 4-bromo-3-fluoroaniline (500 mg, 2.63 mmol) was added to a stirred mixture of p-chloranil (0.776 g, 3.16 mmol) in BuOH (5.0 mL) / HCl (5 mL, 60.9 mmol) at room temperature and the mixture was stirred at 120°C, and then (*E*)-but-2-enal (9.31 mL, 113 mmol) in BuOH (0.3 mL) was added dropwise. The mixture was stirred at 120°C for 40 min. After cooling to rt, it was diluted with H₂O (10 mL) and extracted with EtOAc (3 x 10 mL). The aqueous layer was alkalinized with NaOH (37%) to pH > 9, and extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with brine (saturated, 20 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.225% HCOOH, to give 6-bromo-7-fluoro-2-methylquinoline (**C2_A**). ¹H NMR (400 MHz, MeOD) δ 8.67 (d, *J* = 8.6 Hz, 1H), 8.54 (d, *J* = 7.0 Hz, 1H), 7.85 (d, *J* = 9.0 Hz, 1H), 7.76 (d, *J* = 8.6 Hz, 1H), 2.89 (s, 3H). LCMS (ESI) calc'd for C₁₀H₇BrFN [M+H]⁺: 240.0, found: 240.0

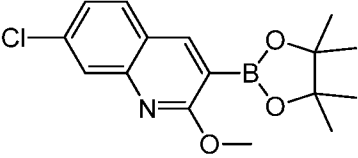
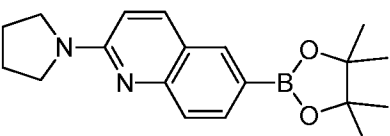
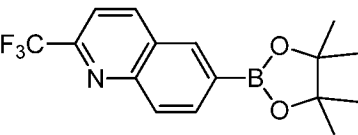
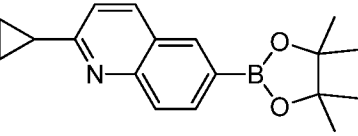
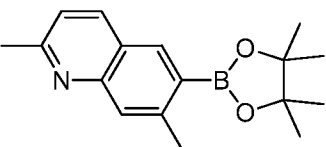
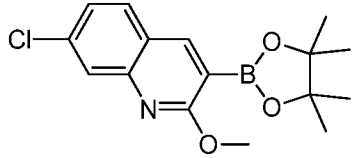
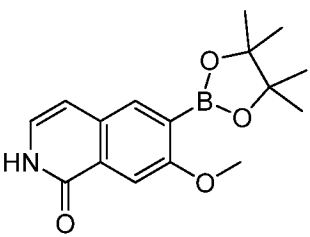
Step 2: (7-fluoro-2-methylquinolin-6-yl)boronic acid (**C2**): *n*BuLi (1.7 mL, 4.25 mmol) was added to a stirred mixture of 6-bromo-7-fluoro-2-methylquinoline (**C2_A**, 500 mg, 2.083 mmol) in THF (10 mL) at -78°C, then triisopropyl borate (1 mL, 4.31 mmol) was added and the mixture was stirred at room temperature for 2 h. Aqueous NH₄Cl (saturated, 10 mL) was added and the mixture was extracted with ethyl acetate (3 x 8 mL). The combined organic fractions were washed with brine (saturated, 15 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography,

eluting with MeOH/DCM = 0-20% to give (7-fluoro-2-methylquinolin-6-yl)boronic acid (**C2**).

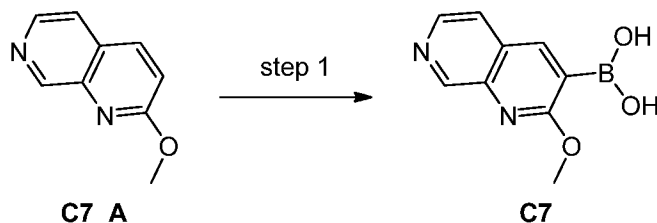
LCMS (ESI) calc'd for $C_{10}H_9BFNO_2$ $[M+H]^+$: 206.1, found: 206.1

The following intermediates were prepared in a similar manner as described for intermediates **C1** and **C2** from commercial reagents or reported intermediates.

ID	Structure	Observed $[M+H]^+$
C3		204.0
C4		298.2
C5		290.0
C6		289.9
C8		204.1
C10		316.1
C13		286.1

C15		319.9
C16		325.2
C22		324.1
C24		296.1
C26		283.7
C27		319.9
C35		302.1

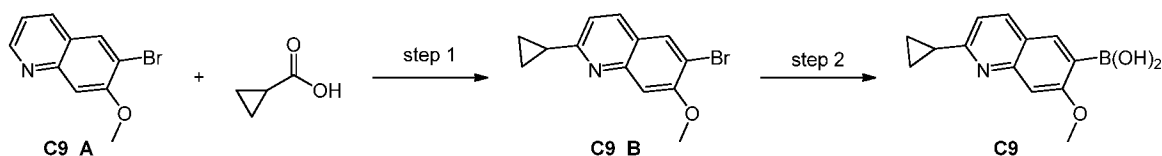
Example 30
Preparation of Intermediate C7



Step 1: preparation of (2-methoxy-1,7-naphthyridin-3-yl)boronic acid (**C7**): LDA (1.873 mL, 3.75 mmol) was added to a stirred mixture of 2-methoxy-1,7-naphthyridine (**C7_A**, 400 mg, 2.497 mmol) and triisopropyl borate (939 mg, 4.99 mmol) in THF (3 mL) at -78°C, and the mixture was stirred at -78°C for 3 h, followed by stirring at 18°C for 10 h. The mixture was quenched with NH₄Cl (10 mL), extracted with EtOAc (10 mL*3), the combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated. The crude product was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~10% DCM/MeOH gradient @ 40 mL/min) to give (2-methoxy-1,7-naphthyridin-3-yl)boronic acid (**C7**). ¹H NMR (400 MHz, MeOD) δ 9.17-9.10 (m, 1H), 8.45-8.39 (m, 1H), 8.30-8.23 (m, 1H), 7.85-7.79 (m, 1H), 4.12 (s, 1H). LCMS (ESI) calc'd for C₉H₉BN₂O₃ [M+H]⁺: 205.1, found: 205.1.

Example 31

Preparation of Intermediate **C9**

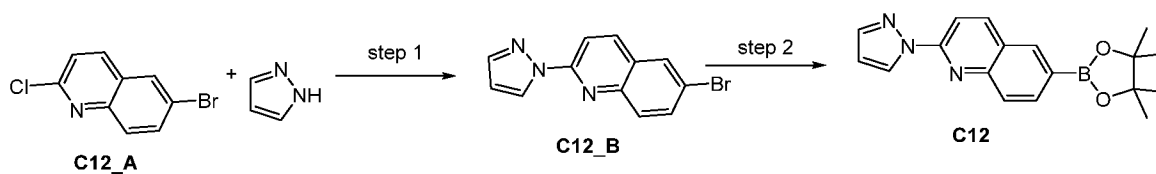


Step 1: Preparation of 6-bromo-2-cyclopropyl-7-methoxyquinoline (**C9_B**): AgNO₃ (43 mg, 0.253 mmol), cyclopropanecarboxylic acid (37 mg, 0.430 mmol) and 6-bromo-7-methoxyquinoline (**C9_A**, 100 mg, 0.420 mmol) was added to a stirred mixture of H₂SO₄ (0.05 mL, 0.938 mmol) in water (3 mL) at 20°C and the mixture was warmed to 70°C, and stirred at 70°C for 6 h. Then (NH₄)₂S₂O₈ (288 mg, 1.260 mmol) in water (2 mL) was added drop-wise. After adding, the mixture was cooled to room temperature. Then the mixture was stirred at 70°C for 12 h. The mixture was cooled, diluted with EtOAc (10 mL), washed with water (3 x 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with EtOAc / petroleum ether = 0 - 60% to give 6-bromo-2-cyclopropyl-7-methoxyquinoline (**C9_B**). LCMS (ESI) calc'd for C₁₃H₁₂BrNO [M+H]⁺: 278.0, found: 278.0. ¹H NMR (400 MHz, CDCl₃) δ 7.95 (s, 1H), 7.85 (d,

Step 2: Preparation of (2-cyclopropyl-7-methoxyquinolin-6-yl)boronic acid (C9): PdCl₂(dppf) (30 mg, 0.041 mmol) was added to a stirred mixture of BPD (110 mg, 0.433 mmol), and 6-

5 bromo-2-cyclopropyl-7-methoxyquinoline (**C9_B**, 100 mg, 0.360 mmol) in 1,4-dioxane (1 mL) at room temperature and the mixture was stirred at 80°C for 4 h under N₂. The mixture was cooled, diluted with EtOAc (10 mL), washed with brine (saturated, 3 x 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with EtOAc / petroleum ether = 0-70% to give
10 (2-cyclopropyl-7-methoxyquinolin-6-yl)boronic acid (**C9**). LCMS (ESI) calc'd for C₁₃H₁₄BNO₃ [M+H]⁺; 244.1, found: 244.1.

Preparation of Intermediate C12



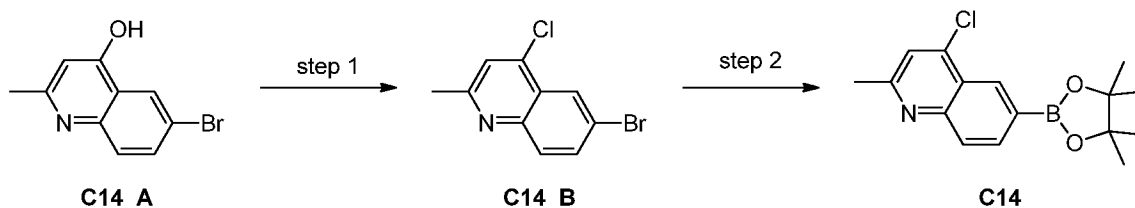
15 Step 1: Preparation of 6-bromo-2-(1H-pyrazol-1-yl)quinoline (C12_B): A mixture of 6-bromo-2-chloroquinoline (C12_A, 1.00 g, 4.12 mmol), 1H-pyrazole (0.84 g, 12.36 mmol) and Cs₂CO₃ (2.69 g, 8.24 mmol) in DMF (30 mL) was stirred at 100°C for 17 h. The reaction mixture was evaporated *in vacuo*. To the residue was added water (150 mL) and then it was extracted with EtOAc (60 mL × 3). The organic layers were combined, washed with brine (80 mL), dried over
20 anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by silica column chromatography (petroleum ether: EtOAc = 15: 1) to afford 6-bromo-2-(1H-pyrazol-1-yl)quinoline (C12_B). LCMS (ESI) calc'd for C₁₂H₈BrN₃ [M+H]⁺: 274.0, found: 273.9. ¹H NMR (400 MHz, CDCl₃) δ 6.53 (s, 1H), 7.74-7.82 (m, 2H), 7.83-7.91 (m, 1H), 7.98 (d, *J* = 1.96 Hz, 1H), 8.14-8.28 (m, 2H), 8.77 (d, *J* = 1.96 Hz, 1H).

25 Step 2: Preparation of 2-(1*H*-pyrazol-1-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (C12): Potassium acetate (1164 mg, 11.86 mmol) was added to the mixture of PdCl₂(dppf) (400 mg, 0.547 mmol), 6-bromo-2-(1*H*-pyrazol-1-yl)quinoline (C12_B, 1300 mg, 4.74 mmol) and BPD (2200 mg, 8.66 mmol) in 1,4-dioxane (30 mL). The resultant mixture was stirred at 70°C under N₂ for 8 h. The mixture was filtered, and the filtrate was concentrated *in*
30 *vacuo*. The residue was purified by silica column (petroleum ether: EtOAc = 4:1) to afford 2-

(1*H*-pyrazol-1-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (**C12**). LCMS (ESI) calc'd for $C_{18}H_{20}BN_3O_2$ $[M+H]^+$: 322.2, found: 322.0.

Example 33

Preparation of Intermediate **C14**



Step 1: Preparation of 6-bromo-4-chloro-2-methylquinoline (**C14_B**): A suspension of 6-bromo-2-methylquinoline-4-ol (**C14_A**, 1.2 g, 5.06 mmol) in *N,N*-dimethylaniline (1.3 mL) was treated with phosphorous oxychloride (3.6 mL) and the mixture was heated at 60°C for 2 h. The mixture was evaporated *in vacuo* and the residue was taken up with 30 mL water, neutralized with 10 mL saturated aqueous sodium bicarbonate and extracted with EtOAc (3 x 30 mL). The combined organic fractions were washed with sat. NaCl (30 mL), dried (Na_2SO_4), filtered and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel with ethyl acetate / petroleum ether = 1: 2 to give 6-bromo-4-chloro-2-methylquinoline (**C14_B**). LCMS (ESI) calc'd for $C_{10}H_7BrClN$ $[M+H]^+$: 257.9, found: 258.1.

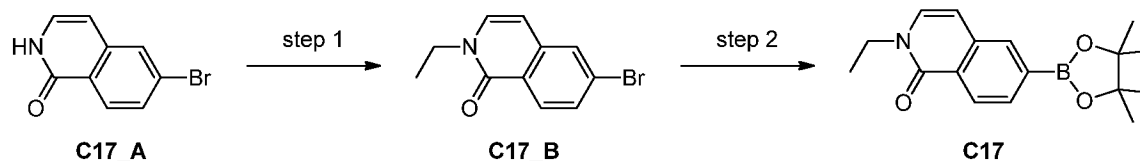
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Step 2: Preparation of 4-chloro-2methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (**C14**): A mixture of 6-bromo-4-chloro-2-methylquinoline (**C14_B**, 500 mg, 1.96 mmol), BPD (645 mg, 2.53 mmol), KOAc (495 mg, 4.38 mmol) and $PdCl_2(dppf)$ (140 mg, 0.19 mmol) in dioxane (20 mL) was degassed and backfilled with N_2 three times. The mixture was heated to 90°C for 2 h. The mixture was filtered and the filtrate was concentrated. The residue was purified by chromatography on silica gel with ethyl acetate / petroleum ether = 1: 5 to give 4-chloro-2methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (**C14**). LCMS (ESI) calc'd for $C_{16}H_{19}BrClNO_2$ $[M+H]^+$: 304.1, found: 304.1.

20

Example 34

Preparation of Intermediate **C17**



Step 1: Preparation of 6-bromo-2-ethylisoquinolin-1(2*H*)-one (**C17_B**): To a solution of 6-bromoisoquinolin-1(2*H*)-one (**C17_A**, 500 mg, 2.232 mmol) in DMF (10 mL) was added sodium

hydride (214 mg, 5.35 mmol) under N₂. After 30 min, iodoethane (1392 mg, 8.93 mmol) was added. The mixture was stirred at 25°C for 1 h. The mixture was quenched with water (20 mL) and extracted with EtOAc (20 mL*3), the combined oil was concentrated *in vacuo*. The crude was purified by silica column (petroleum ether: EtOAc = 3: 1) to afford 6-bromo-2-ethylisoquinolin-1(2*H*)-one (**C17_B**).

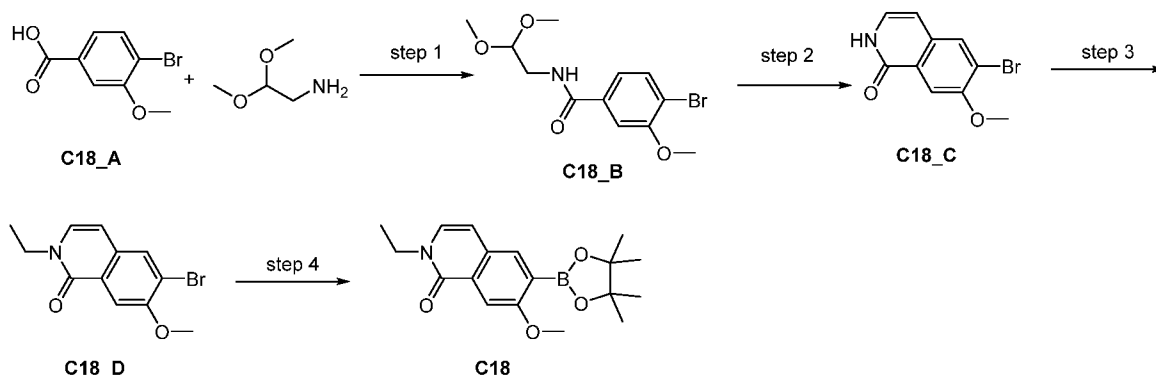
Step 2: Preparation of 2-ethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2*H*)-one (**C17**): Potassium acetate (631 mg, 6.43 mmol) was added to the mixture of

PdCl₂(dppf) (157 mg, 0.215 mmol), 6-bromo-2-ethylisoquinolin-1(2*H*)-one (**C17_B**, 540 mg, 2.142 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1632 mg, 6.43

mmol) in 1,4-dioxane (20 mL). The resultant mixture was stirred at 70°C under N₂ for 8 h. The mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica column (petroleum ether: EtOAc = 3: 1) to afford 2-ethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2*H*)-one (**C17**). LCMS (ESI) calc'd for C₁₇H₂₂BNO₃ [M+H]⁺: 300.2, found: 300.1.

Example 35

Preparation of Intermediate **C18**



Step 1: Preparation of 4-bromo-N-(2,2-dimethoxyethyl)-3-methoxybenzamide (**C18_B**): HATU (3.61 g, 9.5 mmol) and TEA (1.042 g, 10.32 mmol) were added to a stirred mixture of 4-bromo-3-methoxybenzoic acid (2 g, 8.6 mmol) in DCM (20 mL) at room temperature and the mixture was stirred at room temperature for 15 min. Then 4-bromo-3-methoxyaniline (**C18_A**, 997 mg, 9.5 mmol) was added. The solution was stirred for 1 h. Then the solvent was removed to give the title compound (**C18_B**) which was used to the next step without further purification.

Step 2: Preparation of 6-bromo-7-methoxyisoquinolin-1(2*H*)-one (**C18_C**): H₂SO₄ (20 mL)

was added slowly to a stirring round-bottomed flask charged with 4-bromo-N-(2,2-dimethoxyethyl)-3-methoxybenzamide (**C18_B**, 2.72 g crude, 8.6 mmol) at room temperature and the mixture was stirred at room temperature for 2 h. The reaction was poured into ice water,

the resulting precipitate was collected by filtration and the filter cake was washed with water (50 mL) and dried to afford the title compound (**C18_C**) which was used directly in the next step.

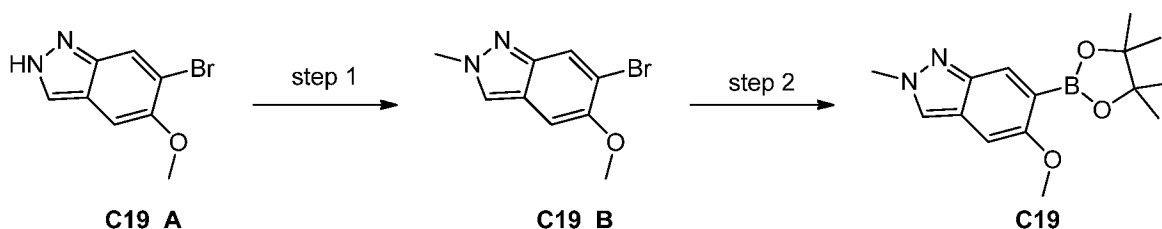
Step 3: Preparation of 6-bromo-2-ethyl-7-methoxyisoquinolin-1(2H)-one (C18_D**):** Iodoethane (1.4 g, 8.97 mmol) was added to a stirred mixture of 6-bromo-7-methoxyisoquinolin-1(2H)-one (**C18_C**, 1.52 g, 5.98 mmol) and Cs₂CO₃ (2.9 g, 8.97 mmol) in DMF (20 mL) at room temperature and the mixture was stirred at room temperature around for 2 h. The mixture was filtered and the filter cake was washed with DMF (10 mL). The filtrate was poured into water (50 mL) and the precipitate was collected with filtration and the filter cake was washed with water (50 mL) and dried to give 6-bromo-2-ethyl-7-methoxyisoquinolin-1(2H)-one (**C18_D**).

LCMS (ESI) calc'd for C₁₂H₁₂BrNO₂ [M+H]⁺: 282.0, found: 284.0.

Step 4: Preparation of 2-ethyl-7-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one (C18**):** Potassium acetate (1.660 g, 17 mmol) and BPD (2.16 g, 8.51 mmol) were added to a stirred mixture of 6-bromo-2-ethyl-7-methoxyisoquinolin-1(2H)-one (**C18_D**, 1.6 g, 5.67 mmol) in 1,4-dioxane (20 mL) at room temperature, the mixture was replaced with N₂, then PdCl₂(dppf) (0.414 g, 0.567 mmol) was added. The mixture was heated with stirring at 80°C for 18 h. The mixture was cooled to room temperature, filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 30: 70 to give 2-ethyl-7-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one (**C18**). LCMS (ESI) calc'd for C₁₈H₂₄BNO₄ [M+H]⁺: 330.2, found: 330.2

Example 36

Preparation of Intermediate **C19**



Step 1: Preparation of 6-bromo-5-methoxy-2-methyl-2H-indazole (C19_B**):** Trimethylxoxonium tetrafluoroborate (0.782 g, 5.28 mmol) was added to a stirred mixture of 6-bromo-5-methoxy-1H-indazole (**C19_A**, 1 g, 4.40 mmol) in ethyl acetate (20 mL) at room temperature and the mixture was stirred at room temperature for 2 h. Water (50 mL) was added and the mixture was extracted with ethyl acetate (2x 50 mL). The combined organic fractions were washed with brine (saturated, 2 x 50 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting

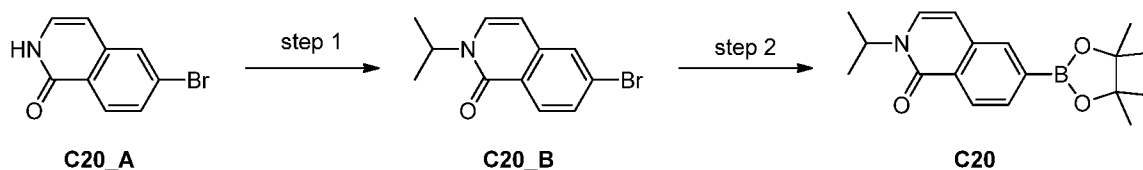
with petroleum ether / EtOAc = 4:1 to give 6-bromo-5-methoxy-2-methyl-2*H*-indazole (**C19_B**). LCMS (ESI) calc'd for C₉H₉BrN₂O [M+H]⁺: 241.0, found: 242.9. ¹H NMR (400 MHz, DMSO-d₆) δ 8.22 (s, 1H), 7.90 (s, 1H), 7.19 (s, 1H), 4.11 (s, 3H), 3.83 (s, 3H).

Step 2: Preparation of 5-methoxy-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-

indazole (**C19**): Potassium acetate (855 mg, 8.71 mmol) and BPD (1475 mg, 5.81 mmol) were added to a stirred mixture of 6-bromo-5-methoxy-2-methyl-2*H*-indazole (**C19_B**, 700 mg, 2.90 mmol) in 1,4-dioxane (10 mL) at room temperature, the mixture was replaced with N₂, and then PdCl₂(dppf) (212 mg, 0.290 mmol) was added. The mixture was heated with stirring at 80°C for 18 h. The mixture was filtered and the filter cake was washed with ethyl acetate (40 mL) and dried under vacuum. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 3:1 to give 5-methoxy-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-indazole (**C19**). LCMS (ESI) calc'd for C₁₅H₂₁BN₂O₃ [M+H]⁺: 289.1, found: 289.1.

Example 37

Preparation of Intermediate **C20**



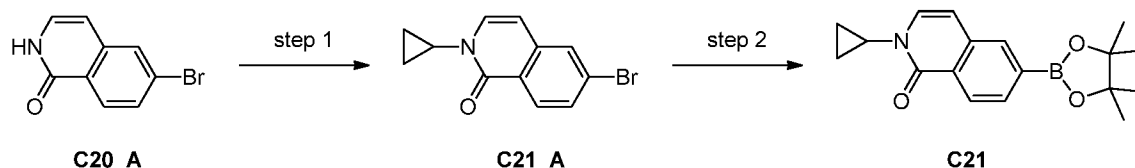
Step 1: Preparation of 6-bromo-2-isopropylisoquinolin-1(2*H*)-one (**C20_B**): To a solution of 6-bromoisoquinolin-1(2*H*)-one (**C20_A**, 500 mg, 2.232 mmol) in DMF (15 mL) was added NaH (357 mg, 8.93 mmol) at 0°C, the mixture was stirred at 0°C for 30 min, then 2-iodopropane (1.5 g, 8.82 mmol) was added to the mixture, and the reaction mixture was stirred at room temperature for 16 h. Water (10 mL) was added, it was extracted with EtOAc (25 mL*3), washed with brine (15 mL), dried over Na₂SO₄, concentrated, and the residue was purified by prep-TLC (SiO₂, petroleum ether: EtOAc = 3: 1) to give 6-bromo-2-isopropylisoquinolin-1(2*H*)-one (**C20_B**). LCMS (ESI) calc'd for C₁₂H₁₀BrNO [M+H]⁺: 265.9, found: 265.9.

Step 2: Preparation of 2-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2*H*)-one (**C20**): Potassium acetate (387 mg, 3.94 mmol) was added to the mixture of BPD (1000 mg, 3.94 mmol) and 6-bromo-2-isopropylisoquinolin-1(2*H*)-one (**C20_B**, 350 mg, 1.315 mmol) and PdCl₂(dppf) (96 mg, 0.131 mmol) in dioxane (10 mL). The mixture was stirred at 70°C under N₂ for 16 h. The mixture was filtered, water (15 mL) was added to the filtrate, it was extracted with EtOAc (15 mL*3), dried over Na₂SO₄, filtered and concentrated, and the residue was purified by prep-TLC (SiO₂, petroleum ether: EtOAc = 3: 1) to give 2-isopropyl-6-(4,4,5,5-

tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2*H*)-one (**C20**). LCMS (ESI) calc'd for $C_{18}H_{24}BNO_3$ $[M+H]^+$: 314.2, found: 314.2.

Example 38

Preparation of Intermediate **C21**

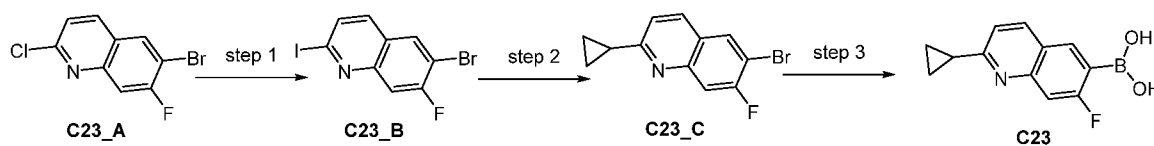


Step 1: Preparation of 6-bromo-2-cyclopropylisoquinolin-1(2*H*)-one (C21_A**):** To 6-bromoisoquinolin-1(2*H*)-one (**C20_A**, 500 mg, 2.232 mmol) in DCM (30 mL) was added cyclopropylboronic acid (767 mg, 8.93 mmol), diacetoxycopper (405 mg, 2.232 mmol), pyridine (706 mg, 8.93 mmol) and Et_3N (1.244 mL, 8.92 mmol), the mixture was stirred at 20°C under O_2 for 16 h. The mixture was filtered, water (15 mL) was added, it was extracted with DCM (15 mL*3), dried over Na_2SO_4 , filtrated, concentrated. The residue was purified by prep-TLC (SiO₂, petroleum ether: EtOAc = 3: 1) to give 6-bromo-2-cyclopropylisoquinolin-1(2*H*)-one (**C21_A**). LCMS (ESI) calc'd for $C_{12}H_{10}BrNO$ $[M+H]^+$: 263.9, found: 264.0.

Step 2: Preparation of 2-cyclopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2*H*)-one (C21**):** Potassium acetate (325 mg, 3.31 mmol) was added to the mixture of $PdCl_2(dppf)$ (150 mg, 0.205 mmol), 6-bromo-2-cyclopropylisoquinolin-1(2*H*)-one (350 mg, 1.325 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (606 mg, 2.386 mmol) in 1,4-dioxane (10 mL). The resultant mixture was stirred at 70°C under N_2 for 8 h. The mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica column (petroleum ether: EtOAc = 3: 1) to afford 2-cyclopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2*H*)-one (**C21**). LCMS (ESI) calc'd for $C_{18}H_{22}BNO_3$ $[M+H]^+$: 312.2, found: 312.1.

Example 39

Preparation of Intermediate **C23**



Step 1: Preparation of 6-bromo-7-fluoro-2-iodoquinoline (C23_B**):** $AcCl$ (0.2 mL, 2.81 mmol) was added to a stirred mixture of 6-bromo-2-chloro-7-fluoroquinoline (**C23_A**, 0.6 g, 2.303 mmol) and sodium iodide (3.45 g, 23.03 mmol) in acetonitrile (2.5 mL) at 80°C and the mixture was stirred at 80°C for 12 h. The mixture was cooled, diluted with ethyl acetate (10 mL),

washed with aq Na₂SO₃ (3 x 15 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with EtOAc/petroleum ether = 0-20% to give 6-bromo-7-fluoro-2-iodoquinoline (**C23_B**). LCMS (ESI) calc'd for C₉H₄BrFIN [M+H]⁺: 351.9, found: 351.8. ¹H NMR (400 MHz, CDCl₃) δ 8.05 (d, *J* = 7.04 Hz, 1H), 7.72-7.78 (m, 2H), 7.66-7.71 (m, 1H).

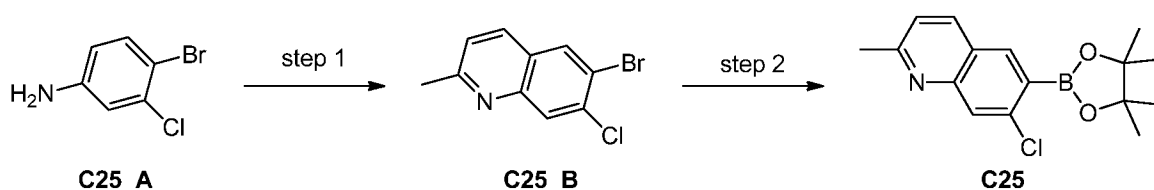
Step 2: Preparation of 6-bromo-2-cyclopropyl-7-fluoroquinoline (C23_C**):**

Tricyclohexylphosphine (121 mg, 0.432 mmol) and diacetoxypalladium (48 mg, 0.214 mmol) was added to a stirred mixture of K₃PO₄ (917 mg, 4.32 mmol), cyclopropylboronic acid (185 mg, 2.159 mmol) and 6-bromo-7-fluoro-2-iodoquinoline (**C23_B**, 760 mg, 2.159 mmol) in toluene (5 mL) at room temperature and the mixture was stirred at 100°C for 8 h. The mixture was cooled, diluted with ethyl acetate (10 mL), washed with brine (saturated, 3 x 15 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with EtOAc/petroleum ether = 0-10% to give 6-bromo-2-cyclopropyl-7-fluoroquinoline (**C23_C**). LCMS (ESI) calc'd for C₁₂H₉BrFN [M+H]⁺: 266.0, found: 267.7.

Step 3: Preparation of (2-cyclopropyl-7-fluoroquinolin-6-yl)boronic acid (C23**):** *n*BuLi (2.5 M, 1.5 mL, 3.75 mmol) was added to a stirred mixture of triisopropyl borate (424 mg, 2.255 mmol), and 6-bromo-2-cyclopropyl-7-fluoroquinoline (**C23_C**, 300 mg, 1.127 mmol) in THF (2 mL) at -78°C and the mixture was stirred at room temperature for 4 h. Aqueous ammonium chloride (20 %, 10 mL) was added and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with brine (saturated, 15 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with MeOH/DCM = 0-20% to give (2-cyclopropyl-7-fluoroquinolin-6-yl)boronic acid (**C23**). LCMS (ESI) calc'd for C₁₂H₁₁BFNO₂ [M+H]⁺: 232.1, found: 231.7.

Example 40

Preparation of Intermediate C25



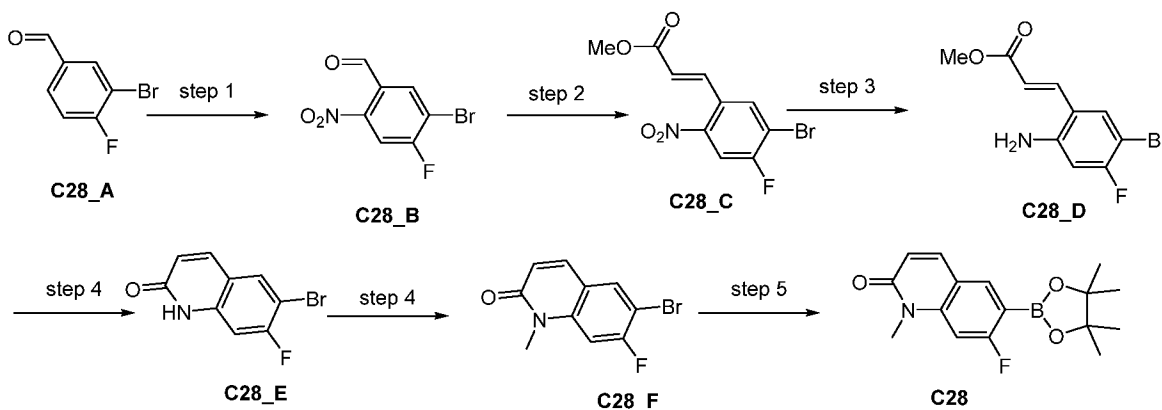
Step 1: Preparation of 6-bromo-7-chloro-2-methylquinoline (C25_B**):** (*E*)-but-2-enal (2.03 g, 29.1 mmol) was added dropwise to a stirred mixture of 4-bromo-3-chloroaniline (**C25_A**, 4 g, 19.37 mmol) and conc. HCl (12.7 mL, 155 mmol) in water (4.0 mL) at 110°C and the mixture

was stirred at 110°C for 2 h. Then the mixture was neutralized with NH₄OH until the pH reached 7. The organic phase was extracted with DCM (50 mL*3). The combined organic phases were dried over MgSO₄, filtered and concentrated. The crude product was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.1 TFA, to give 6-bromo-7-chloro-2-methylquinoline (**C25_B**). LCMS (ESI) calc'd for C₁₀H₇BrClN [M+H]⁺: 255.9, found: 258.0.

Step 2: Preparation of 7-chloro-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (C25**):** PdCl₂(dppf) (61 mg, 0.084 mmol) was added to a stirred mixture of KOAc (494 mg, 5.03 mmol), BPD (724 mg, 2.85 mmol), and 6-bromo-7-chloro-2-methylquinoline (**C25_B**, 430 mg, 1.676 mmol) in dioxane (10 mL) at room temperature and the mixture was stirred at 70°C for 1 h under N₂. The solvent was evaporated under reduced pressure. The residue was purified by silica gel, eluting with EtOAc/petroleum ether = 1/1 to give 7-chloro-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (**C25**). LCMS (ESI) calc'd for C₁₆H₁₉BClNO₂ [M+H]⁺: 304.1, found: 304.1.

Example 41

Preparation of Intermediate **C28**



Step 1: Preparation of 5-bromo-4-fluoro-2-nitrobenzaldehyde (C28_B**):** 3-bromo-4-fluorobenzaldehyde (**C28_A**, 9.00 g, 44.34 mmol) was added to a stirred solution of concentrated nitric acid (67percent, 6.0 mL, 88.65 mmol) in concentrated sulfuric acid (54.0 mL) at 0°C. After the addition was complete, the ice bath was removed and the reaction was allowed to stir at room temperature for 5 h. Then the mixture was poured into ice and filtered to give of 5-bromo-4-fluoro-2-nitrobenzaldehyde (**C28_B**) which was used to the next step without further purification.

Step 2: Preparation of (E)-methyl 3-(5-bromo-4-fluoro-2-nitrophenyl)acrylate (C28_C**):** 5-bromo-4-fluoro-2-nitrobenzaldehyde (**C28_B**, 10.00 g, 40.00 mol) and

(methoxycarbonylmethylene) triphenylphosphorane (14.80 g, 44.00 mmol) are mixed in toluene (40 mL) and stirred at 120°C for 30 min. After it was cooled to room temperature, the mixture was diluted with water (200 mL) and extracted with ethyl acetate (200 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica chromatography (EtOAc/petroleum ether = 1/5 to 1/4) to afford the title compound (**C28_C**).

Step 3: Preparation of (E)-methyl 3-(2-amino-5-bromo-4-fluorophenyl)acrylate (C28_D): A mixture of (E)-methyl 3-(5-bromo-4-fluoro-2-nitrophenyl)acrylate (**C28_C**, 6.68 g, 22.00 mmol), Fe power (5.43 g, 96.80 mmol), and NH₄Cl (106 mg, 9.68 mmol) in EtOH /H₂O (80 mL / 40 mL) was stirred under reflux conditions under N₂ for 2 h. The reaction was cooled to room temperature, filtered through a Celite pad, washed with EtOH, and the resulting elute was concentrated to give (E)-methyl 3-(2-amino-5-bromo-4-fluorophenyl)acrylate (**C28_D**) which was used in next step without further purification. LCMS (ESI) calc'd for C₁₀H₁₀BrFNO₂ [M+Na]⁺: 274.0, found: 276.0

Step 4: Preparation of 6-bromo-7-fluoroquinolin-2(1H)-one (C28_E): A mixture of (E)-methyl 3-(2-amino-5-bromo-4-fluorophenyl)acrylate (**C28_D**, 2.50 g, 9.12 mmol) in THF (10.0 mL) and 3 M hydrochloric acid (10.0 mL) was heated at 65°C for 18 h. The mixture was cooled to room temperature and the precipitate was filtered, washed with water and dried *in vacuo* to give 6-bromo-7-fluoroquinolin-2(1H)-one (**C28_E**). LCMS (ESI) calc'd for C₁₁H₈BrFN₂O [M+H]⁺: 242.0, found: 242.0. ¹H NMR (400 MHz, DMSO-d₆) δ 11.89 (s, 1H), 8.07 (d, *J* = 7.50 Hz, 1H), 7.84 (d, *J* = 9.70 Hz, 1H), 7.14 (d, *J* = 9.92 Hz, 1H), 6.48 (d, *J* = 9.70 Hz, 1H).

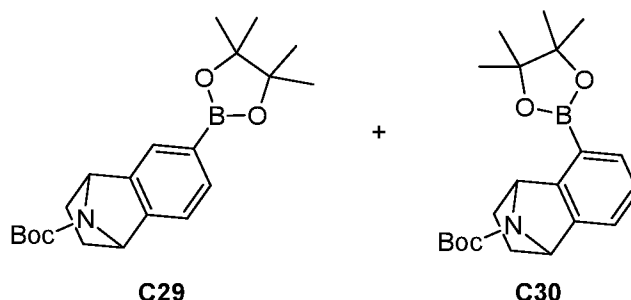
Step 5: Preparation of 6-bromo-7-fluoro-1-methylquinolin-2(1H)-one (C28_F): NaH (206 mg, 5.14 mmol) was added to a stirred solution of 6-bromo-7-fluoroquinolin-2(1H)-one (**C28_E**, 830 mg, 3.43 mmol) at room temperature. Then iodomethane (1660 mg, 11.70 mmol) was added at room temperature and the mixture was stirred at room temperature for 0.5 h. The mixture were poured into ice water (50 mL) and the precipitate was collected with filtration and the filter cake was washed with water (100 mL) and dried to give 6-bromo-7-fluoro-1-methylquinolin-2(1H)-one (**C28_F**). LCMS (ESI) calc'd for C₁₀H₇BrFNO [M+H]⁺: 256.0, found: 258.0.

Step 6: Preparation of compound 7-fluoro-1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-2(1H)-one (C28): Potassium acetate (834 mg, 8.49 mmol) and BPD (3451 mg, 13.59 mmol) were added to a stirred mixture of 6-bromo-7-fluoro-1-methylquinolin-2(1H)-one (**C28_F**, 870 mg, 3.40 mmol) in dioxane (10 mL) at room temperature, the mixture was replaced with N₂, then PdCl₂(dppf) (124 mg, 0.170 mmol) was added. The mixture was heated with stirring at 100°C for 24 h. The reaction solution was concentrated and the residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 5:1-2:1. The

obtained product was washed with petroleum ether (10 mL) to give 7-fluoro-1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-2(1*H*)-one (**C28_F**). LCMS (ESI) calc'd for $C_{16}H_{19}BFNO_3$ $[M+H]^+$: 304.1, found: 304.2.

Example 42

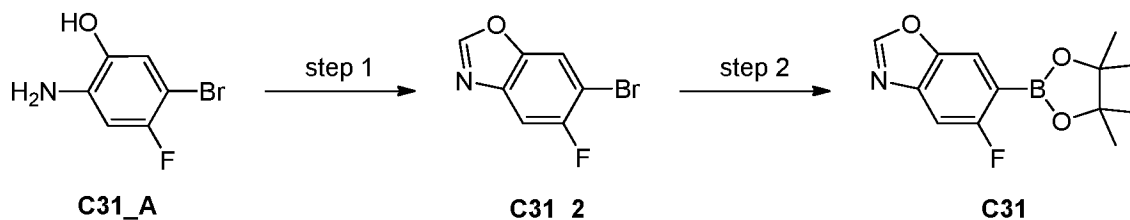
Preparation of Intermediates **C29** and **C30**



To a degassed solution of tert-butyl 1,2,3,4-tetrahydro-1,4-epiminonaphthalene-9-carboxylate (100 mg, 0.408 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (311 mg, 1.223 mmol) and (*R*)-(+)-2,2'-bis[di(3,5-xylyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl (28.3 mg, 0.041 mmol) in hexane (3.0 mL) was added (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (13.51 mg, 0.020 mmol) under N_2 . The mixture was stirred at 90°C for 16 h under N_2 and then concentrated. The residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.225% $HCOOH$, to give tert-butyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,4-epiminonaphthalene-9-carboxylate (**C29**). LCMS (ESI) calc'd for $C_{21}H_{30}BNO_4$ $[M+H]^+$: 372.2, found: 316.1. And tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,4-epiminonaphthalene-9-carboxylate (**C30**). LCMS (ESI) calc'd for $C_{21}H_{30}BNO_4$ $[M+H]^+$: 372.2, found: 272.1

Example 43

Preparation of Intermediate **C31**



Step 1: 6-bromo-5-fluorobenzo[d]oxazole (C31_B**):** A mixture of 2-amino-5-bromo-4-fluorophenol (**C31_A**, 1.2 g, 5.82 mmol) and triethoxymethane (10 mL, 60.1 mmol) was stirred at 100°C for 10 h. The reaction mixture was cooled to room temperature and concentrated. The residue was purified by column chromatography on silica gel using eluent 0-20 % ethyl acetate in petroleum ether to give 6-bromo-5-fluorobenzo[d]oxazole (**C31_B**). LCMS (ESI) calc'd for

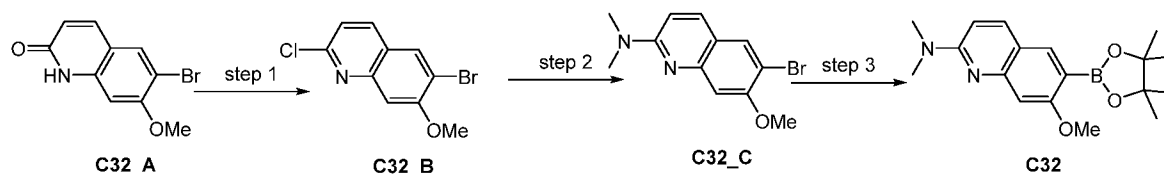
C_7H_3BrFNO $[M+H]^+$: 215.9, found: 215.5. ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.80 (d, J = 5.51 Hz, 1H), 7.54 (d, J = 7.94 Hz, 1H).

Step 2: 5-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]oxazole (C31):

Potassium acetate (518 mg, 5.28 mmol) and BPD (536 mg, 2.111 mmol) were added to a stirred mixture of 6-bromo-5-fluorobenzo[d]oxazole (C31_B, 380 mg, 1.759 mmol) in 1,4-dioxane (5 mL) at room temperature, the mixture was replaced with N_2 , and $PdCl_2(dppf)$ (129 mg, 0.176 mmol) was added. The mixture was heated with stirring at 80°C for 2 h under N_2 . The mixture was cooled to room temperature, water (10 mL) was added and the mixture was extracted with ethyl acetate (2 x 10 mL). The combined organic fractions were washed with brine (saturated, 10 mL), dried (Na_2SO_4), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 0-50% to give 5-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]oxazole (C31). LCMS (ESI) calc'd for $C_{13}H_{15}BFNO_3$ $[M+H]^+$: 264.1, found: 264.0.

Example 44

Preparation of Intermediate C32



Step 1: Preparation of 6-bromo-2-chloro-7-methoxyquinoline (C32_B): 6-Bromo-7-

methoxyquinolin-2(1H)-one (C32_A, described in WO2016/34512 A1, 2.47 g, 9.72 mmol) was added to $POCl_3$ (14.8 mL, 159 mmol) slowly in portions at rt and the mixture was stirred at 110°C for 2.5 h. The mixture was cooled to rt and poured into warm water (200 mL) slowly with vigorous stirring. $NaOH$ (solid) was added to adjust the pH to between 7 and 8 and the mixture was extracted with EtOAc (100 mL x 2). The combined organic fractions were washed with brine (saturated, 100 mL), dried (Na_2SO_4), filtered and the solvent was evaporated under reduced pressure to give 6-bromo-2-chloro-7-methoxyquinoline (C32_B). LCMS (ESI) calc'd for $C_{10}H_7BrClNO$ $[M+H]^+$: 271.9, found: 273.7. ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.39 (s, 1H), 7.29 (d, J = 8.6 Hz, 1H), 4.03 (s, 3H).

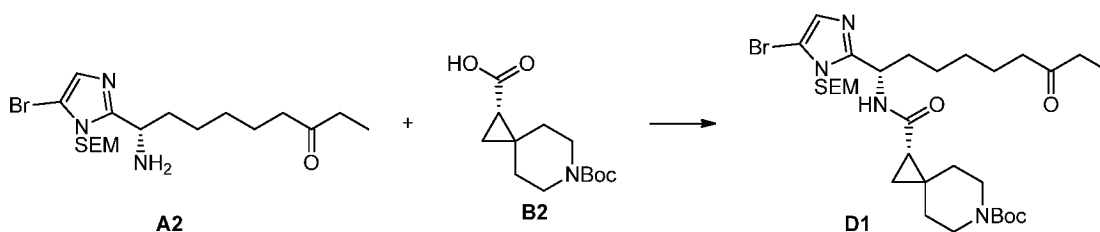
Step 2: Preparation of 6-bromo-7-methoxy-N,N-dimethylquinolin-2-amine (C32_C): A mixture of 6-bromo-2-chloro-7-methoxyquinoline (C32_B, 900 mg, 3.30 mmol), dimethylamine hydrochloride (539 mg, 6.60 mmol) and Cs_2CO_3 (3766 mg, 11.56 mmol) in DMF (20 mL) was stirred at 90°C for 12 h. The combined mixture was cooled to rt, water (250 mL) was added and the mixture was extracted with ethyl acetate (100 x 2 mL). The combined organic fractions were

washed with brine (saturated, 100 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 8:1 to give 6-bromo-7-methoxy-*N,N*-dimethylquinolin-2-amine (**C32_C**). LCMS (ESI) calc'd for C₁₂H₁₃BrN₂O [M+H]⁺: 281.0, found: 281.0. ¹H NMR (400 MHz, CDCl₃) δ 7.76 (s, 1H), 7.71 (d, *J* = 9.2 Hz, 1H), 7.12 (s, 1H), 6.75 (d, *J* = 9.2 Hz, 1H), 4.00 (s, 3H), 3.22 (s, 6H).

Step 3: Preparation of 7-methoxy-*N,N*-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-2-amine (**C32**): PdCl₂(dppf) (195 mg, 0.267 mmol) was added to a stirring mixture of 6-bromo-7-methoxy-*N,N*-dimethylquinolin-2-amine (**C32_C**, 750 mg, 2.67 mmol), BPD (1355 mg, 5.34 mmol) and potassium acetate (785 mg, 8.00 mmol) in 1,4-dioxane (25 mL) at rt and the mixture was stirred at 80°C under N₂ atmosphere for 12 h. The combined mixture was cooled to rt and filtered through Celite. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 33%-67% to give 7-methoxy-*N,N*-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-2-amine (**C32**). LCMS (ESI) calc'd for C₁₈H₂₅BN₂O₃ [M+H]⁺: 329.2, found: 329.2.

Example 45

Preparation of Intermediate **D1**

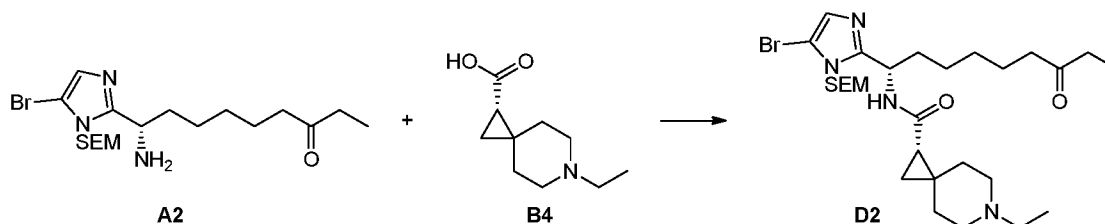


T3P (50% in EtOAc, 14.71 g, 23.12 mmol) was added to a stirred mixture of (*S*)-9-amino-9-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)nonan-3-one (**A2**, 5 g, 11.56 mmol), (*S*)-6-(tert-butoxycarbonyl)-6-azaspiro[2.5]octane-1-carboxylic acid (**B2**, 3.54 g, 13.87 mmol) and DIPEA (6 mL, 34.4 mmol) in THF (50 mL) at room temperature and the mixture was stirred at room temperature for 18 h. The mixture was quenched with water (50 mL) and the mixture was extracted with ethyl acetate (4 x 50 mL). The combined organic fractions were washed with brine (saturated, 2 x 40 mL), dried Na₂SO₄, filtered and the solvent was evaporated under reduced pressure. The residue, which was combined with another residue from the same reaction starting from 1 g amine, was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 1: 1 to give (*S*)-tert-butyl 1-(((*S*)-1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-

azaspiro[2.5]octane-6-carboxylate (**D1**). LCMS (ESI) calc'd for $C_{31}H_{53}BrN_4O_5Si$ $[M+H]^+$: 669.3, found: 670.8

Example 46

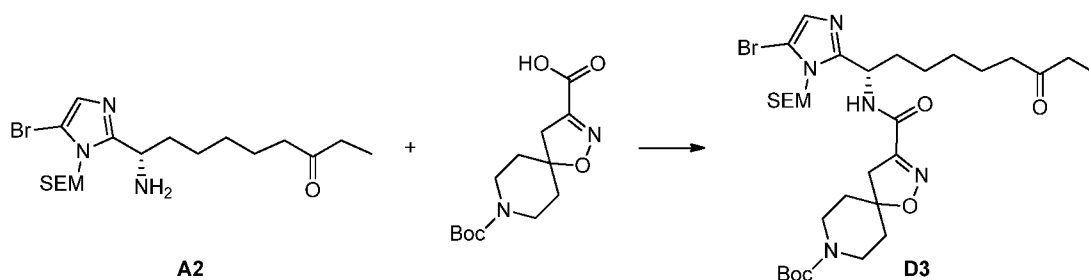
Preparation of Intermediate **D2**



HATU (0.967 g, 2.54 mmol) and Et_3N (1.6 mL, 11.48 mmol) were added to a stirred mixture of (*S*)-6-ethyl-6-azaspiro[2.5]octane-1-carboxylic acid (**B4**, 0.466 g, 2.54 mmol) in DMF (15 mL) at room temperature and the mixture was stirred at room temperature for 15 min. Then (*S*)-9-amino-9-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)nonan-3-one (**A2**, 1.0 g, 2.312 mmol) was added. The mixture was stirred at room temperature for 1 h. Water (10 mL) was added and it was extracted with ethyl acetate (3 x 10 mL). The combined organic fractions were washed with brine (saturated, 1 x 10 mL) and dried with Na_2SO_4 , filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (ISCORF75; Sepa flash column), eluting with DCM / MeOH = 1~10 / 1 to give (*S*)-*N*-((*S*)-1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-ethyl-6-azaspiro[2.5]octane-1-carboxamide (**D2**). LCMS (ESI) calc'd for $C_{28}H_{49}BrN_4O_3Si$ $[M+H]^+$: 597.3 and 599.3, found: 597.3 and 599.3. ^1H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.15-6.27 (m, 1H), 5.54-5.66 (m, 1H), 5.08-5.17 (m, 1H), 5.01-5.07 (m, 1H), 3.44-3.56 (m, 2H), 2.47-2.56 (m, 1H), 2.27-2.45 (m, 8H), 1.74-2.01 (m, 4H), 1.62-1.73 (m, 1H), 1.44-1.61 (m, 3H), 1.18-1.42 (m, 6H), 1.11-1.17 (m, 1H), 1.06 (s, 6H), 0.83-0.97 (m, 2H), 0.74-0.82 (m, 1H), 0.00 (s, 9H).

Example 47

Preparation of Intermediate **D3**

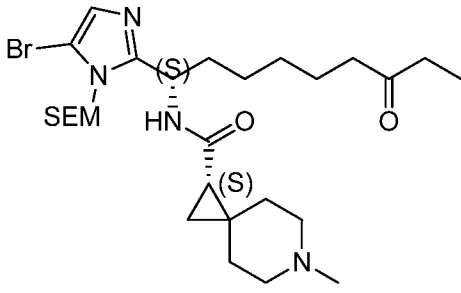
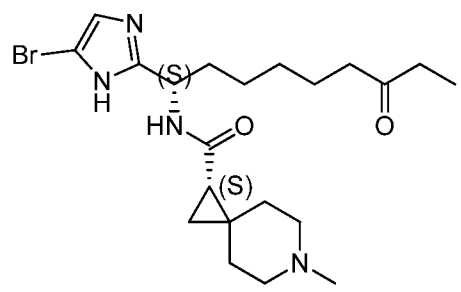
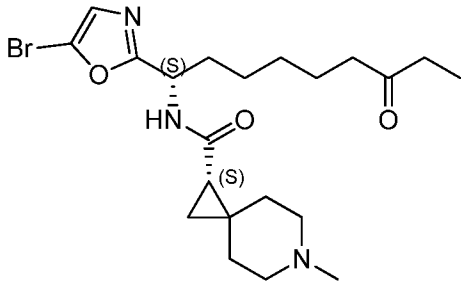


EDCI (1.618 g, 8.44 mmol) and 1*H*-benzo[*d*][1,2,3]triazol-1-ol (1.141 g, 8.44 mmol)

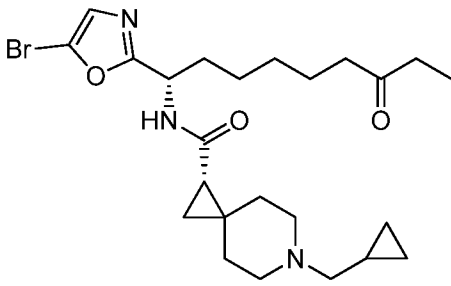
were added to a stirred mixture of 8-(tert-butoxycarbonyl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxylic acid (2 g, 7.03 mmol) and DIPEA (1.843 mL, 10.55 mmol) in DMF (20 mL) at room temperature, then (*S*)-9-amino-9-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)nonan-3-one (**A2**, 3.04 g, 7.03 mmol) was added. The mixture was kept at 20°C for 1 h.

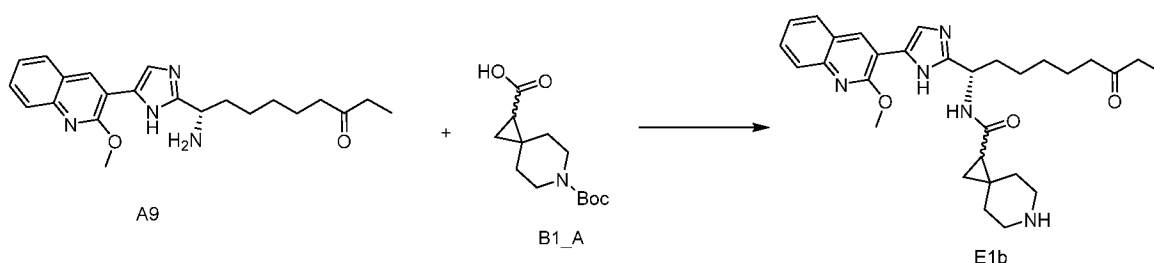
- 5 Water (50 mL) was added to the reaction solution and then it was extracted with EtOAc (50 mLx2). The organic phase was washed with brine (50 mL) and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with EtOAc: petroleum ether = 1:1 to give (*S*)-tert-butyl 3-((1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamoyl)-1-oxa-2,8-
- 10 diazaspiro[4.5]dec-2-ene-8-carboxylate (**D3**). LCMS (ESI) calc'd for C₃₁H₅₂BrN₅O₆Si [M+H]⁺: 698.3, found: 700.3

The following intermediates were prepared using similar procedures as described for intermediates **D1**, **D2** and **D3**

Intermediate ID	Structures	Observed [M+H] ⁺
D4		583.2
D5		455.1
D6		456.2

D7		470.2
D8		540.2
D9		571.2
D10		623.3
D11		480.2

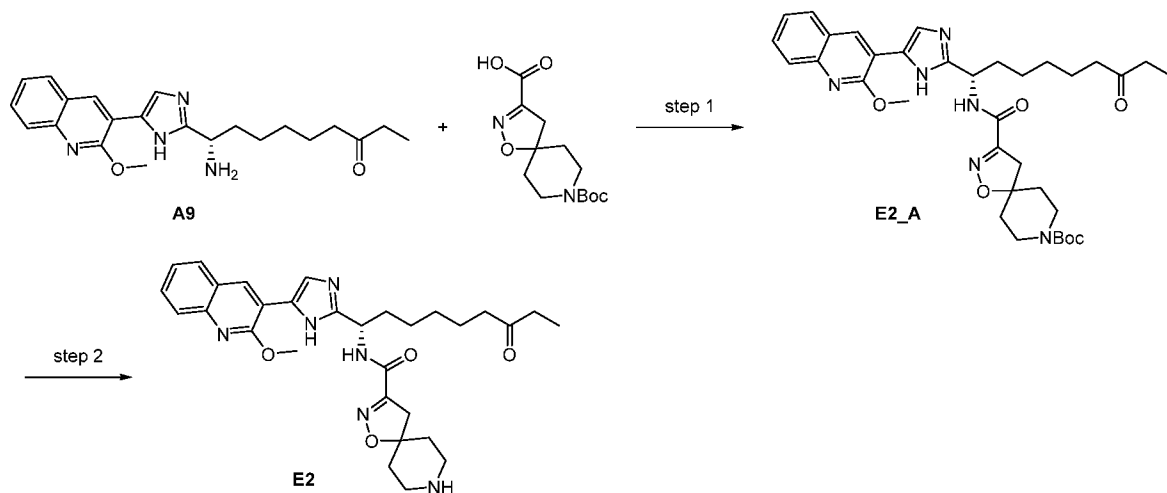
D12		496.2
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Example 48**Preparation of Intermediate E1b**

To a 40 mL pressure vial with pressure release cap was added **B1_A** (266 mg, 1.041 mmol), HATU (429 mg, 1.128 mmol), **A9** (330 mg, 0.867 mmol), DMF (8673 μ l), and DIPEA (757 μ l, 4.34 mmol). The reaction was stirred at 25°C for 4 hours. The product was purified by C18 chromatography (CH₃CN in water with 0.1% TFA: 0% to 90%) to give tert-butyl 1-(((S)-1-(5-(2-methoxyquinolin-3-yl)-1H-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate, TFA. To a 250 flask was added tert-butyl 1-(((S)-1-(5-(2-methoxyquinolin-3-yl)-1H-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (538 mg, 0.871 mmol), CH₂Cl₂ (4354 μ l), and 2,2,2-trifluoroacetic acid (1334 μ l, 17.42 mmol). The reaction was stirred at 25°C for 2 hours. The reaction mixture was concentrated and dried under vacuum for 16 hours to give **E1b**. LCMS (ESI) calc'd for C₃₀H₃₉N₅O₃: 517.3; found: 518.4 [M+H]⁺.

The following intermediates were prepared using similar procedures as described for intermediate **E1b**

Intermediate ID	Structures	Observed $[M+H]^+$
E1a		518.4
E4		519.3
E38		520.3

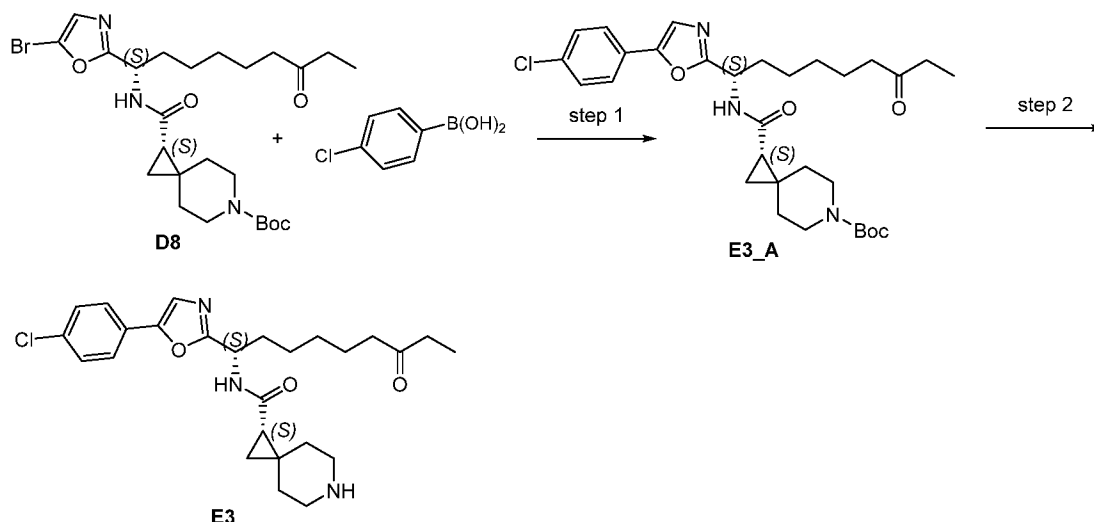
Example 49**Preparation of Intermediate E2**

Step 1: Preparation of (S)-tert-butyl 3-((1-(5-(2-methoxyquinolin-3-yl)-1H-imidazol-2-yl)-7-oxononyl)carbamoyl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylate (**E2_A**): Et₃N (0.2 mL, 1.435 mmol), and T₃P (301 mg, 0.473 mmol) was added to a stirred mixture of 8-(tert-butoxycarbonyl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxylic acid (120 mg, 0.422 mmol), and (S)-9-amino-9-(5-(2-methoxyquinolin-3-yl)-1H-imidazol-2-yl)nonan-3-one (**A9**, 150 mg, 0.394 mmol) in DMF (2 mL) at 20°C and the mixture was stirred at 20°C for 12 h. The mixture was diluted with ethyl acetate (15 mL), washed with brine (saturated, 4 x 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 50-100% to give (S)-tert-butyl 3-((1-(5-(2-methoxyquinolin-3-yl)-1H-imidazol-2-yl)-7-oxononyl)carbamoyl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylate (**E2_A**). LCMS (ESI) calc'd for C₃₅H₄₆N₆O₆ [M+H]⁺: 647.3, found: 647.4.

Step 2: Preparation of (S)-N-(1-(5-(2-methoxyquinolin-3-yl)-1H-imidazol-2-yl)-7-oxononyl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide (**E2**): TFA (0.1 mL, 1.298 mmol) was added to a stirred mixture of (S)-tert-butyl 3-((1-(5-(2-methoxyquinolin-3-yl)-1H-imidazol-2-yl)-7-oxononyl)carbamoyl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylate (**E2_A**, 210 mg, 0.325 mmol) in DCM (2 mL) at 10°C and the mixture was stirred at 10°C for 1 h. Most of the DCM was removed, and it was concentrated to give (S)-N-(1-(5-(2-methoxyquinolin-3-yl)-1H-imidazol-2-yl)-7-oxononyl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide (**E2**) which was used to the next step without further purification. LCMS (ESI) calc'd for C₃₀H₃₈N₆O₄ [M+H]⁺: 547.3, found: 547.3.

Example 50

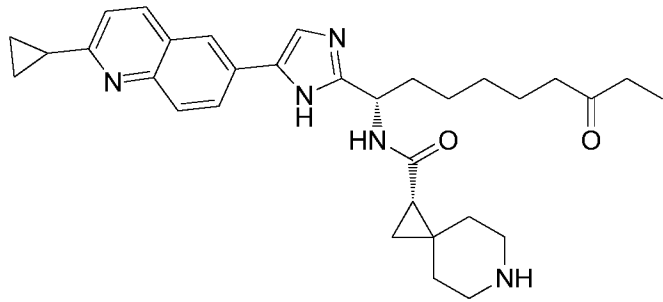
Preparation of Intermediate **E3**

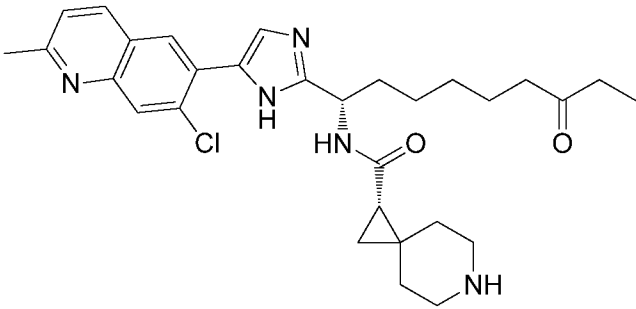
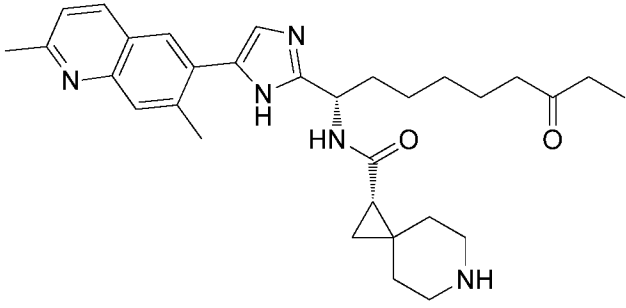
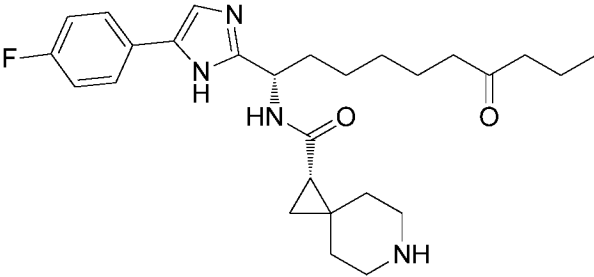
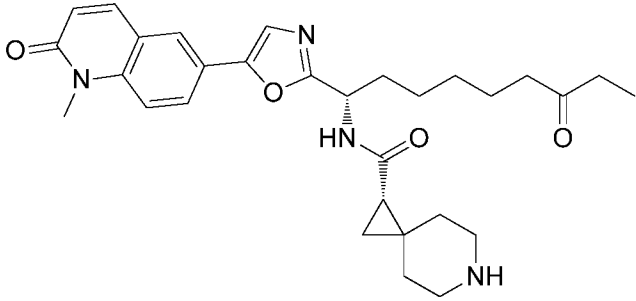
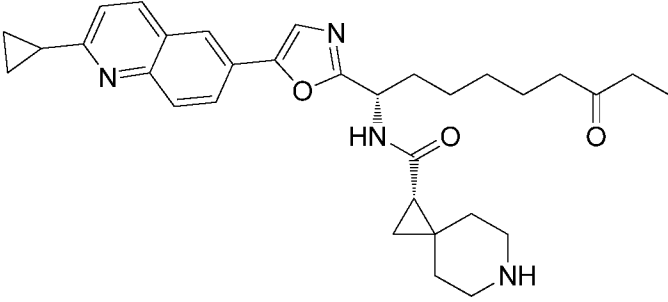


Step 1: Preparation of (S)-tert-butyl 1-(((S)-1-(5-(4-chlorophenyl)oxazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**E3_A**): PdCl₂(DTBPF) (400 mg, 0.614 mmol) was added to a stirred mixture of K₂CO₃ (2685 mg, 19.43 mmol), (4-chlorophenyl)boronic acid (1013 mg, 6.48 mmol), and (S)-tert-butyl 1-(((S)-1-(5-bromooxazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**D8**, 3.5 g, 6.48 mmol) in THF (15 mL) at room temperature and the mixture was stirred at 70°C for 6 h. The mixture was cooled, diluted with ethyl acetate (30 mL), washed with water (3 x 20 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with EtOAc/petroleum ether = 0 - 50% to give (S)-tert-butyl 1-(((S)-1-(5-(4-chlorophenyl)oxazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**E3_A**). LCMS (ESI) calc'd for C₃₁H₄₂ClN₃O₅ [M+H]⁺: 572.3, found: 572.3. ¹H NMR (400 MHz, CDCl₃) δ 7.59-7.72 (m, 1H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.37-7.45 (m, 2H), 7.24 (s, 1H), 5.22-5.33 (m, 1H), 3.46 (d, *J* = 3.5 Hz, 2H), 3.34 (brs, 2H), 2.33-2.47 (m, 4H), 1.95-2.03 (m, 1H), 1.79-1.92 (m, 1H), 1.50-1.71 (m, 6H), 1.43 (brs, 9H), 1.26-1.39 (m, 6H), 1.04 (t, *J* = 7.4 Hz, 3H), 0.88 (dd, *J* = 4.5, 7.63 Hz, 1H).

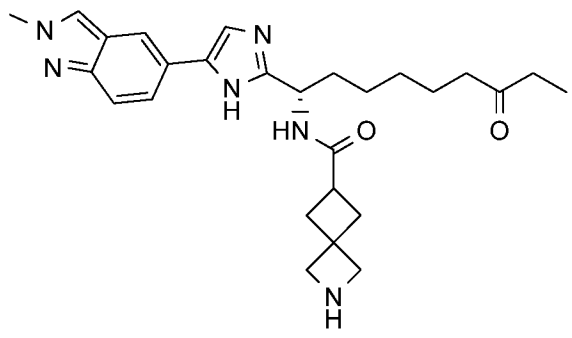
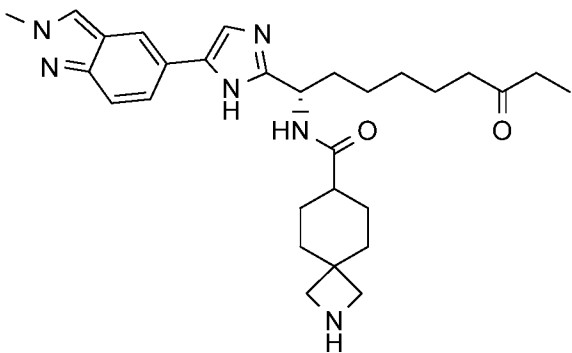
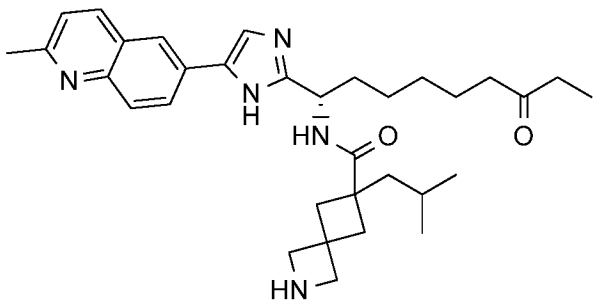
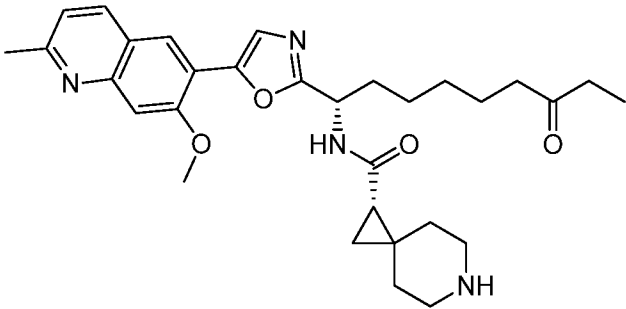
Step 2: Preparation of (S)-N-((S)-1-(5-(4-chlorophenyl)oxazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**E3**): TFA (5 mL, 64.9 mmol) was added to a stirred mixture of (S)-tert-butyl 1-(((S)-1-(5-(4-chlorophenyl)oxazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**E3_A**, 3.0 g, 5.24 mmol) in DCM (15 mL) at room temperature and the mixture was stirred at room temperature for 2 h. Most of the DCM was removed, and it was concentrated to give (S)-N-((S)-1-(5-(4-chlorophenyl)oxazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**E3**). LCMS (ESI) calc'd for C₂₆H₃₄ClN₃O₃ [M+H]⁺: 472.2, found: 472.2

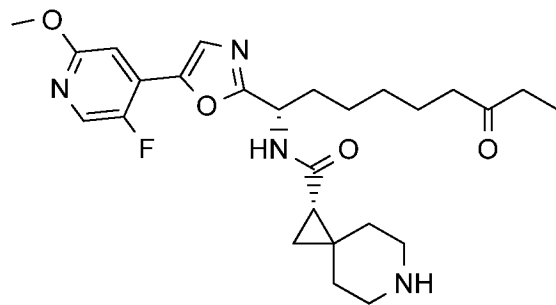
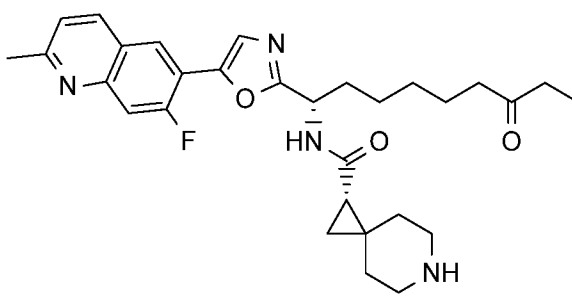
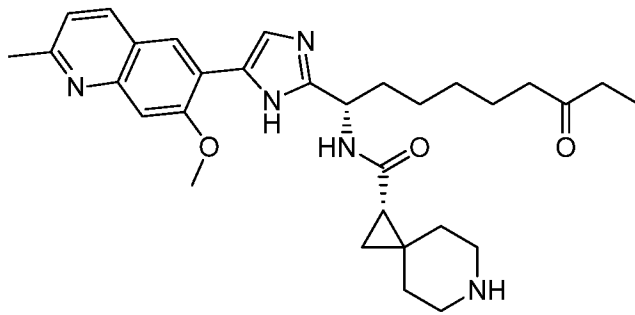
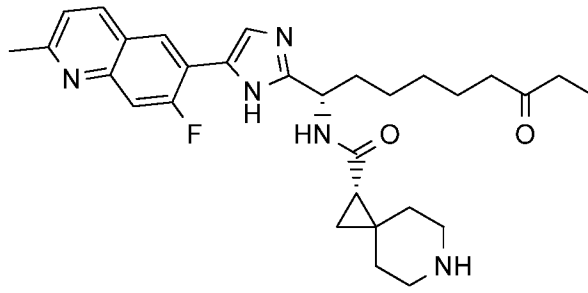
The following intermediates were prepared using similar procedures as described for intermediates **E1**, **E2** and **E3**

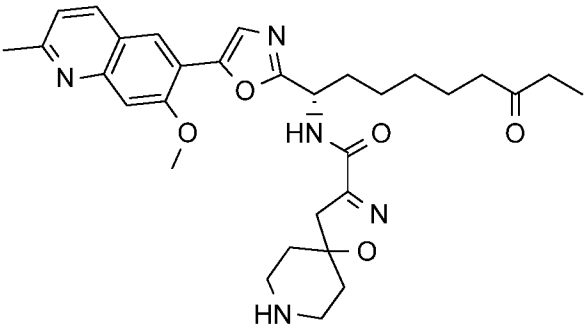
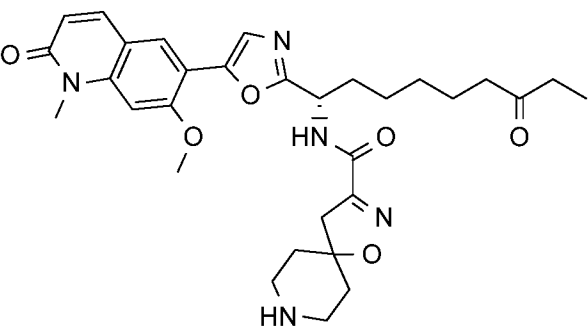
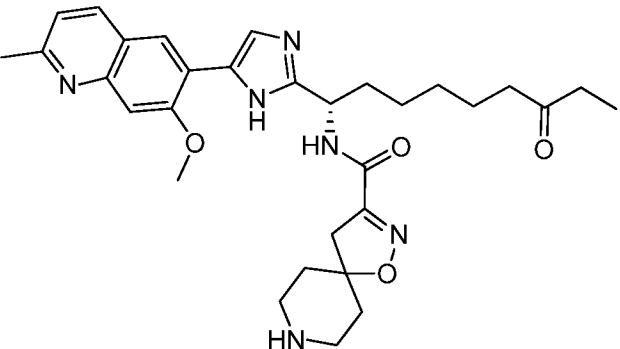
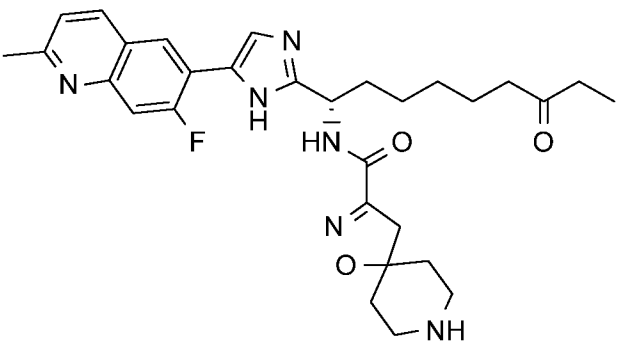
ID	Structure	Observed [M+H] ⁺
E5		528.3

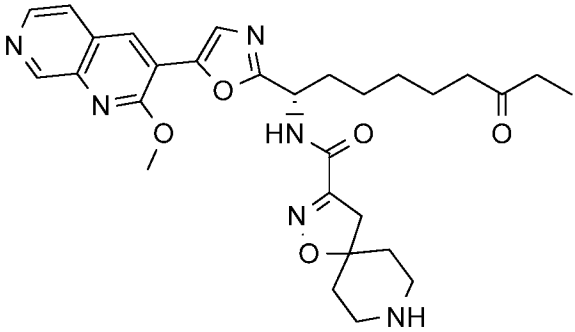
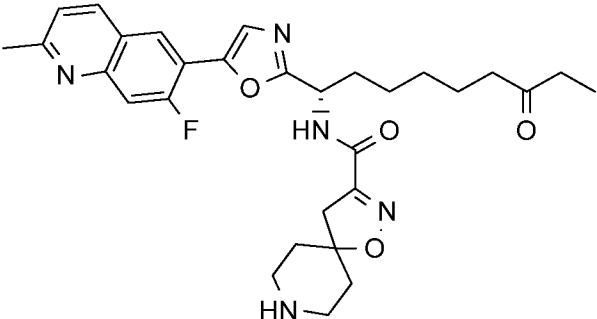
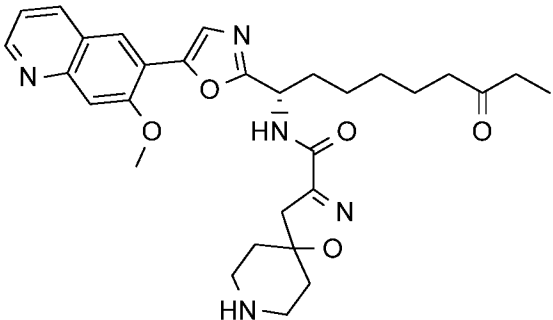
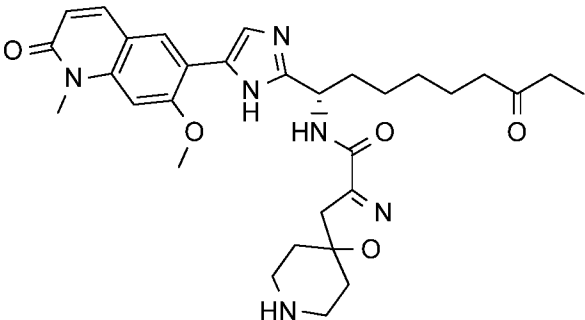
E6		536.3
E7		516.3
E8		469.3
E9		519.4
E10		529.3

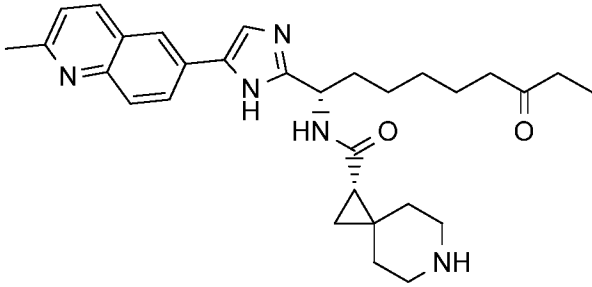
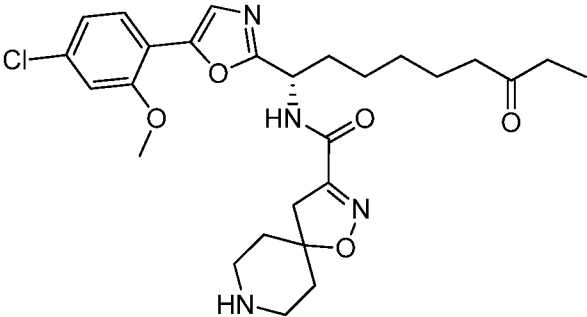
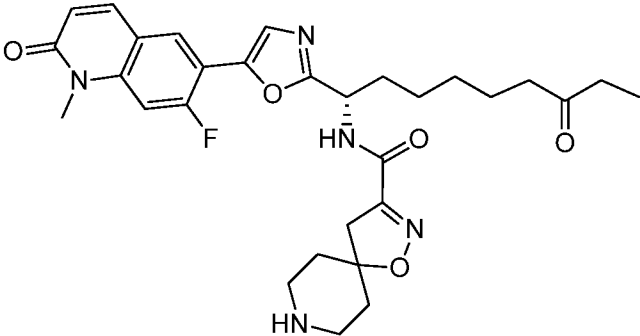
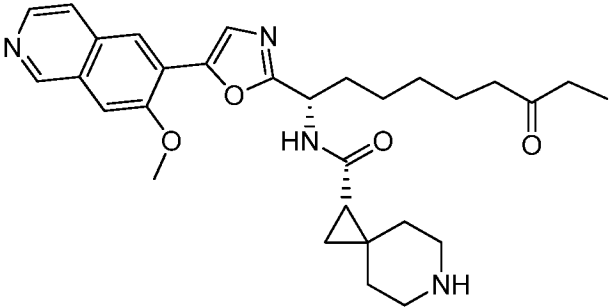
E11		549.3
E12		558.3
E13		505.4
E14		520.4

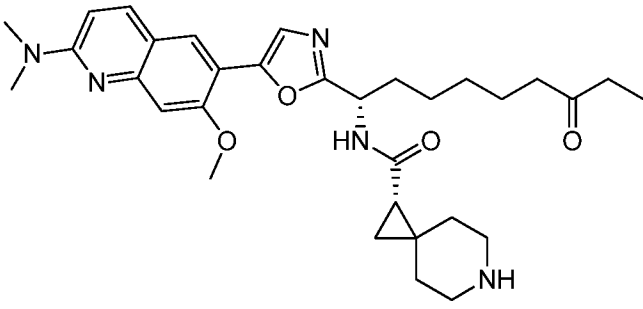
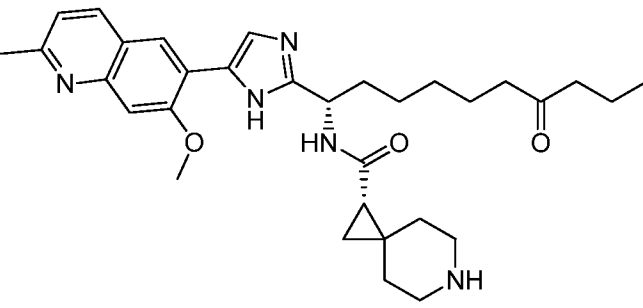
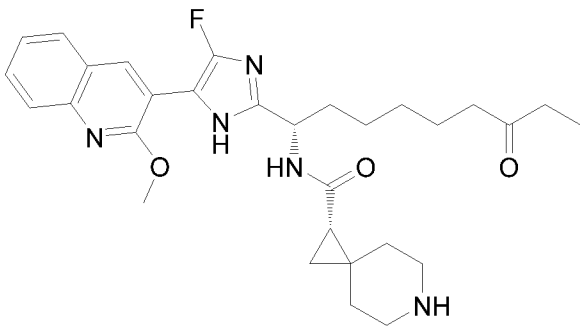
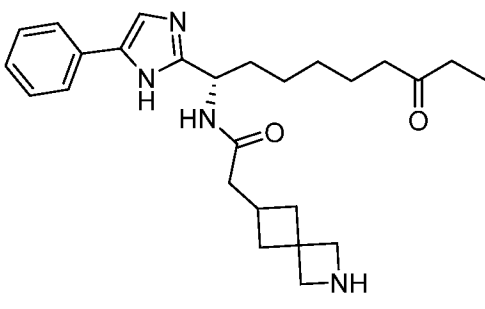
E15		477.2
E16		505.1
E17		544.4
E18		533.4

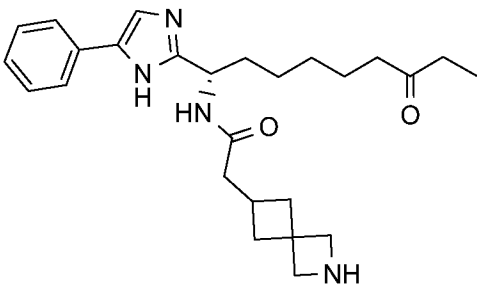
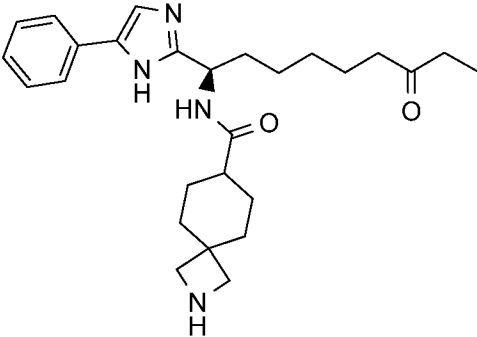
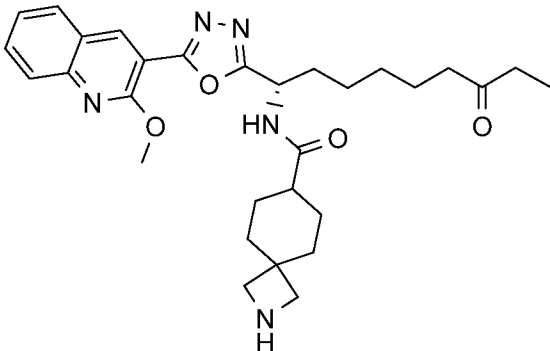
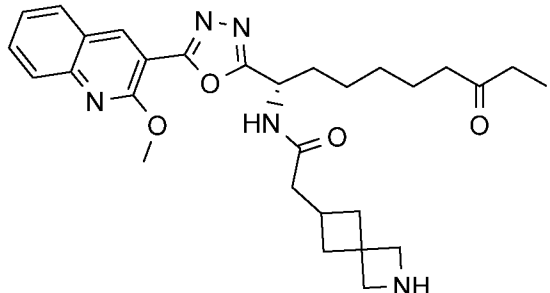
E19		487.3
E20		521.4
E21		532.3
E22		520.4

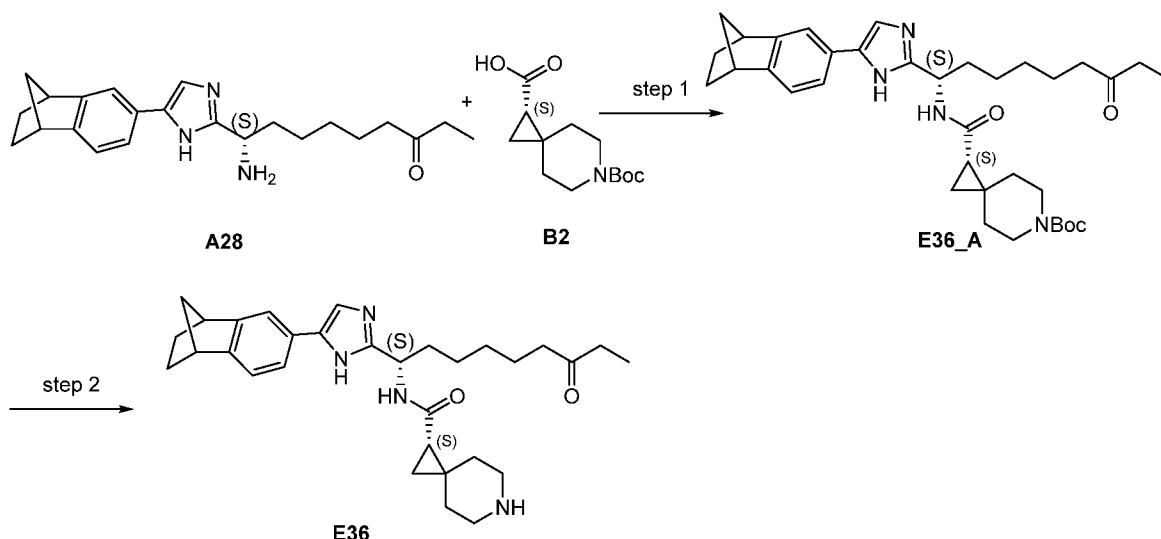
E23		562.4
E24		578.4
E24		561.4
E25		549.3

E26		549.3
E27		550.3
E28		548.1
E29		577.4

E30		502.3
E31		531.3
E32		566.3
E33		519.3

E34		562.4
E35		546.3
E37		536.3
E39		437.3

297		437.0
298		451.4
299		534.5
301		520.4

Example 51**Preparation of Intermediate E36**

Step 1: Preparation of (S)-tert-butyl 1-(((S)-7-oxo-1-(5-((1R,4S)-1,2,3,4-tetrahydro-1,4-

methanonaphthalen-6-yl)-1H-imidazol-2-yl)nonyl)carbamoyl)-6-azaspiro[2.5]octane-6-

carboxylate (E36_A): The mixture of (S)-6-(tert-butoxycarbonyl)-6-azaspiro[2.5]octane-1-

carboxylic acid (**B2**, 64 mg, 0.251 mmol), HATU (100 mg, 0.263 mmol) and triethylamine (0.20 mL, 1.435 mmol) in DMF (10 mL) was stirred at rt for 10 min, then a mixture of (S)-9-amino-9-(5-((1R,4S)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)-1H-imidazol-2-yl)nonan-3-one

hydrochloride (**A28**, 100 mg, 0.249 mmol) in DMF (2 mL) was added. The resulting mixture was stirred at rt for 1 h under nitrogen atmosphere. The mixture combined with a same reaction from 50 mg amine was concentrated to remove DMF. The residue was purified by silica gel column flash chromatography, eluting with MeOH in DCM = 0~6% to give the title compound (**E36_A**). LCMS (ESI) calc'd for $C_{36}H_{50}N_4O_4$ $[M+H]^+$: 603.4 found: 603.4.

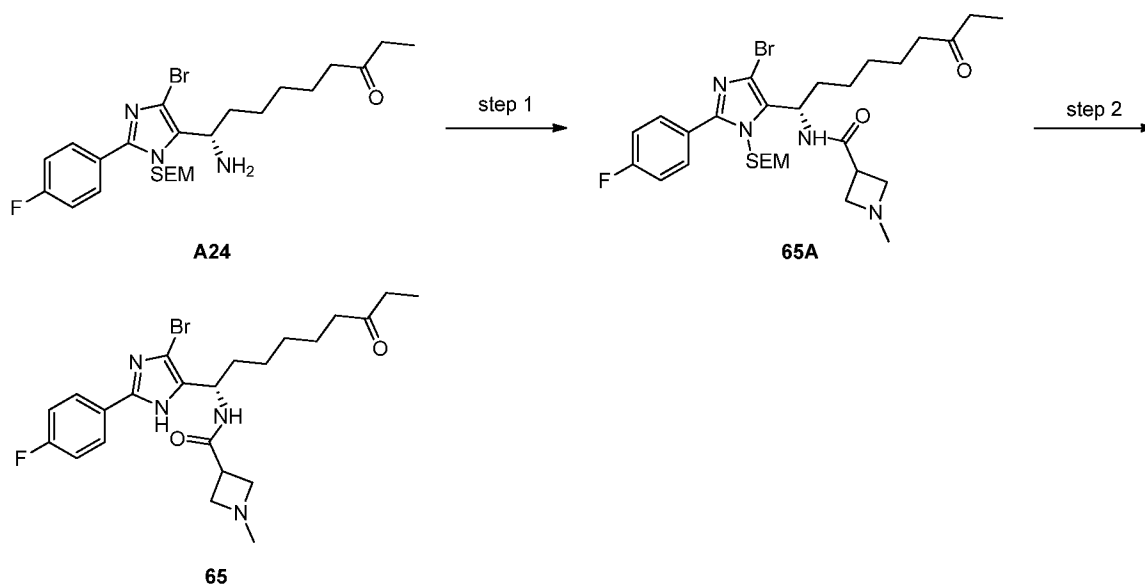
Step 2: Preparation of (S)-N-((S)-7-oxo-1-(5-((1R,4S)-1,2,3,4-tetrahydro-1,4-

methanonaphthalen-6-yl)-1H-imidazol-2-yl)nonyl)-6-azaspiro[2.5]octane-1-carboxamide (E36):

The mixture of (S)-tert-butyl 1-(((S)-7-oxo-1-(5-((1R,4S)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)-1H-imidazol-2-yl)nonyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**E36_A**, 200 mg, 0.332 mmol) and TFA (0.5 mL, 6.49 mmol) in DCM (5 mL) was stirred at rt for 2 h. The mixture was concentrated to remove solvent, the residue was triturated with EtOAc (20 mL), washed with aqueous $NaHCO_3$ (saturated, 2 x 5 mL), dried (Na_2SO_4), filtered and the solvent was evaporated under reduced pressure to give the title compound (**E36**). LCMS (ESI) calc'd for $C_{31}H_{42}N_4O_2$ $[M+H]^+$: 503.3, found: 525.2 $[M+Na]^+$.

Example 52

N-{(1*S*)-1-[4-bromo-2-(4-fluorophenyl)-1*H*-imidazol-5-yl]-7-oxononyl}-1-methylazetidine-3-carboxamide (**65**)



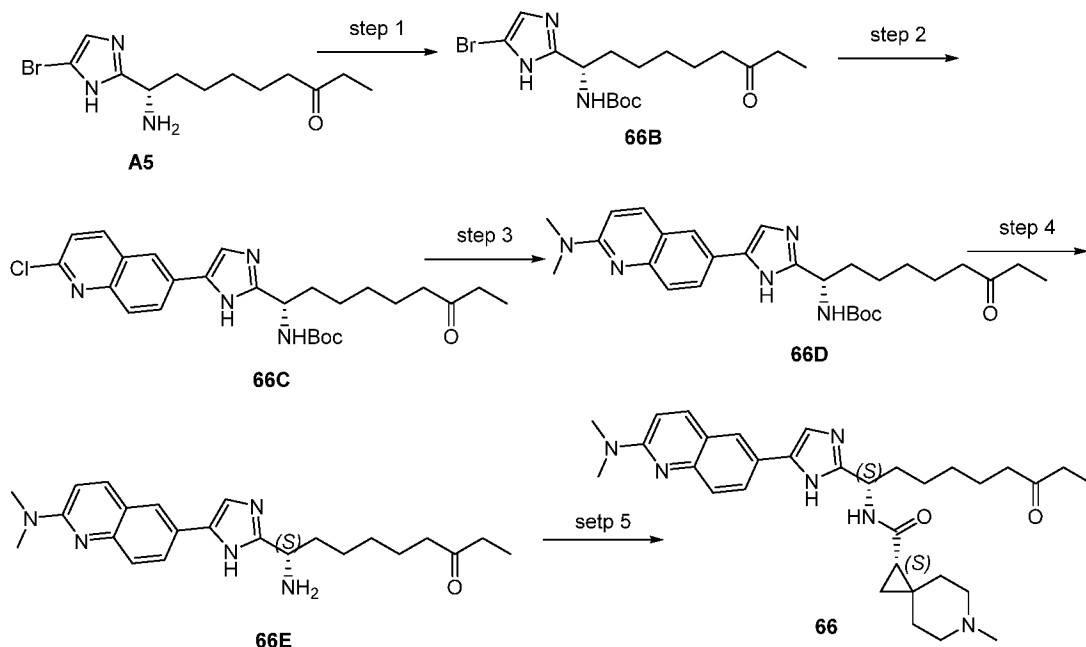
- 5 Step 1: Preparation of (*S*)-*N*-(1-(5-bromo-2-(4-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-4-yl)-7-oxononyl)-1-methylazetidine-3-
carboxamide (**65A**): Et₃N (0.349 mL, 2.507 mmol) was added to a stirred mixture of HATU
 (104 mg, 0.273 mmol), 1-methylazetidine-3-carboxylic acid (29 mg, 0.252 mmol), (*S*)-9-amino-
 9-(5-bromo-2-(4-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-4-yl)nonan-3-
 10 one (**A24**, 120 mg, 0.228 mmol) in THF (5 mL) at 30°C and the mixture was stirred at 30°C for
 18 h. The solvent was evaporated under reduced pressure. The residue was purified by silica gel
 flash chromatography (ISCORF75; Sepa flash column), eluting with DCM / MeOH = 10/1 to
 give (*S*)-*N*-(1-(5-bromo-2-(4-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-4-
 yl)-7-oxononyl)-1-methylazetidine-3-carboxamide (**65A**). LCMS (ESI) calc'd for
 15 C₂₉H₄₄BrFN₄O₃Si [M+H]⁺: 623.2, found: 625.1
- Step 2: Preparation of (*S*)-*N*-(1-(4-bromo-2-(4-fluorophenyl)-1*H*-imidazol-5-yl)-7-oxononyl)-
1-methylazetidine-3-carboxamide (**65**): (*S*)-*N*-(1-(4-bromo-2-(4-fluorophenyl)-1-((2-
 (trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)-7-oxononyl)-1-methylazetidine-3-
 carboxamide (**65A**, 110 mg, 0.176 mmol) was dissolved in hydrogen chloride /MeOH (1.00 mL,
 4.00 mmol) at 30°C and the mixture was stirred at 30°C for 18 h. The solvent was evaporated
 20 under reduced pressure at 30°C. The residue was purified by preparative HPLC (reverse phase
 C-18 column), eluting with ACN/water + 0.1% TFA, to give (*S*)-*N*-(1-(4-bromo-2-(4-
 fluorophenyl)-1*H*-imidazol-5-yl)-7-oxononyl)-1-methylazetidine-3-carboxamide (**65**). LCMS

(ESI) calc'd for $C_{23}H_{30}BrFN_4O_2$ $[M+H]^+$: 493.2, found: 495.1. ^1H NMR (400 MHz, $CDCl_3$) δ 11.62 (brs, 1H), 9.40-9.95 (m, 1H), 7.93-8.21 (m, 2H), 7.08-7.24 (m, 2H), 4.94-5.17 (m, 1H), 4.51-4.70 (m, 2H), 3.67-4.07 (m, 5H), 2.39 (quin, $J = 7.24$ Hz, 4H), 1.72-1.96 (m, 2H), 1.51 (d, $J = 5.09$ Hz, 2H), 1.27 (brs, 5H), 1.02 (t, $J = 7.43$ Hz, 3H).

5

Example 53

(1*S*)-*N*-[(1*S*)-1-{5-[2-(dimethylamino)quinolin-6-yl]-1*H*-imidazol-2-yl]-7-oxononyl]-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**66**)



Step 1: Preparation of (*S*)-tert-butyl (1-(5-bromo-1*H*-imidazol-2-yl)-7-oxononyl) carbamate

(66B): (Boc)₂O (3.5 mL, 15.07 mmol) was added to a stirred mixture of (*S*)-9-amino-9-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)nonan-3-one hydrochloride (**A5**, 5.00 g, 10.66 mmol) and Et₃N (2.3 mL, 16.50 mmol) in DCM (50.0 mL) at room temperature. The mixture was stirred at rt for 3 h. The mixture was concentrated. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 2:1 to give (*S*)-tert-butyl (1-(5-bromo-1*H*-imidazol-2-yl)-7-oxononyl)carbamate (**66B**). LCMS (ESI) calc'd for $C_{17}H_{28}BrN_3O_3$ $[M+H]^+$: 402.1, found: 403.8.

Step 2: Preparation of (*S*)-tert-butyl (1-(5-(2-chloroquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl) carbamate (66C**):**

PdCl₂(DTBPF) (0.16 g, 0.245 mmol) was added to a stirred mixture of (*S*)-tert-butyl (1-(5-bromo-1*H*-imidazol-2-yl)-7-oxononyl)carbamate (**66B**, 1.00 g, 2.486 mmol), (2-chloroquinolin-6-yl)boronic acid (0.67 g, 3.23 mmol) and K₃PO₄ (1.58 g, 7.44 mmol) in THF (10.0 mL) and water (0.5 mL) at room temperature and the mixture was stirred at 80°C for 12 h under N₂. The mixture was concentrated. The residue was purified by silica gel

column flash chromatography, eluting with petroleum ether / EtOAc = 10:1 - 1:1 to give (*S*)-tert-butyl (1-(5-(2-chloroquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamate (**66C**). LCMS (ESI) calc'd for C₂₆H₃₃ClN₄O₃ [M+H]⁺: 485.2, found: 485.0

Step 3: Preparation of (*S*)-tert-butyl (1-(5-(2-(dimethylamino)quinolin-6-yl)-1*H*-imidazol-2-yl)-

- 5 7-oxononyl)carbamate (**66D**): Dimethylamine hydrochloride (202 mg, 2.474 mmol) was added to a stirred mixture of K₂CO₃ (427 mg, 3.09 mmol) and (*S*)-tert-butyl (1-(5-(2-chloroquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamate (**66C**, 150 mg, 0.309 mmol) in DMF (3.0 mL) at room temperature and the mixture was stirred at 70°C for 48 h. The mixture was filtered and the filter cake was washed with DCM (10 mL). The filtrate was concentrated to dryness. The
10 residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 10:1 - 5:3 to give (*S*)-tert-butyl (1-(5-(2-(dimethylamino)quinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamate (**66D**). LCMS (ESI) calc'd for C₂₈H₃₉N₅O₃ [M+H]⁺: 494.3, found: 494.2

Step 4: Preparation of (*S*)-9-amino-9-(5-(2-(dimethylamino)quinolin-6-yl)-1*H*-imidazol-2-

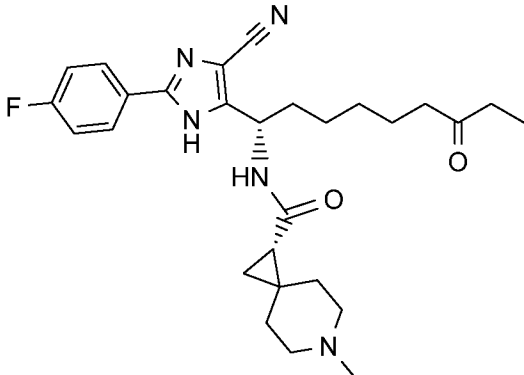
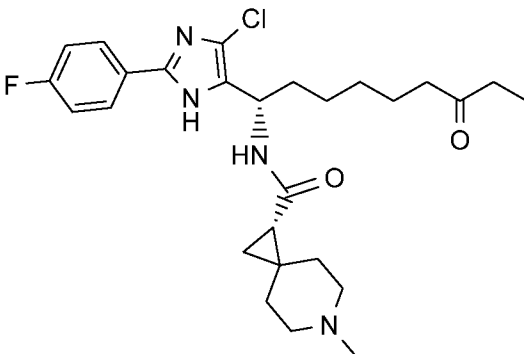
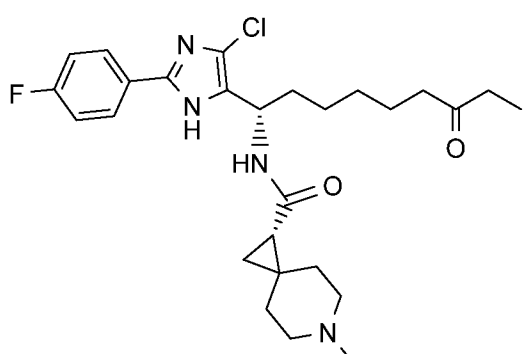
- 15 yl)nonan-3-one (**66E**): HCl / MeOH (1.0 mL, 4.00 mmol) was added to a stirred mixture of (*S*)-tert-butyl (1-(5-(2-(dimethylamino)quinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamate (**66D**, 100 mg, 0.203 mmol) in MeOH (2.0 mL) at room temperature and the mixture was stirred at rt for 2 h. The mixture was concentrated to afford crude (*S*)-9-amino-9-(5-(2-(dimethylamino)quinolin-6-yl)-1*H*-imidazol-2-yl)nonan-3-one (**66E**) which was used to the next
20 step without further purification. LCMS (ESI) calc'd for C₂₃H₃₁N₅O [M+H]⁺: 394.3, found: 394.2

Step 5: Preparation of (*S*)-*N*-((*S*)-1-(5-(2-(dimethylamino)quinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**66**): (*S*)-9-amino-9-(5-(2-

- (dimethylamino)quinolin-6-yl)-1*H*-imidazol-2-yl)nonan-3-one hydrochloride (**66E**, 80 mg, 0.186
25 mmol) was added to a stirred mixture of HATU (71 mg, 0.187 mmol), (*S*)-6-methyl-6-azaspiro[2.5]octane-1-carboxylic acid (**B3**, 30 mg, 0.177 mmol) and Et₃N (0.2 mL, 1.435 mmol) in DMF (2.0 mL) at room temperature. The mixture was stirred at room temperature for 2 h. The residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.05% NH₃·H₂O, to give (*S*)-*N*-((*S*)-1-(5-(2-(dimethylamino)quinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**66**). LCMS
30 (ESI) calc'd for C₃₂H₄₄N₆O₂ [M+H]⁺: 545.4, found: 545.3. ¹H NMR (400 MHz, MeOD) δ 7.96 (d, *J* = 9.04 Hz, 2H), 7.84 (brs, 1H), 7.65 (d, *J* = 8.60 Hz, 1H), 7.33 (brs, 1H), 7.05 (d, *J* = 9.26 Hz, 1H), 5.01 (t, *J* = 7.50 Hz, 1H), 3.22 (s, 6H), 2.27-2.67 (m, 8H), 2.18 (brs, 3H), 1.97 (d, *J* =

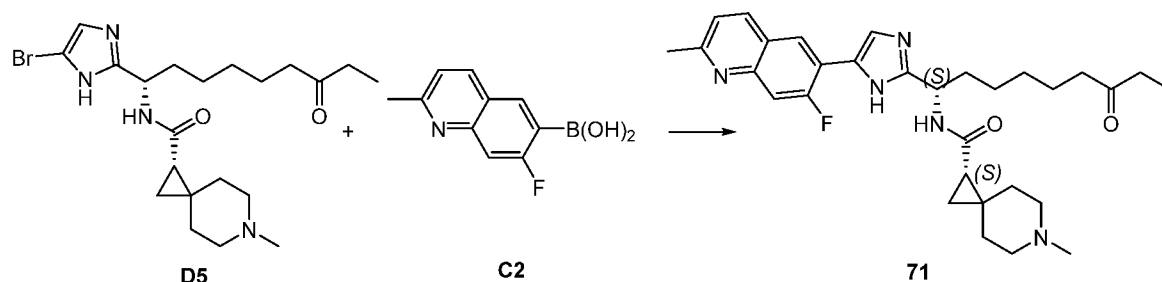
7.94 Hz, 2H), 1.50-1.74 (m, 6H), 1.26-1.48 (m, 5H), 1.11 (t, $J = 4.63$ Hz, 1H), 0.98 (t, $J = 7.28$ Hz, 3H), 0.83 (dd, $J = 4.41, 7.72$ Hz, 1H).

The following compounds were prepared by using similar procedures as described for compound **66**.

ID	Structure	Observed $[M+H]^+$
76		494.1
91		503.2
240		503.2

Example 54

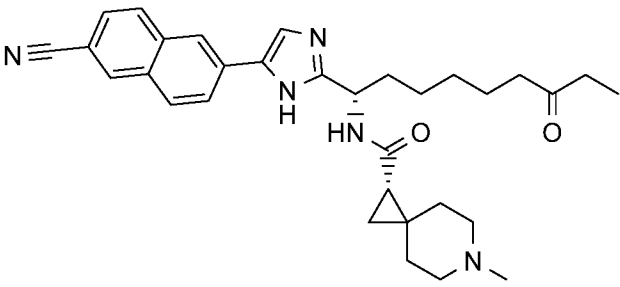
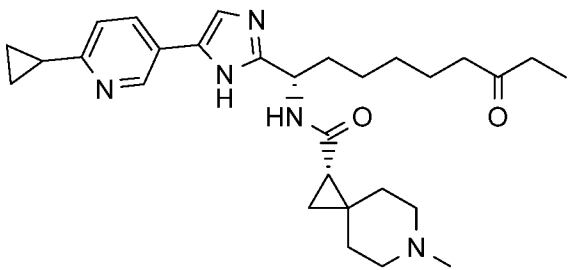
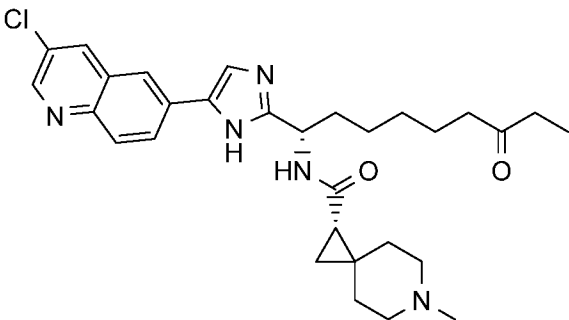
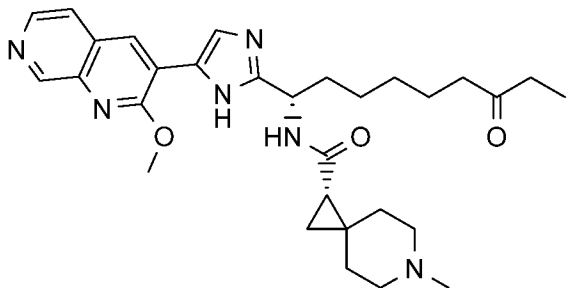
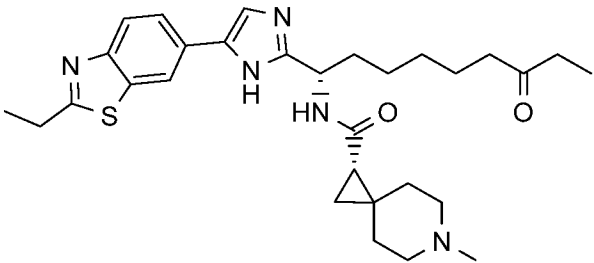
(1*S*)-*N*-{(1*S*)-1-[5-(7-fluoro-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl]-7-oxononyl}-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (71)

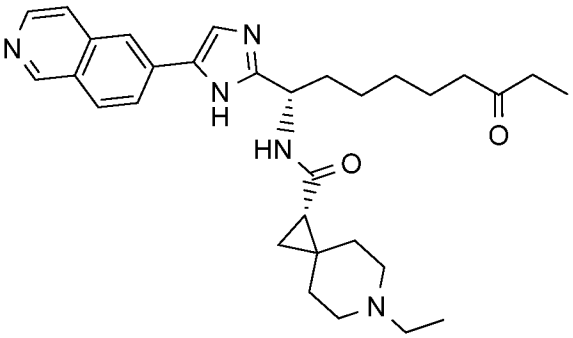
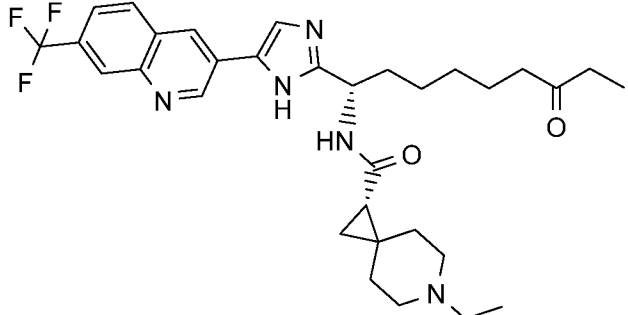
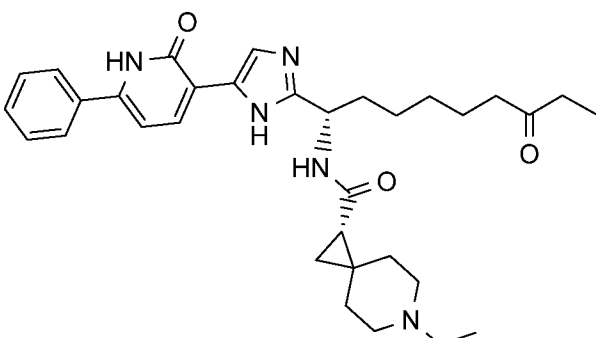
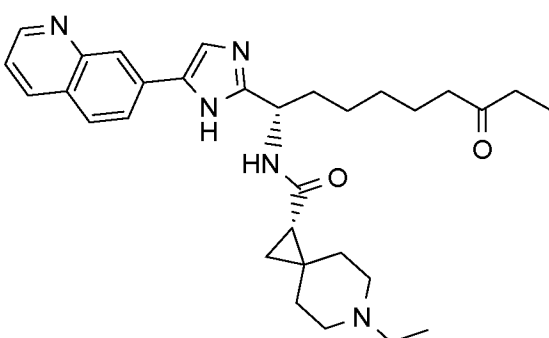


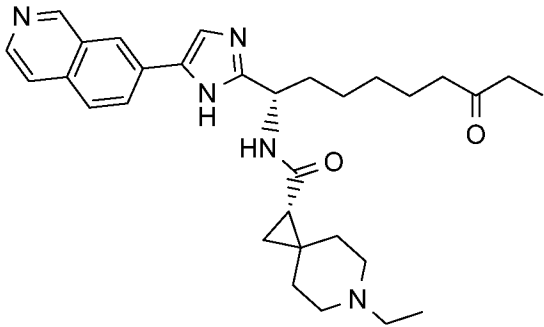
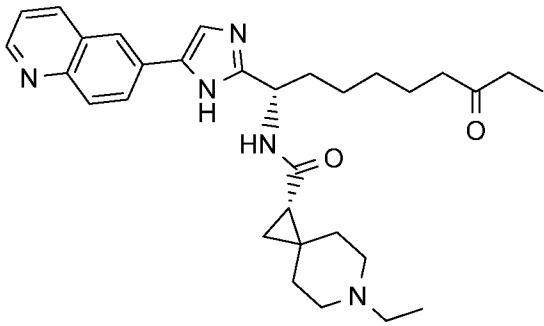
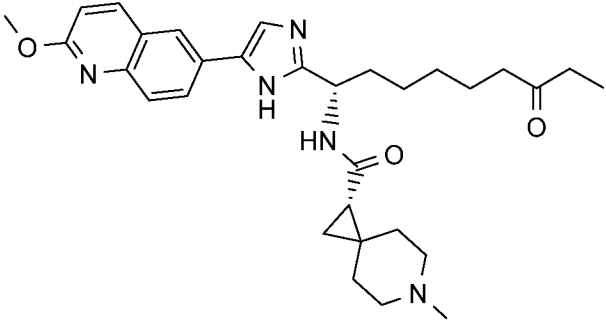
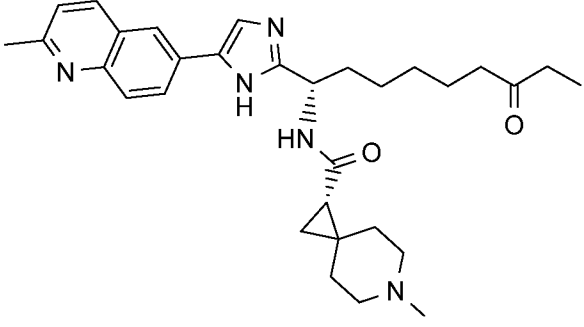
5 K_3PO_4 (211 mg, 0.992 mmol), and $PdCl_2(DTBPf)$ (5 mg, 7.67 μ mol) was added to a stirred mixture of (*S*)-*N*-((*S*)-1-(5-bromo-1*H*-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**D5**, 150 mg, 0.331 mmol) and (7-fluoro-2-methylquinolin-6-yl)boronic acid (**C2**, 100 mg, 0.488 mmol) in water (0.5 mL) / THF (2 mL) at rt and the mixture was stirred at 70°C for 18 h. The mixture was cooled, diluted with ethyl acetate (3 mL), washed
10 with brine (saturated, 3 x 8 mL), dried (Na_2SO_4), filtered and the solvent was evaporated under reduced pressure. The residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.05% $NH_3 \cdot H_2O$, to give (*S*)-*N*-((*S*)-1-[5-(7-fluoro-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl]-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**71**). LCMS (ESI) calc'd for $C_{31}H_{40}FN_5O_2$ $[M+H]^+$: 534.3, found: 534.3. ^1H NMR
15 (400 MHz, $CDCl_3$) δ 8.46 (brs, 1H), 8.07 (d, $J = 8.2$ Hz, 1H), 7.67 (d, $J = 12.9$ Hz, 1H), 7.47 (d, $J = 3.9$ Hz, 1H), 7.24 (d, $J = 8.6$ Hz, 1H), 6.54 (d, $J = 7.4$ Hz, 1H), 4.97 (q, $J = 7.4$ Hz, 1H), 2.72 (s, 3H), 2.35-2.49 (m, 5H), 2.20-2.34 (m, 3H), 2.17 (s, 3H), 2.04 (d, $J = 7.8$ Hz, 3H), 1.59 (td, $J = 7.2, 14.48$ Hz, 4H), 1.30-1.51 (m, 6H), 1.21 (d, $J = 4.3$ Hz, 1H), 1.03 (t, $J = 7.4$ Hz, 3H), 0.83 (dd, $J = 4.3, 7.43$ Hz, 1H).

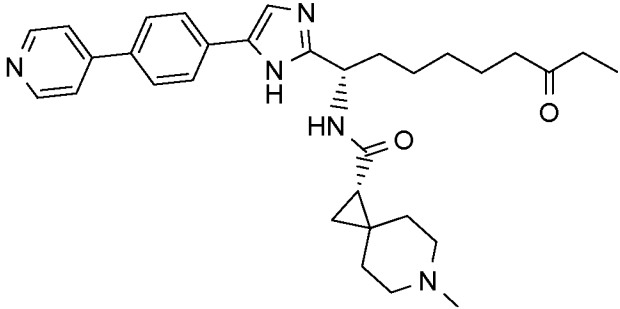
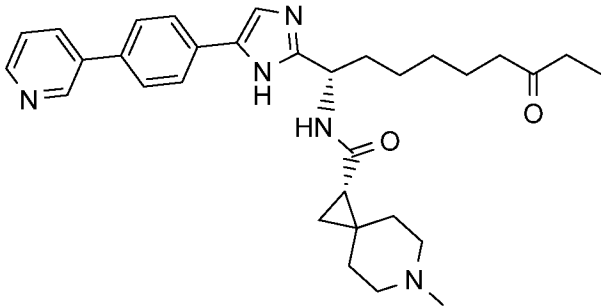
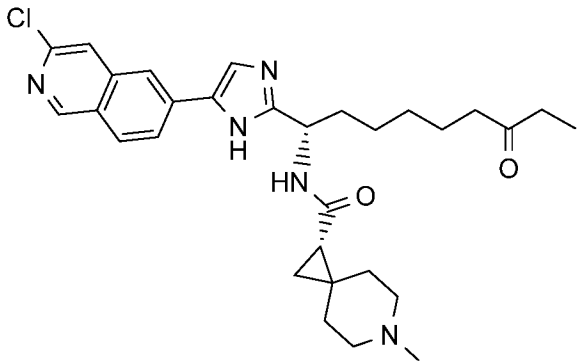
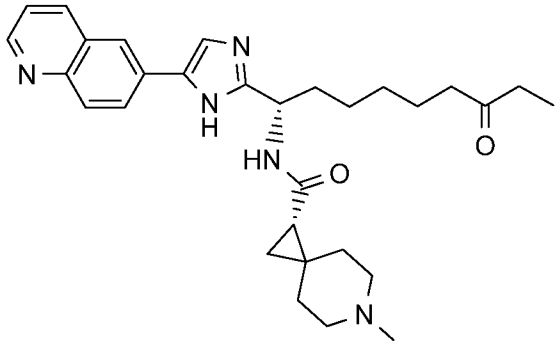
20 The following compounds were prepared using the similar procedures as described for compound 71:

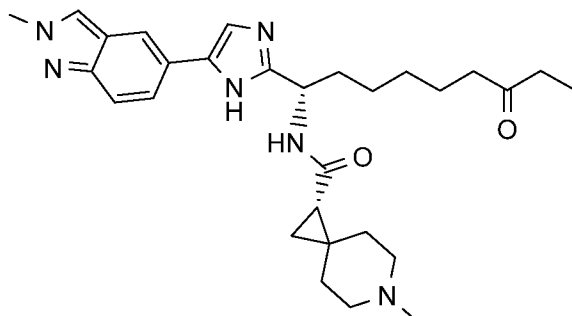
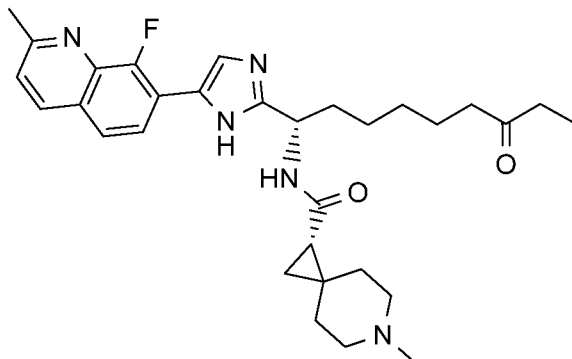
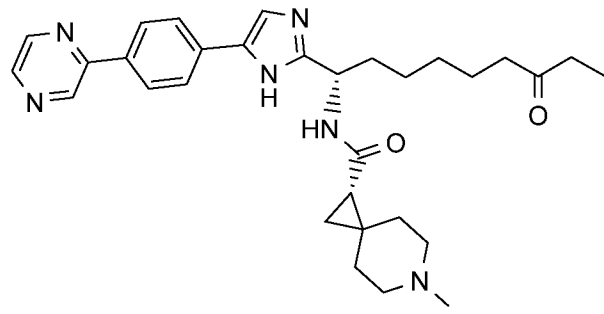
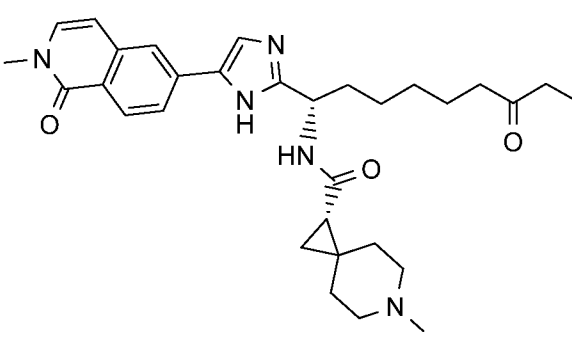
ID	Structure	Observed $[M+H]^+$
89		492.3

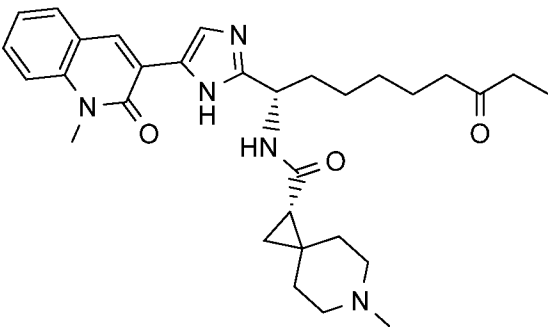
90		526.3
139		492.3
140		536.2
148		533.3
149		536.3

243		516.3
341		584.1
342		558.5
344		516.4

345		516.4
346		516.4
347		532.4
348		516.4

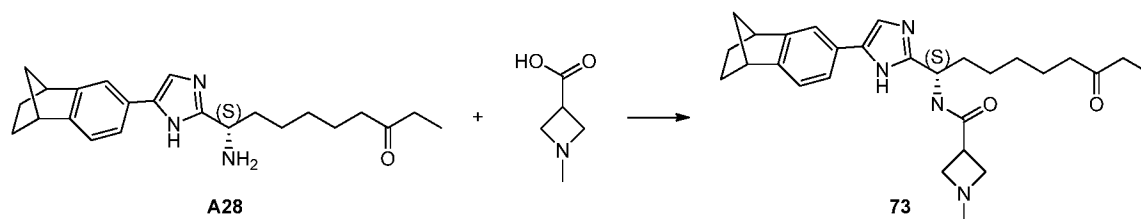
349		528.5
350		528.4
351		536.0
352		502.4

353		505.1
354		534.5
357		529.5
358		532.4

356		532.5
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Example 55

1-methyl-*N*-{(1*S*)-7-oxo-1-[5-(1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)-1*H*-imidazol-2-yl]nonyl}azetidine-3-carboxamide (**73**)



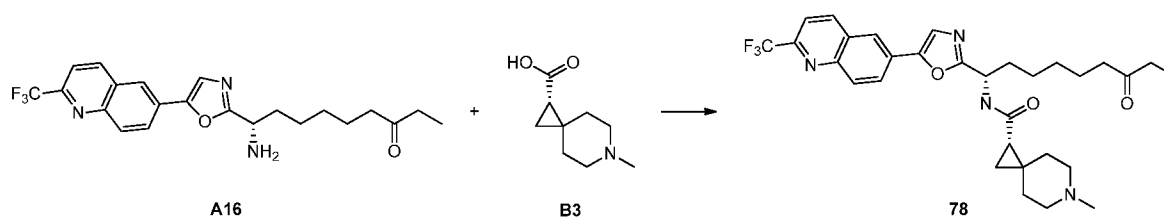
The mixture of 1-methylazetidine-3-carboxylic acid (61 mg, 0.530 mmol), HATU (212 mg, 0.557 mmol) and Et₃N (0.30 mL, 2.15 mmol) in DMF (5 mL) was stirred at rt for 10 min, then a mixture of (*S*)-9-amino-9-(5-((1*R*,4*S*)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)-1*H*-imidazol-2-yl)nonan-3-one hydrochloride (**73E**, 140 mg, 0.348 mmol) in DMF (5 mL) was added. The resulting mixture was stirred at 40°C for 16 h under nitrogen atmosphere. The mixture was concentrated to remove DMF, the residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.1% TFA, lyophilized (adding HCl before) to give the title compound (**73**). LCMS (ESI) calc'd for C₂₈H₃₈N₄O₂ [M+H]⁺: 463.3, found: 463.2. ¹H NMR (400 MHz, MeOD) δ 7.69 (s, 1H), 7.50 (s, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 5.13 (brs, 1H), 4.54-4.34 (m, 2H), 4.23-4.03 (m, 2H), 3.69 (brs, 1H), 3.60 (q, *J* = 7.1 Hz, 2H), 3.41 (brs, 2H), 2.92 (brs, 3H), 2.47-2.42 (m, 3H), 2.03-1.97 (m, 4H), 1.74 (d, *J* = 8.4 Hz, 1H), 1.63-1.52 (m, 3H), 1.45 (brs, 1H), 1.35 (brs, 3H), 1.17 (t, *J* = 7.1 Hz, 5H), 0.99 (t, *J* = 7.3 Hz, 2H).

The following compound was prepared using similar procedures as described for compound **73**:

ID	Structure	Observed [M+H] ⁺
141		610.3

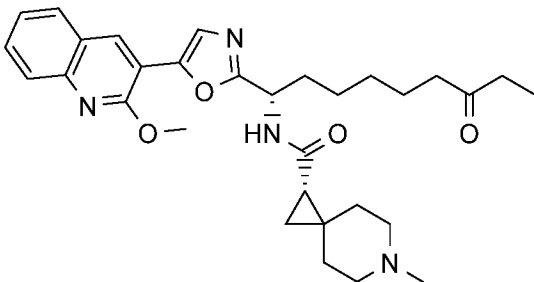
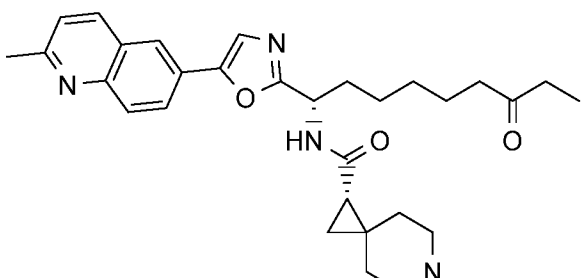
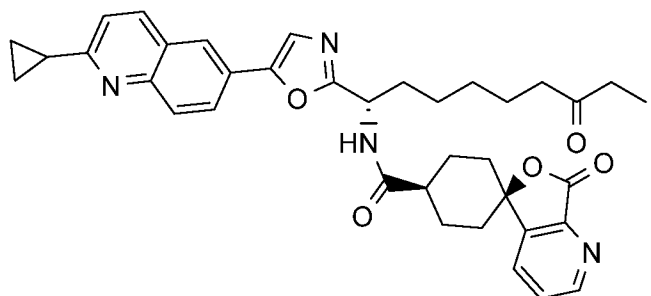
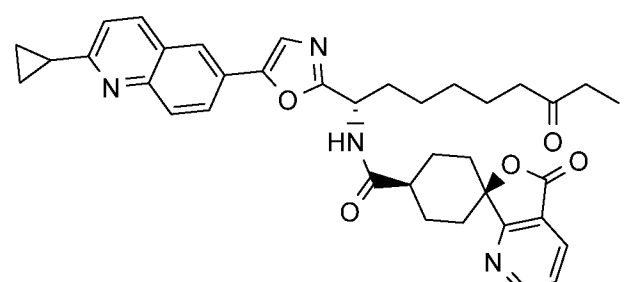
Example 56

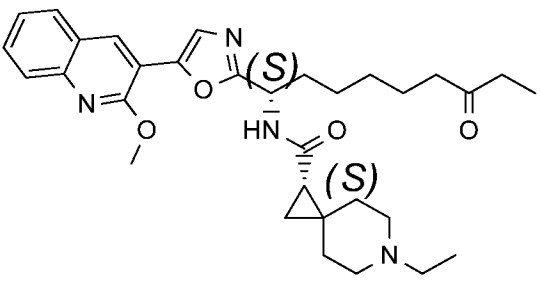
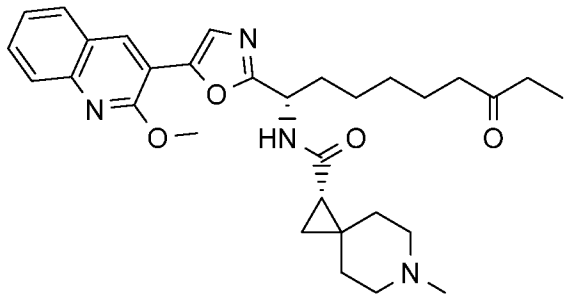
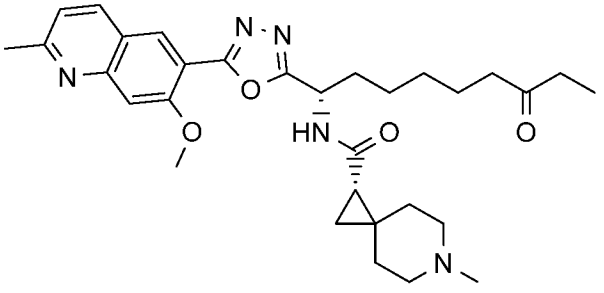
(1*S*)-6-methyl-*N*-[(1*S*)-7-oxo-1-{5-[2-(trifluoromethyl)quinolin-6-yl]-1,3-oxazol-2-yl}nonyl]-6-azaspiro[2.5]octane-1-carboxamide (78)



(*S*)-9-amino-9-(5-(2-(trifluoromethyl)quinolin-6-yl)oxazol-2-yl)nonan-3-one (**A16**, 90 mg, 0.215 mmol) was added to a stirred mixture of Et₃N (0.18 mL, 1.291 mmol), HATU (90 mg, 0.236 mmol), (*S*)-6-methyl-6-azaspiro[2.5]octane-1-carboxylic acid (**B3**, 36 mg, 0.213 mmol) in DMF (1 mL) at room temperature and the mixture was stirred at room temperature for 1 h. Water (5 mL) was added and the mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic fractions were washed with brine (5 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.1% TFA, to give (*S*)-6-methyl-N-((*S*)-7-oxo-1-(5-(2-(trifluoromethyl)quinolin-6-yl)oxazol-2-yl)nonyl)-6-azaspiro[2.5]octane-1-carboxamide (**78**). LCMS (ESI) calc'd for C₃₁H₃₇F₃N₄O₃ [M+H]⁺: 571.3, found: 571.2. ¹H NMR (400 MHz, CDCl₃) δ 11.74-12.17 (m, 1H), 8.41 (dd, *J* = 8.4, 13.9 Hz, 1H), 8.19-8.30 (m, 1H), 8.14 (d, *J* = 10.6 Hz, 1H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.76 (t, *J* = 9.2 Hz, 1H), 7.37-7.51 (m, 1H), 6.87-7.22 (m, 1H), 5.17-5.37 (m, 1H), 3.23-3.64 (m, 2H), 2.56-2.83 (m, 5H), 2.23-2.48 (m, 5H), 0.82-2.12 (m, 17H).

The following compounds were prepared using similar procedures as described for compound **78**:

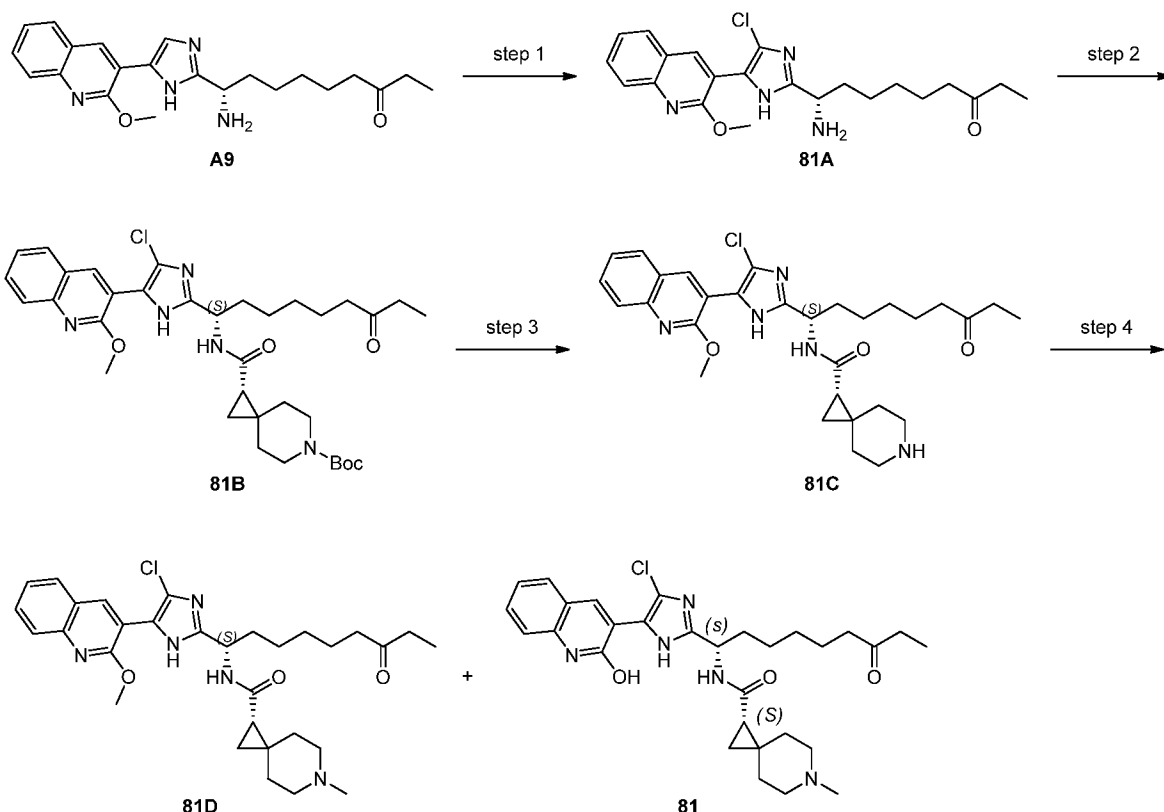
ID	Structure	Observed [M+H] ⁺
77		533.3
80		517.2
122		621.3
123		621.3

124		547.3
125		533.3
191		548.1

Example 57

(1S)-N-((1S)-1-[4-chloro-5-(2-hydroxyquinolin-3-yl)-1H-imidazol-2-yl]-7-oxononyl]-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (81)

5



Step 1: Preparation of (*S*)-9-amino-9-(4-chloro-5-(2-methoxyquinolin-3-yl)-1*H*-imidazol-2-yl)nonan-3-one (81A**):** NCS (175 mg, 1.314 mmol) was added in portions to a stirred mixture of (*S*)-9-amino-9-(5-(2-methoxyquinolin-3-yl)-1*H*-imidazol-2-yl)nonan-3-one (**A9**, 500 mg, 1.314 mmol) in THF (5 mL) at rt and the mixture was stirred at rt for 8 h. The mixture was quenched with water (10 mL), diluted with EtOAc (20 mL x 2), and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with petroleum ether: EtOAc = 5:1-3:1 to give (*S*)-9-amino-9-(4-chloro-5-(2-methoxyquinolin-3-yl)-1*H*-imidazol-2-yl)nonan-3-one (**81A**). LCMS (ESI) calc'd for C₂₂H₂₇ClN₄O₂ [M+H]⁺: 415.1, found: 415.2.

Step 2: Preparation of (*S*)-tert-butyl 1-(((*S*)-1-(4-chloro-5-(2-methoxyquinolin-3-yl)-1*H*-imidazol-2-yl)-7-oxononyl) carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (81B**):** (*S*)-9-amino-9-(4-chloro-5-(2-methoxyquinolin-3-yl)-1*H*-imidazol-2-yl)nonan-3-one (**81A**, 80 mg, 0.193 mmol) in THF (1 mL) was added to a stirred mixture of (*S*)-6-(tert-butoxycarbonyl)-6-azaspiro[2.5]octane-1-carboxylic acid (**B2**, 49 mg, 0.192 mmol), HATU (73 mg, 0.192 mmol) and triethylamine (0.2 mL, 1.435 mmol) in THF (2 mL) at rt and the mixture was stirred at rt for 3 h. The mixture was diluted with ethyl acetate (2 x 20 mL), washed with water (10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with DCM / MeOH = 15:1-10:1 to

give (*S*)-tert-butyl 1-(((*S*)-1-(4-chloro-5-(2-methoxyquinolin-3-yl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**81B**). LCMS (ESI) calc'd for $C_{35}H_{46}ClN_5O_5$ $[M+H]^+$: 652.3, found: 652.4

Step 3: Preparation of (*S*)-*N*-((*S*)-1-(4-chloro-5-(2-methoxyquinolin-3-yl)-1*H*-imidazol-2-yl)-7-

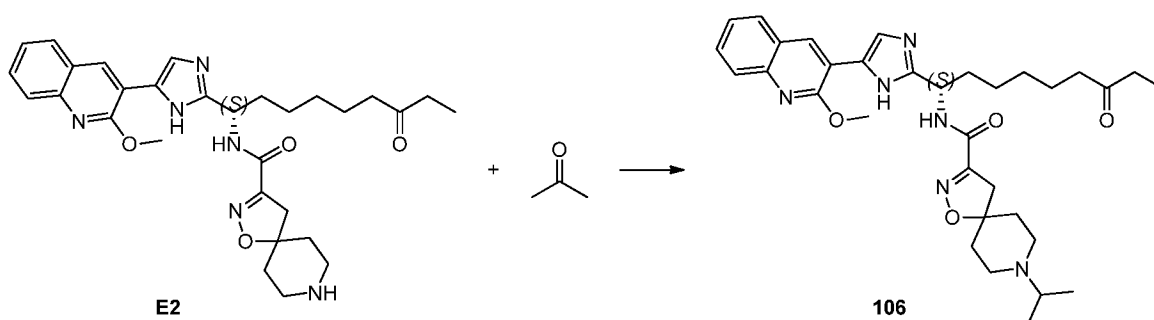
oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**81C**): TFA (0.2 mL, 2.60 mmol) was added to a stirred mixture of (*S*)-tert-butyl 1-(((*S*)-1-(4-chloro-5-(2-methoxyquinolin-3-yl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**81B**, 90 mg, 0.138 mmol) in DCM (5 mL) at room temperature and the mixture was stirred at rt for 2 h. The mixture was extracted with DCM (30 x 2 mL) and washed with water (10 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to get (*S*)-*N*-((*S*)-1-(4-chloro-5-(2-methoxyquinolin-3-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**81C**) which was used in the next step without further purification. LCMS (ESI) calc'd for $C_{30}H_{38}ClN_5O_3$ $[M+H]^+$: 552.2, found: 552.3

Step 4: Preparation of (*S*)-*N*-((*S*)-1-(4-chloro-5-(2-hydroxyquinolin-3-yl)-1*H*-imidazol-2-yl)-7-

oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**81**): Formaldehyde (0.5 mL, 5.02 mmol) and acetic acid (2 drops) were added into a stirred mixture of (*S*)-*N*-((*S*)-1-(4-chloro-5-(2-methoxyquinolin-3-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**81C**, 95 mg, 0.172 mmol) in MeOH (5 mL) at rt and the mixture was stirred at rt for 1 h. Then sodium triacetoxymethylborate (182 mg, 0.860 mmol) was added into the mixture and the mixture was stirred at rt for 1 h. The mixture was quenched with NH_4Cl (2 mL), then evaporated under reduced pressure. The residue was purified by HPLC separation to get (*S*)-*N*-((*S*)-1-(4-chloro-5-(2-methoxyquinolin-3-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**81D**) and (*S*)-*N*-((*S*)-1-(4-chloro-5-(2-hydroxyquinolin-3-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**81**). LCMS (ESI) calc'd for $C_{30}H_{38}ClN_5O_3$ $[M+H]^+$: 552.3, found: 552.4. ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.47-7.72 (m, 3H), 7.39 (d, $J = 7.83$ Hz, 1H), 7.28-7.33 (m, 1H), 5.51 (brs, 1H), 2.90 (brs, 3H), 2.34 (q, $J = 7.43$ Hz, 7H), 1.92 (brs, 9H), 1.46-1.62 (m, 4H), 1.21-1.37 (m, 5H), 1.06-1.19 (m, 2H), 0.98 (t, $J = 7.24$ Hz, 4H).

Example 58

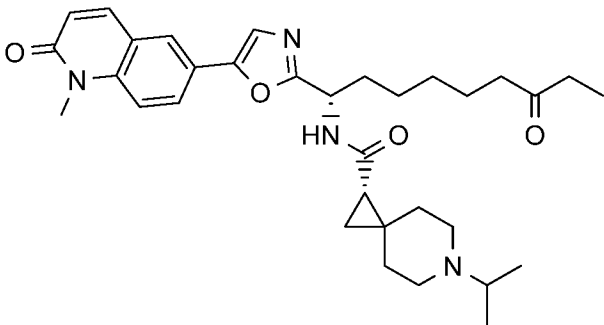
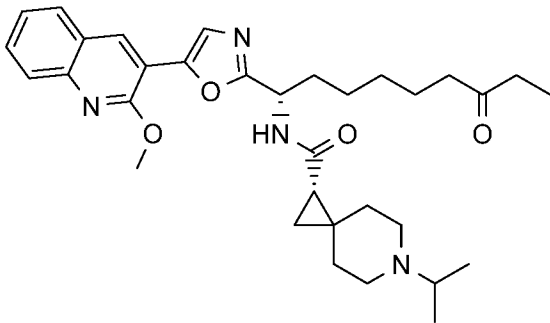
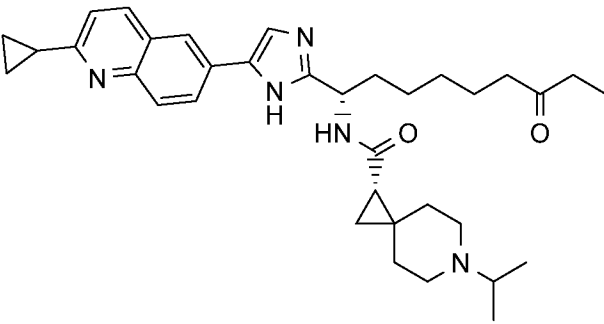
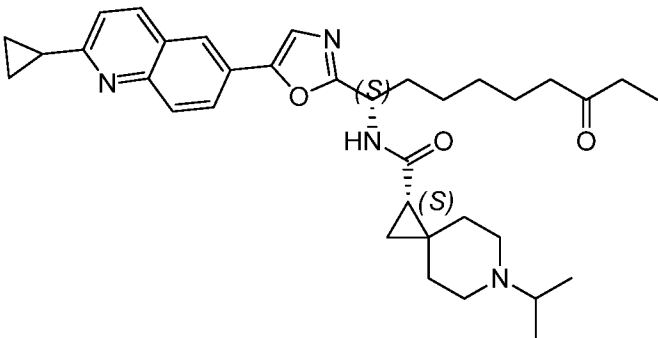
N-{[(1*S*)-1-[5-(2-methoxyquinolin-3-yl)-1*H*-imidazol-2-yl]-7-oxononyl]-8-(1-methylethyl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide (106)



(*S*)-*N*-(1-(5-(2-methoxyquinolin-3-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide (**E2**, 92 mg, 0.168 mmol) was added to acetone (2 ml, 0.168 mmol) at rt and the mixture was stirred at 45°C for 12 h. Then NaBH(OAc)₃ (107 mg, 0.505 mmol) was added at 45°C, and the mixture was stirred at 45°C for 13 h. The residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.05% NH₃·H₂O, to give (*S*)-*N*-(1-(5-(2-methoxyquinolin-3-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-8-methyl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide (**106**). LCMS (ESI) calc'd for C₃₁H₄₀N₆O₄ [M+H]⁺: 589.3, found: 589.3. ¹H NMR (400 MHz, CDCl₃) δ 8.79 (brs, 1H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.48-7.69 (m, 2H), 7.39 (brs, 1H), 5.05 (brs, 1H), 4.21 (brs, 3H), 2.87-3.05 (m, 2H), 2.61-2.83 (m, 3H), 2.50 (brs, 1H), 2.36-2.44 (m, 4H), 2.28 (d, *J* = 5.7 Hz, 1H), 2.01-2.14 (m, 1H), 1.93 (d, *J* = 15.7 Hz, 2H), 1.80 (brs, 4H), 1.56-1.65 (m, 2H), 1.34-1.51 (m, 4H), 0.99-1.15 (m, 9H).

The following compounds were prepared using similar procedures as described for compound **106**.

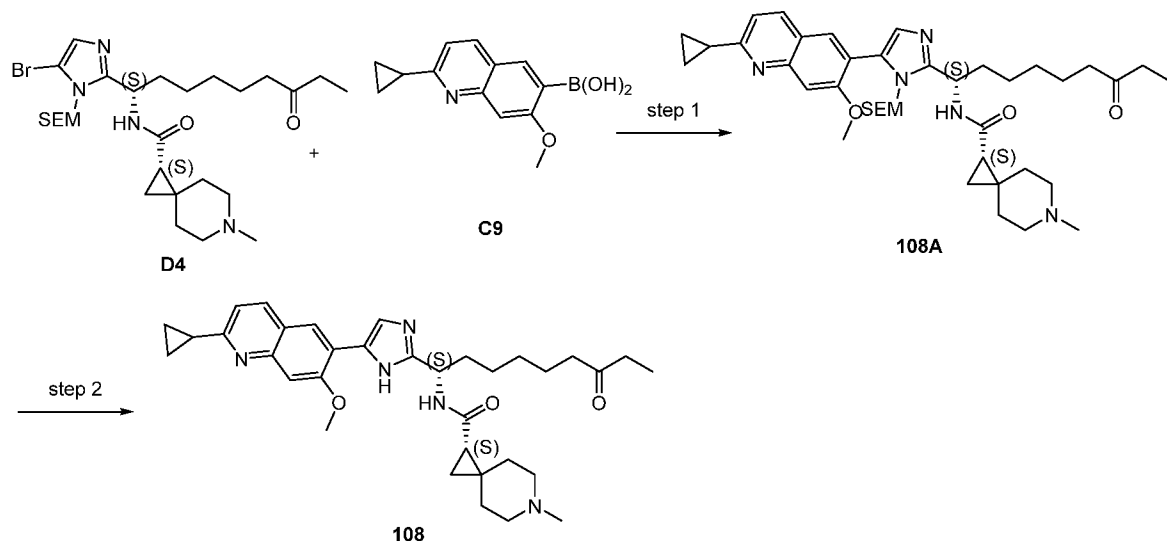
ID	Structure	Observed [M+H] ⁺
83		544.3

96		561.4
99		561.3
100		570.3
116		571.3

136		600.4
182		574.1

Example 59

(1*S*)-*N*-{(1*S*)-1-[5-(2-cyclopropyl-7-methoxyquinolin-6-yl)-1*H*-imidazol-2-yl]-7-oxononyl}-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**108**)



Step 1: Preparation of (*S*)-*N*-((*S*)-1-(5-(2-cyclopropyl-7-methoxyquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**108A**): PdCl₂(DTBPF) (15 mg, 0.023 mmol) was added to a stirred mixture of K₃PO₄ (105 mg, 0.494 mmol), (*S*)-*N*-((*S*)-1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**D4**, 100 mg, 0.171

10

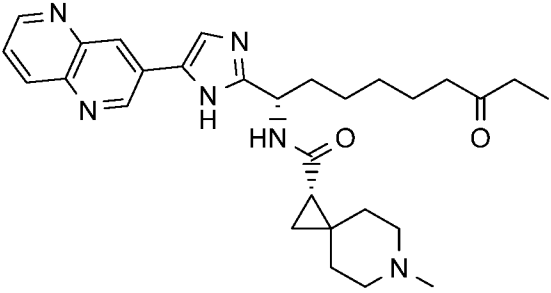
mmol), (2-cyclopropyl-7-methoxyquinolin-6-yl)boronic acid (**C9**, 40 mg, 0.165 mmol) in THF (1 mL) / water (0.5 mL) at room temperature and the mixture was stirred at 70°C for 4 h under N₂. The mixture was cooled, diluted with EtOAc (10 mL), washed with water (3 x 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was

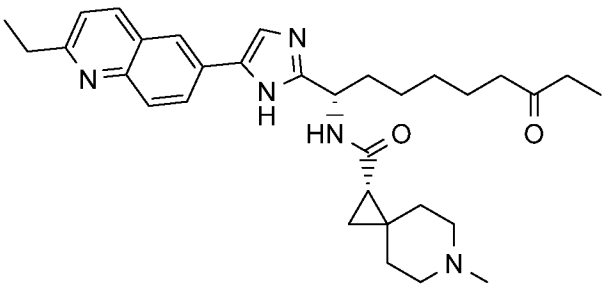
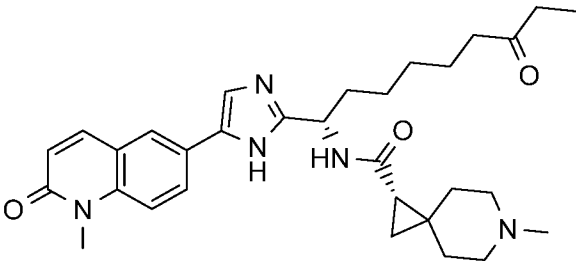
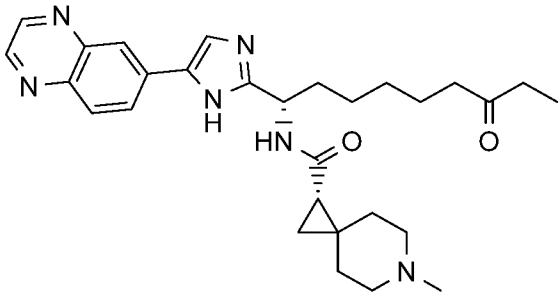
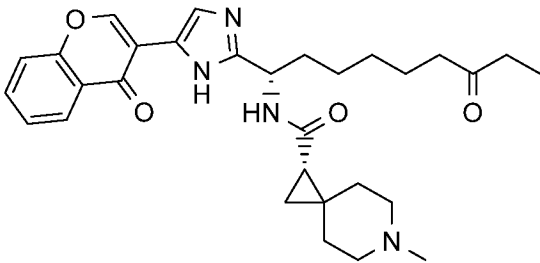
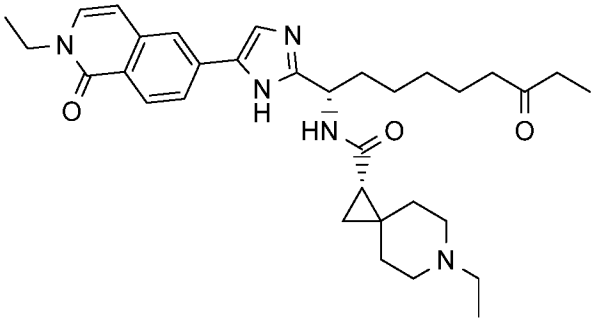
purified by silica gel column flash chromatography, eluting with MeOH / DCM = 0 - 30% to give (*S*)-*N*-((*S*)-1-(5-(2-cyclopropyl-7-methoxyquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**108A**). LCMS (ESI) calc'd for C₄₀H₅₉N₅O₄Si [M+H]⁺: 702.4, found: 702.5

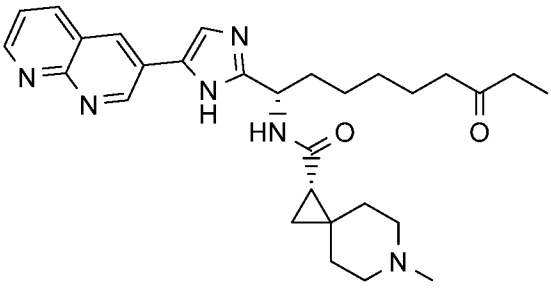
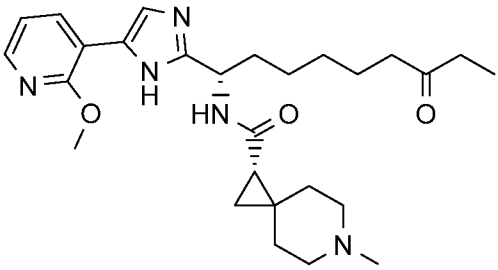
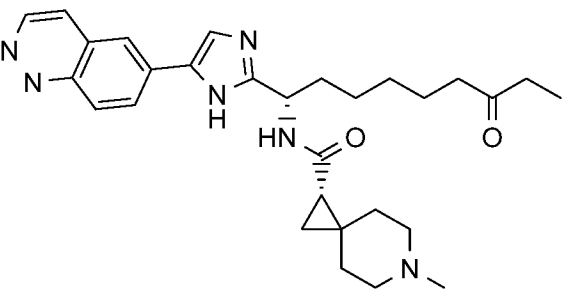
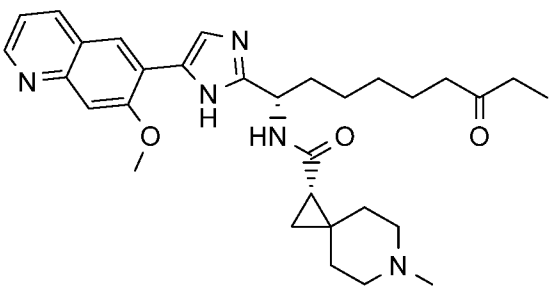
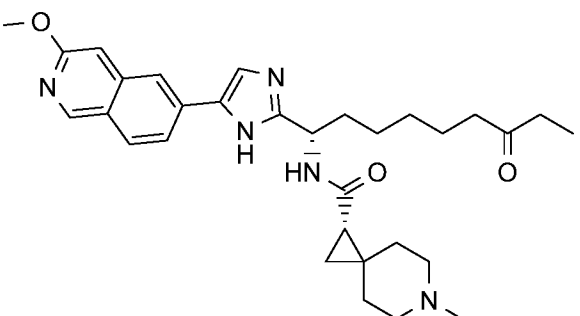
Step 2: Preparation of (*S*)-*N*-((*S*)-1-(5-(2-cyclopropyl-7-methoxyquinolin-6-yl)-1*H*-imidazol-2-

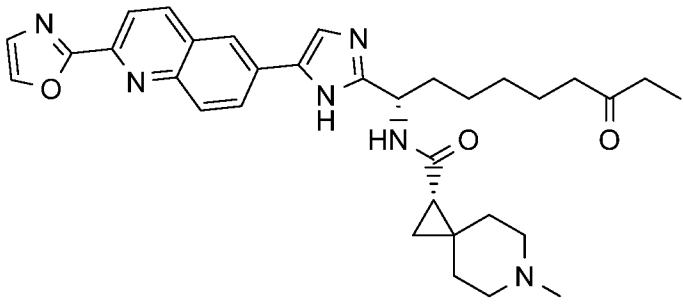
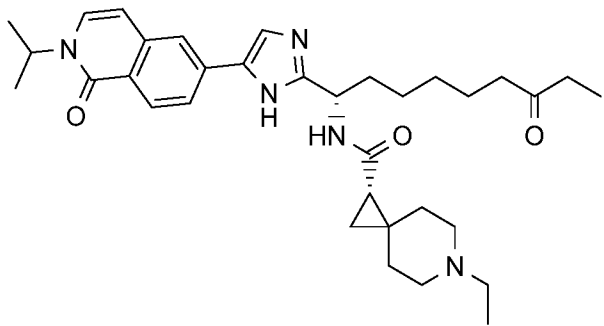
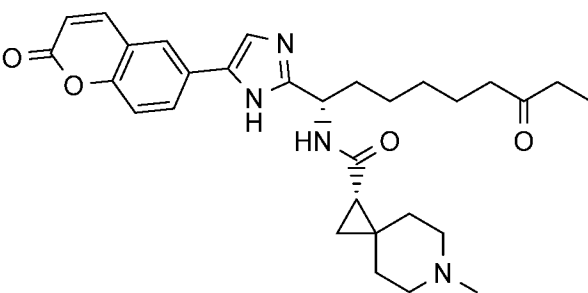
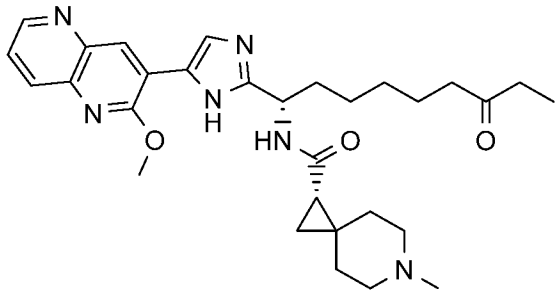
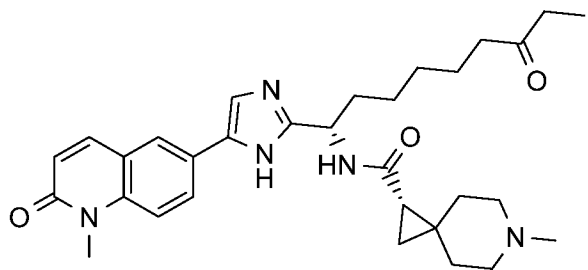
yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**108**): (*S*)-*N*-((*S*)-1-(5-(2-cyclopropyl-7-methoxyquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**108A**, 60 mg, 0.085 mmol) was added in TFA (1.5 mL) at room temperature and the mixture was stirred at room temperature for 2 h. Most of the TFA was removed, and the residue was purified by preparative HPLC Reverse phase (C-18), eluting with acetonitrile/water + 0.1% TFA, and HCl (0.5 mL, 1 *M*) was added, and lyophilized to give (*S*)-*N*-((*S*)-1-(5-(2-cyclopropyl-7-methoxyquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide hydrochloride (**108**). LCMS (ESI) calc'd for C₃₄H₄₅N₅O₃ [M+H]⁺: 572.4, found: 572.4. ¹H NMR (400 MHz, MeOD) δ 8.92 (d, *J* = 8.8 Hz, 1H), 8.81-8.88 (m, 1H), 8.60 (s, 1H), 8.05 and 8.04 (s, 1H), 7.70 (s, 1H), 7.46 (dd, *J* = 2.2, 8.60 Hz, 1H), 5.09 (brs, 1H), 4.24 (d, *J* = 4.2 Hz, 3H), 3.40-3.68 (m, 3H), 2.99-3.25 (m, 2H), 2.82-2.94 (m, 3H), 2.52-2.63 (m, 1H), 2.41-2.52 (m, 4H), 2.05-2.20 (m, 2H), 1.88-1.96 (m, 2H), 1.27-1.68 (m, 11H), 1.13-1.22 (m, 1H), 0.94-1.09 (m, 3H), 0.80 (t, *J* = 7.5 Hz, 1H).

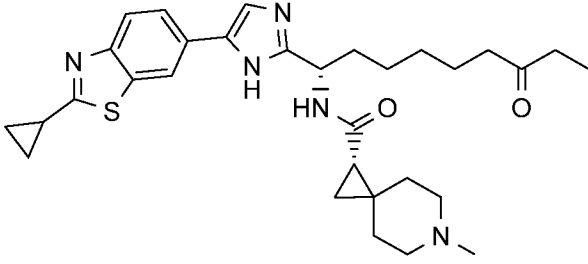
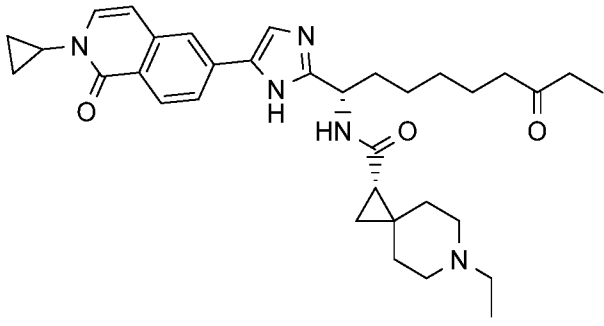
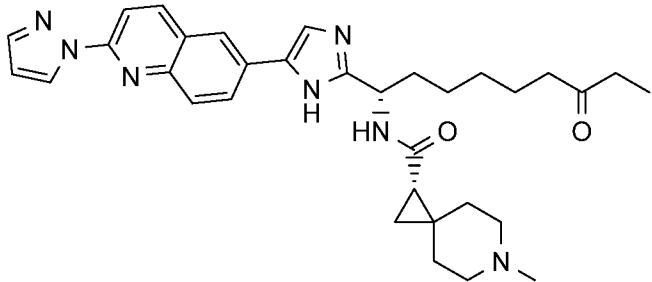
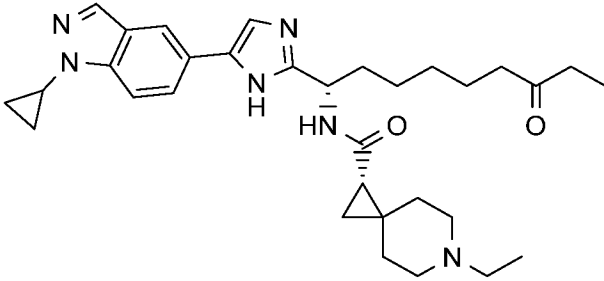
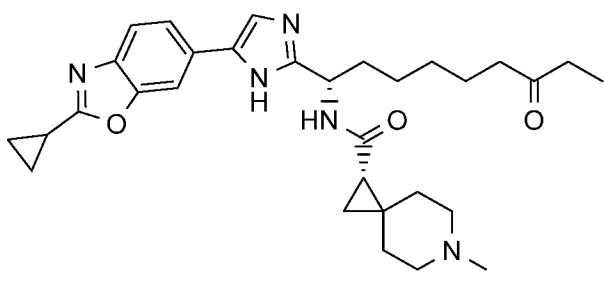
The following compounds were prepared using similar procedures as described for compound **108**.

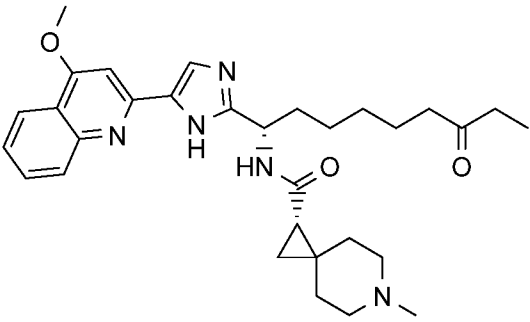
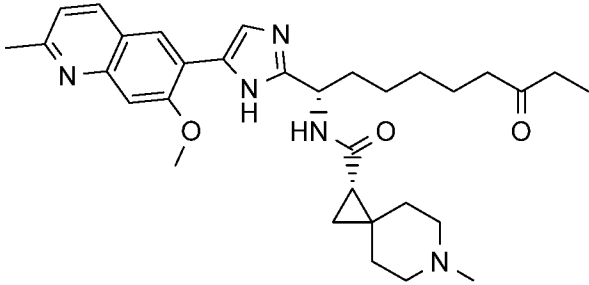
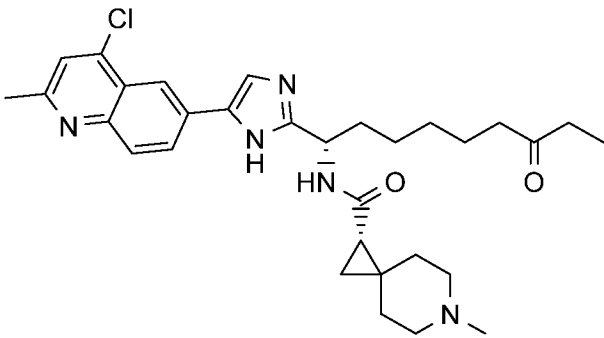
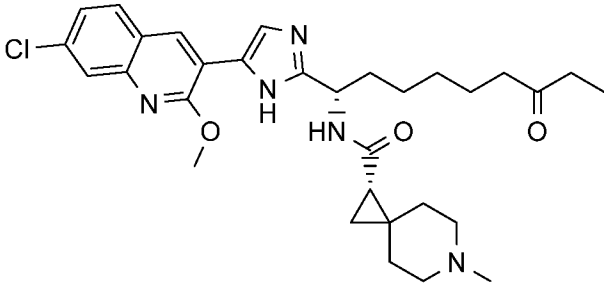
ID	Structure	Observed [M+H] ⁺
67		503.3

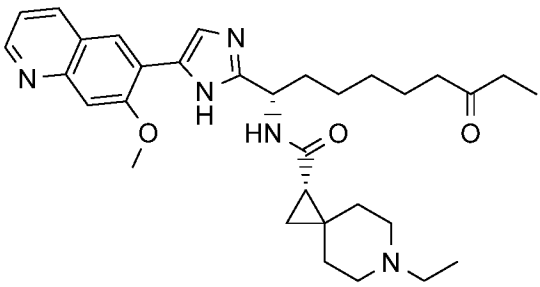
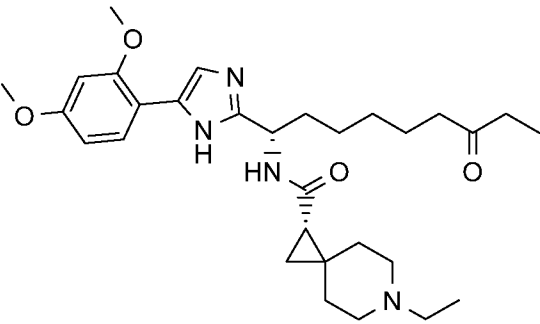
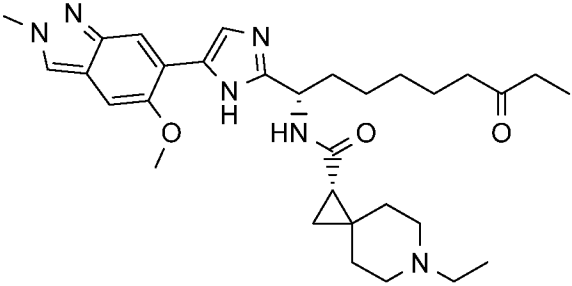
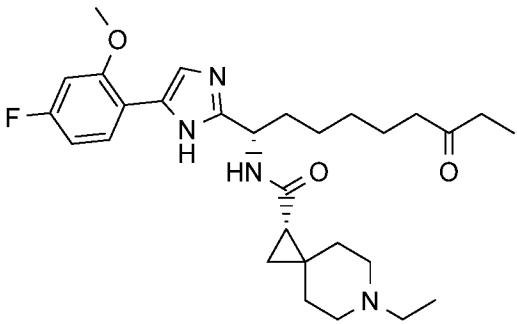
70		530.3
72		532.3
82		503.3
86		519.3
92		560.4

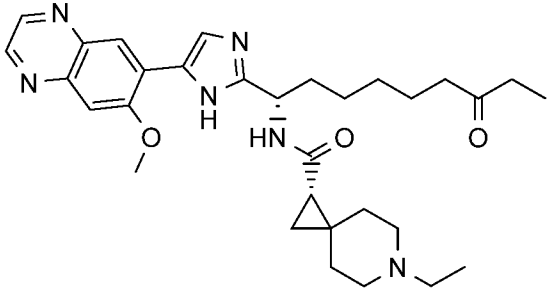
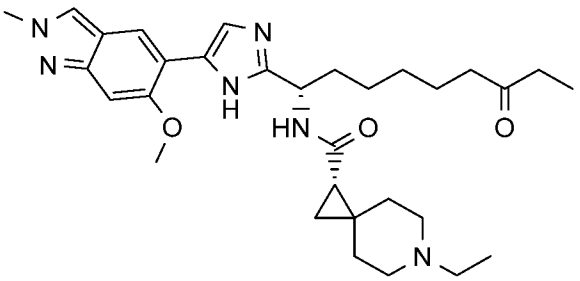
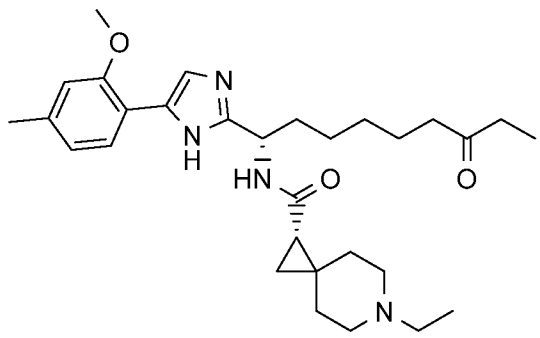
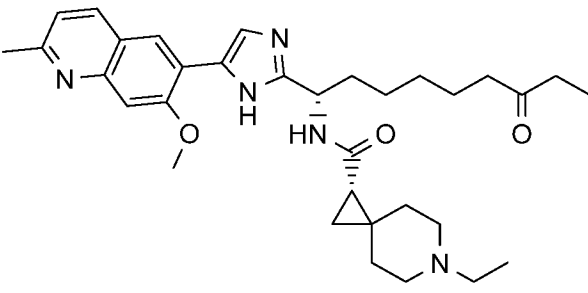
98		503.3
102		482.3
103		503.3
107		532.3
113		532.3

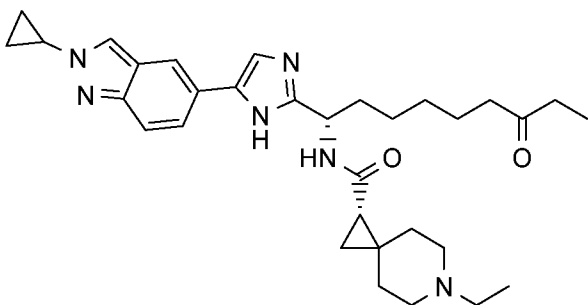
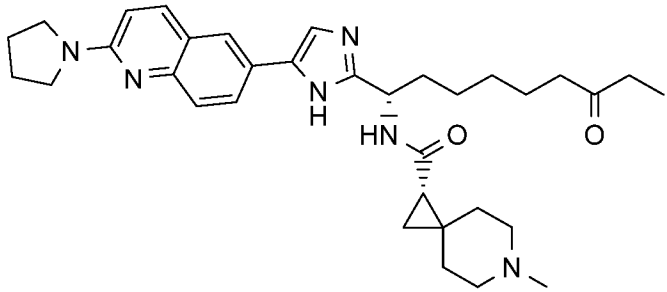
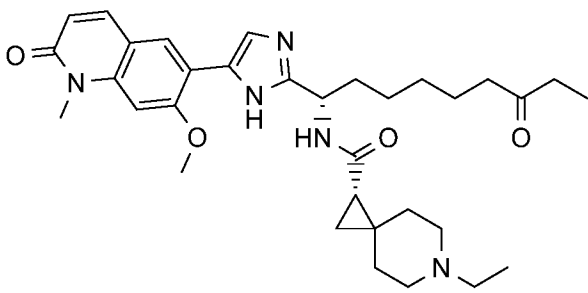
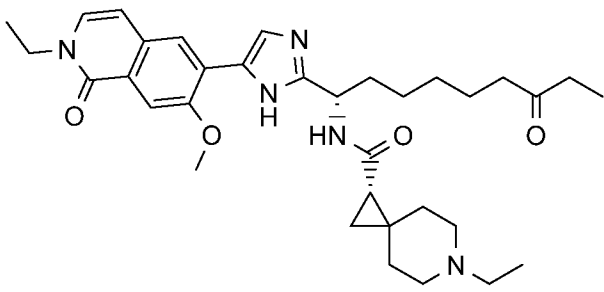
119		569.3
126		574.4
138		519.3
142		533.3
144		532.3

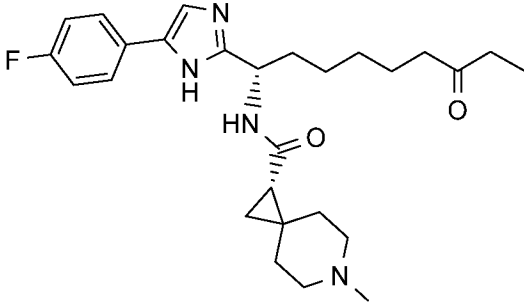
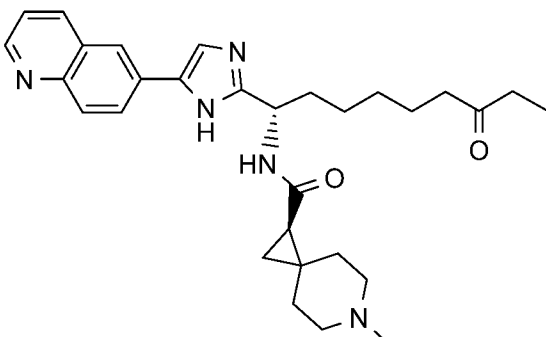
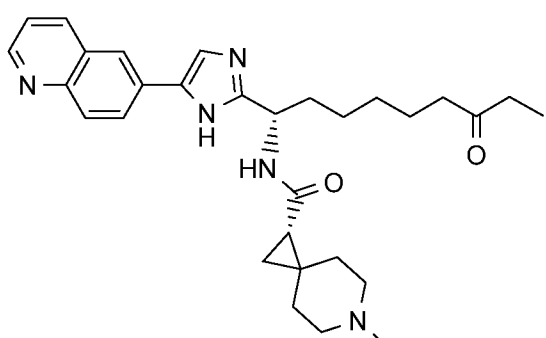
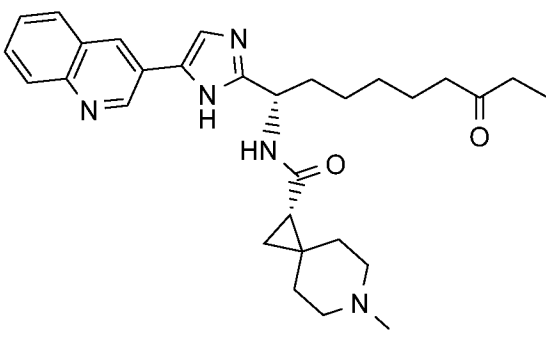
146		548.3
150		572.4
158		568.4
159		545.3
160		532.4

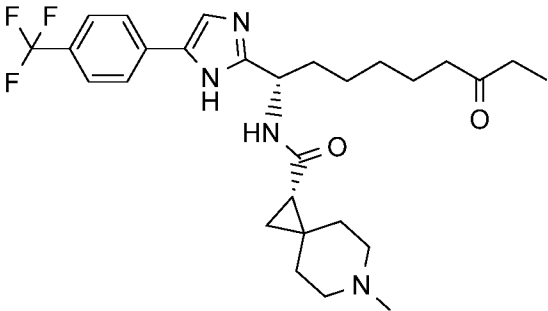
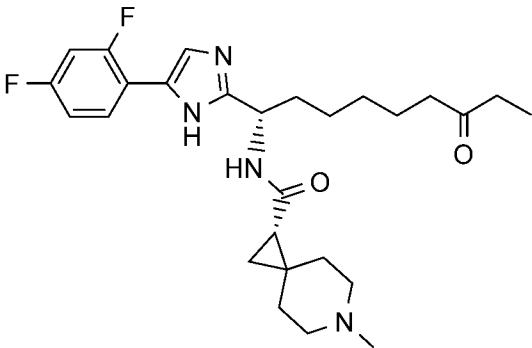
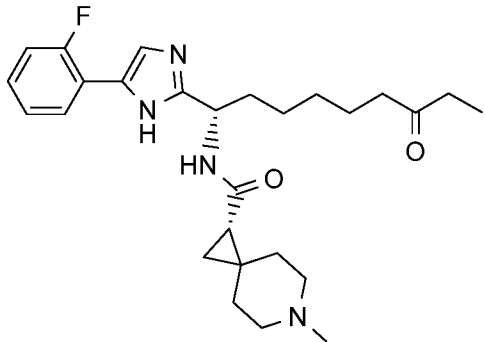
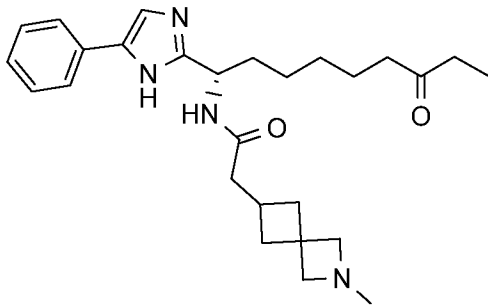
170		532.1
172		546.2
174		550.3
177		566.1

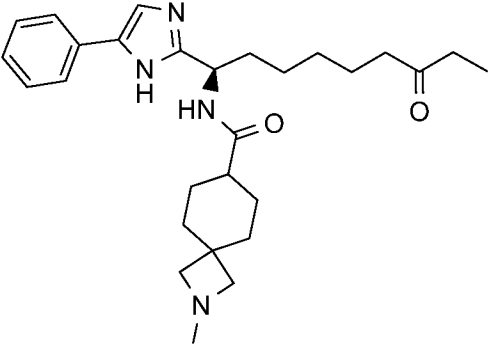
181		546.2
183		525.2
190		549.2
197		513.1

205		547.1
206		549.2
208		509.2
211		560.3

238		545.3
241		571.4
244		576.2
245		590.2

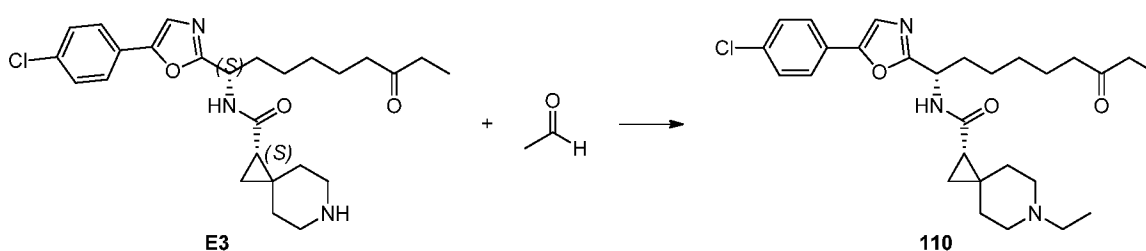
280		469.4
281		502.3
282		502.4
283		502.4

284		519.4
289		487.3
290		469.4
307		451.4

310		465.4
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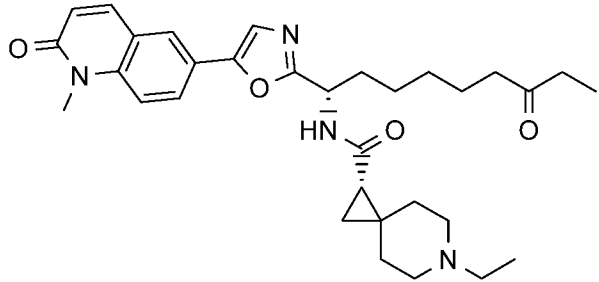
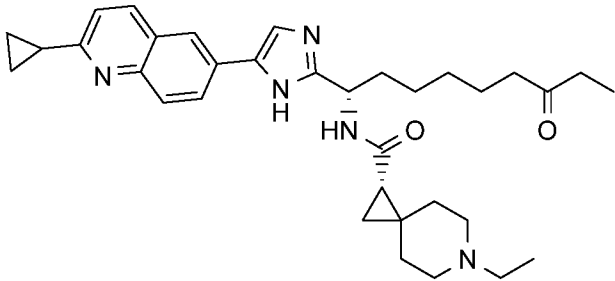
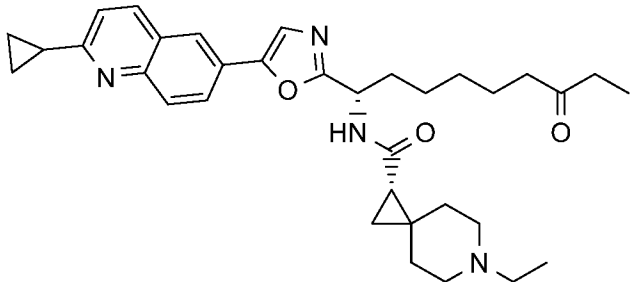
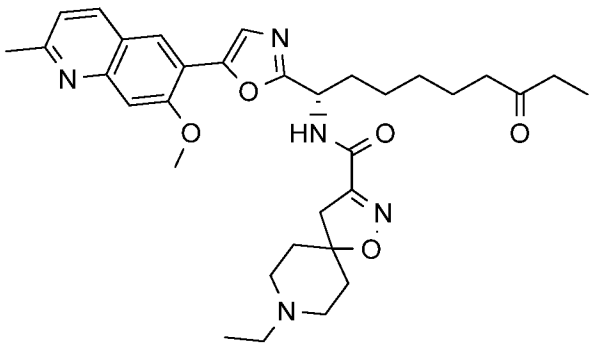
Example 60

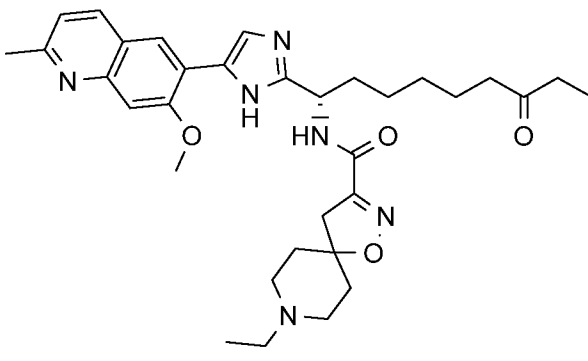
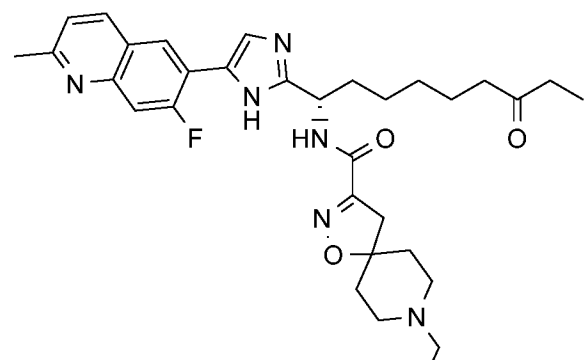
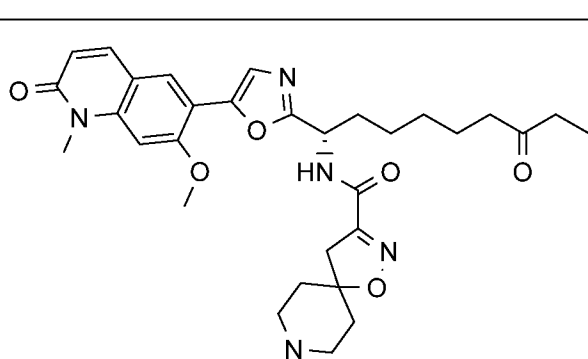
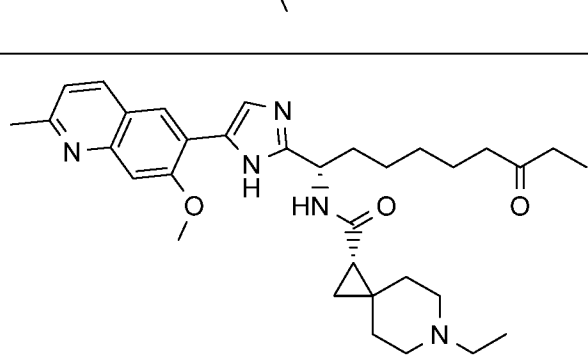
(1*S*)-*N*-{(1*S*)-1-[5-(4-chlorophenyl)-1,3-oxazol-2-yl]-7-oxononyl}-6-ethyl-6-azaspiro[2.5]octane-1-carboxamide (**110**)



Acetaldehyde (5 mL, 5.24 mmol) was added to a stirred mixture of (*S*)-*N*-((*S*)-1-(5-(4-chlorophenyl)oxazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**E3**, 2.475 g, 5.24 mmol) in MeOH (5 mL) at room temperature and the mixture was stirred at room temperature for 4 h. Then, NaBH(OAc)₃ (11.11 g, 52.4 mmol) was added. The mixture was stirred at rt for 1 h. Most of the MeOH was removed, water (15 mL) was added and the mixture was extracted with DCM (3 x 15 mL). The combined organic fractions were washed with brine (saturated, 2 x 20 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with DCM/MeOH = 0-15% and then purified by preparative HPLC, eluting with acetonitrile/water + 0.1% TFA, to give (*S*)-*N*-((*S*)-1-(5-(4-chlorophenyl)oxazol-2-yl)-7-oxononyl)-6-ethyl-6-azaspiro[2.5]octane-1-carboxamide (**110**). LCMS (ESI) calc'd for C₂₈H₃₈ClN₃O₃ [M+H]⁺: 500.3, found: 500.2. ¹H NMR (400 MHz, MeOD) δ 7.64-7.74 (m, 2H), 7.43-7.51 (m, 3H), 5.07-5.16 (m, 1H), 3.48-3.64 (m, 2H), 2.98-3.24 (m, 4H), 2.83 (dd, *J* = 9.0, 19.63 Hz, 1H), 2.46 (q, *J* = 7.3 Hz, 3H), 2.23 (d, *J* = 13.0 Hz, 1H), 1.73-2.09 (m, 6H), 1.54-1.62 (m, 2H), 1.18-1.41 (m, 8H), 0.97-1.10 (m, 3H), 0.80 (t, *J* = 7.5 Hz, 1H).

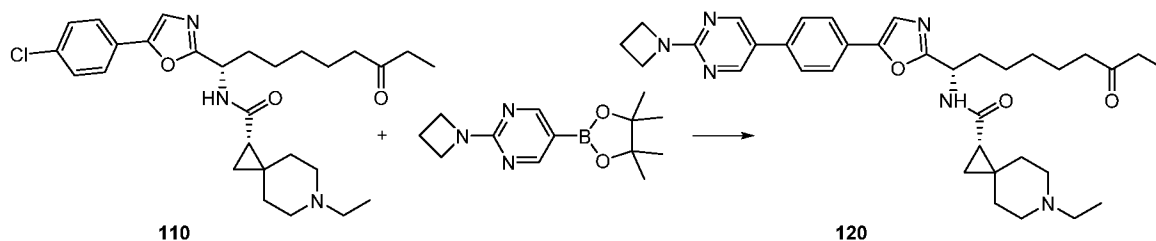
The following compounds were prepared using similar procedures as described for compound **110**.

ID	Structure	Observed [M+H] ⁺
97		547.4
101		556.3
114		557.3
204		590.1

207		589.4
233		577.1
235		606.1
243		560.3

Example 61

(1*S*)-*N*-[(1*S*)-1-{5-[4-(2-azetidin-1-ylpyrimidin-5-yl)phenyl]-1,3-oxazol-2-yl}-7-oxononyl]-6-ethyl-6-azaspiro[2.5]octane-1-carboxamide (**120**)



110 **120**

5 Pd₂(dba)₃ (9 mg, 9.83 μmol) was added to a stirred mixture of K₂CO₃ (83 mg, 0.600 mmol), TCP (7 mg, 0.025 mmol), 2-(azetidin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (63 mg, 0.241 mmol) and (*S*)-*N*-((*S*)-1-(5-(4-chlorophenyl)oxazol-2-yl)-7-oxononyl)-6-ethyl-6-azaspiro[2.5]octane-1-carboxamide (**110**, 100 mg, 0.200 mmol) in dioxane (4.0 mL) and water (0.4 mL) at room temperature and the mixture was stirred at 100°C for 12 h

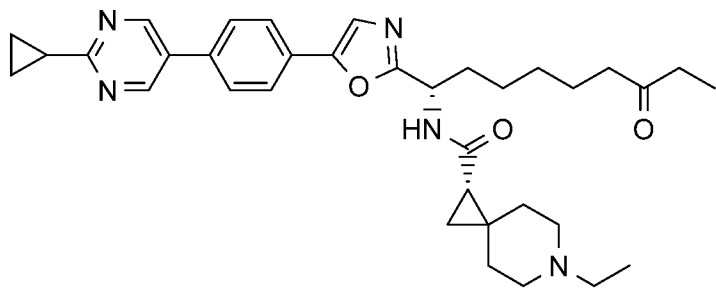
10 under N₂. The residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.1% TFA, to give (*S*)-*N*-((*S*)-1-(5-(4-(2-(azetidin-1-yl)pyrimidin-5-yl)phenyl)oxazol-2-yl)-7-oxononyl)-6-ethyl-6-azaspiro[2.5]octane-1-carboxamide (**120**).

Hydrogen chloride (0.1 M, 1.4 mL, 0.140 mmol) was added to a stirred mixture of (*S*)-*N*-((*S*)-1-(5-(4-(2-(azetidin-1-yl)pyrimidin-5-yl)phenyl)oxazol-2-yl)-7-oxononyl)-6-ethyl-6-

15 azaspiro[2.5]octane-1-carboxamide (**120**, 40 mg, 0.067 mmol) in acetonitrile (4 mL) and water (4 mL) at room temperature. The mixture was freeze-dried to give (*S*)-*N*-((*S*)-1-(5-(4-(2-(azetidin-1-yl)pyrimidin-5-yl)phenyl)oxazol-2-yl)-7-oxononyl)-6-ethyl-6-azaspiro[2.5]octane-1-carboxamide hydrochloride. LCMS (ESI) calc'd for C₃₅H₄₆N₆O₃ [M+H]⁺: 599.4, found: 599.4.

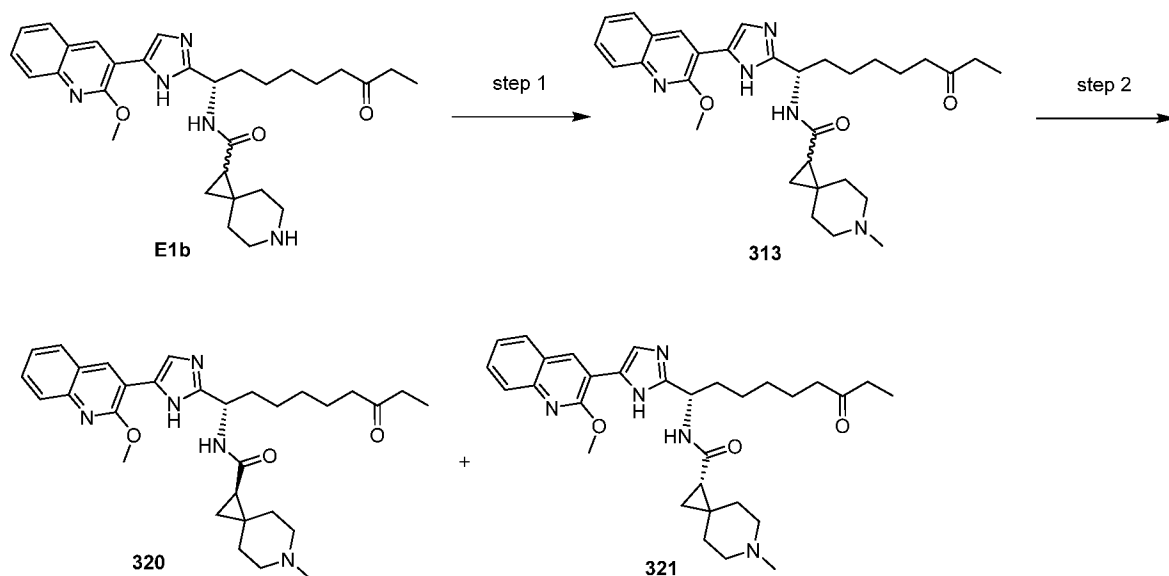
20 ¹H NMR (400 MHz, MeOD) δ 8.93 (brs, 2H), 7.69-7.93 (m, 4H), 7.56 (brs, 1H), 5.07-5.17 (m, 1H), 4.46 (t, *J* = 7.61 Hz, 3H), 3.52-3.77 (m, 2H), 3.37 (m, 1H), 3.15-3.24 (m, 2H), 2.97-3.09 (m, 1H), 2.88 (d, *J* = 10.58 Hz, 1H), 2.61 (m, 2H), 2.46 (q, *J* = 7.57 Hz, 3H), 2.16-2.37 (m, 2H), 1.79-2.10 (m, 5H), 1.19-1.66 (m, 11H), 0.96-1.09 (m, 3H), 0.81 (t, *J* = 7.50 Hz, 1H).

The following compound was prepared using a similar procedures as described for compound **120**.

ID	Structure	Observed [M+H] ⁺
161		584.3

Example 62

N-((S)-1-(5-(2-methoxyquinolin-3-yl)-1H-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (313), (R)-N-((S)-1-(5-(2-methoxyquinolin-3-yl)-1H-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (320), and (S)-N-((S)-1-(5-(2-methoxyquinolin-3-yl)-1H-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (321)

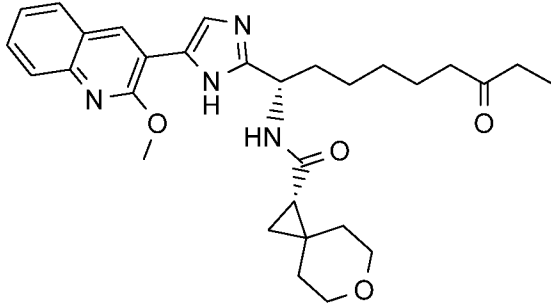
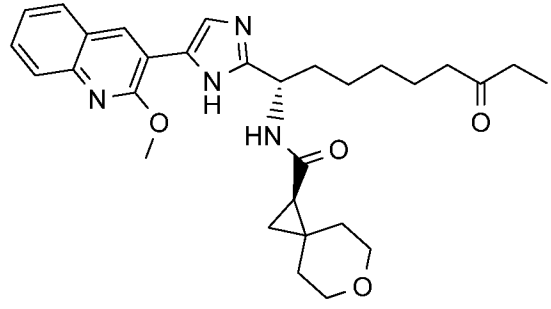
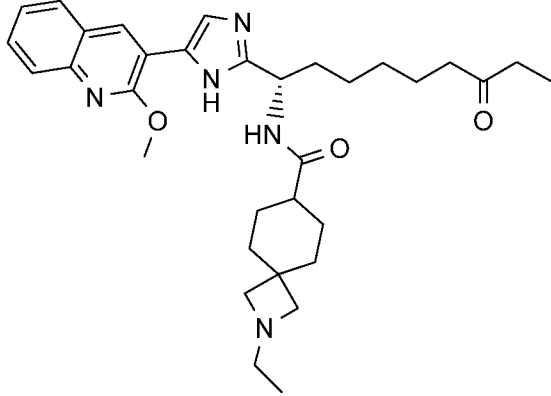


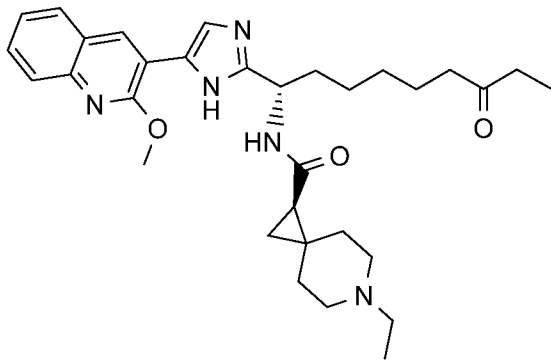
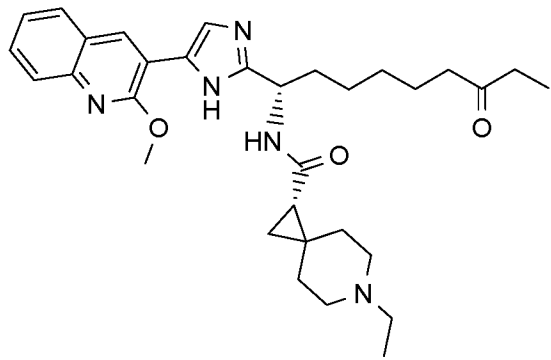
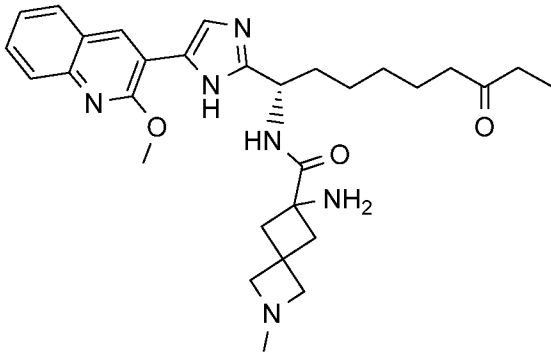
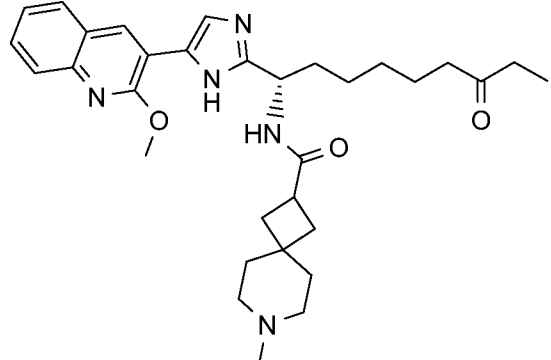
Step 1: E1b (150 mg, 0.29 mmol), formaldehyde (141 μ l, 1.739 mmol), MeOH (1449 μ l), and THF (1449 μ l) was added to a 4 mL pressure vial with a pressure release cap. The reaction was stirred at 25°C for 10 minutes, then sodium triacetoxyborohydride (184 mg, 0.869 mmol) was added. The reaction was stirred 25°C at 2 hours. The product was purified by C18 chromatography (30g, CH₃CN in water with 0.1% TFA: 0% to 90%) to give **313** (TFA salt). LCMS (ESI) calc'd for C₃₁H₄₂N₅O₃ [M+H]⁺: 532.3, found: 532.4.

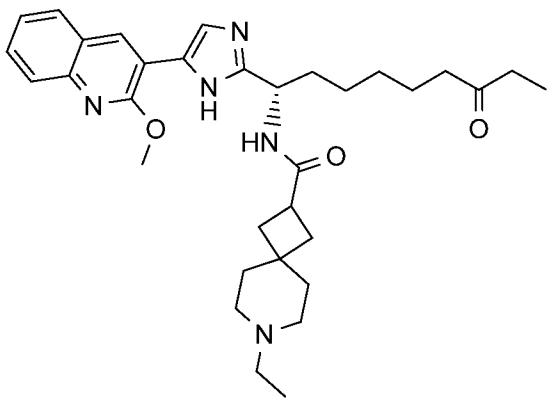
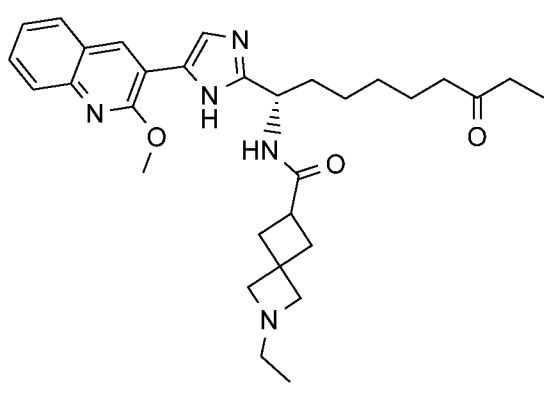
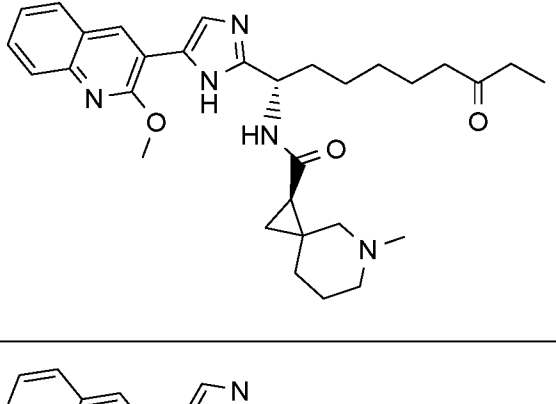
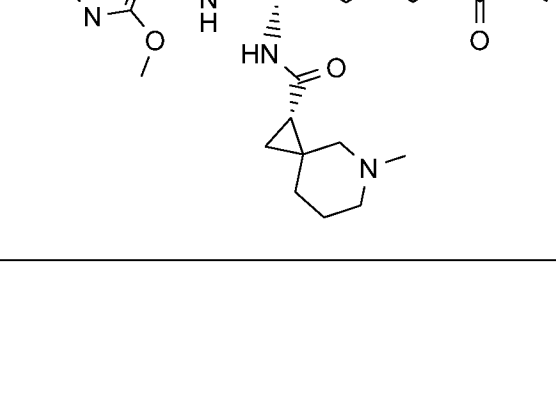
Step 2: **313** (TFA salt, 175 mg, 0.27 mmol) was separated by chiral SFC to **320** (1st peak), LCMS (ESI) calc'd for C₃₁H₄₂N₅O₃ [M+H]⁺: 532.3, found: 532.5, and **321** (2nd peak), LCMS (ESI) calc'd for C₃₁H₄₂N₅O₃ [M+H]⁺: 532.3, found: 532.4. SFC conditions: Column: 2.1 x 25.0

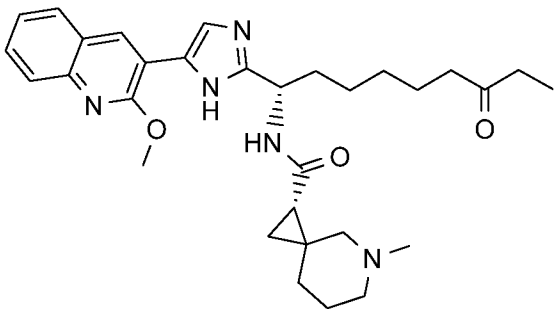
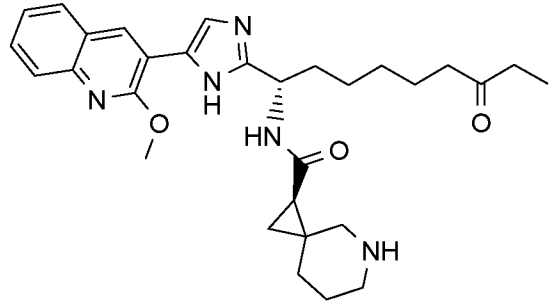
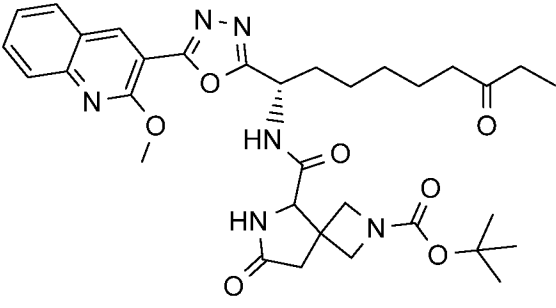
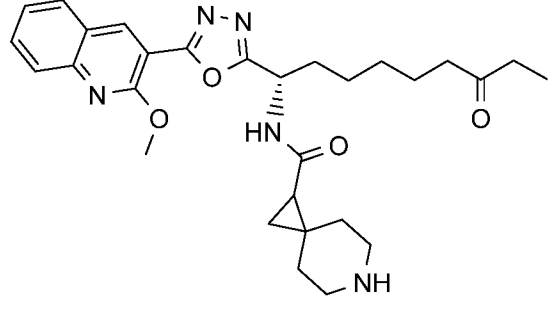
cm Chiralpak AD-H; CO₂ co-solvent: isopropanol with 0.25% isopropylamine; Mobile phase: 40% co-solvent; flow rate: 80 mL/min, temperature: 25°C

The following compounds were prepared using similar procedures as described for compound **321**.

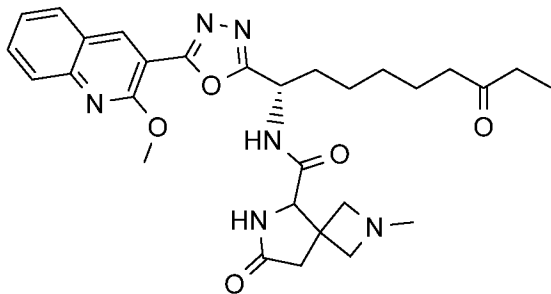
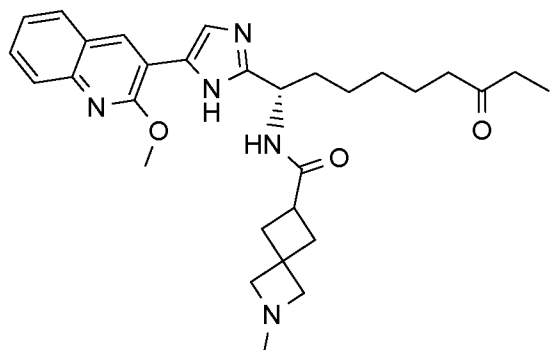
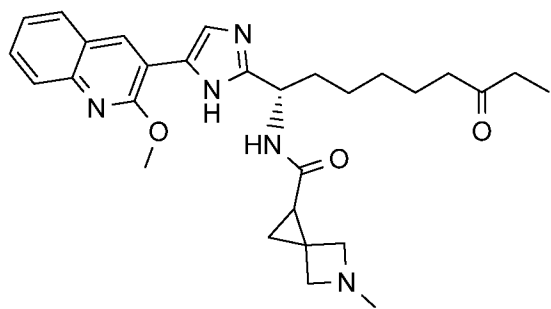
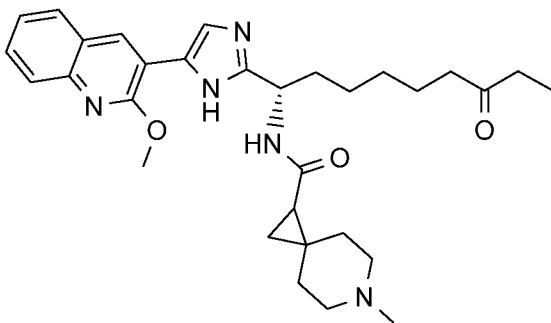
ID	Structure	Observed [M+H] ⁺
63		519.3
64		519.3
271		560.4

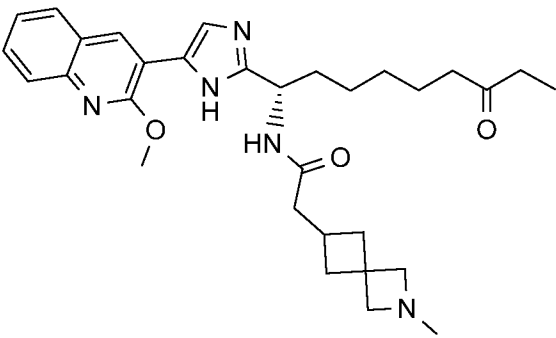
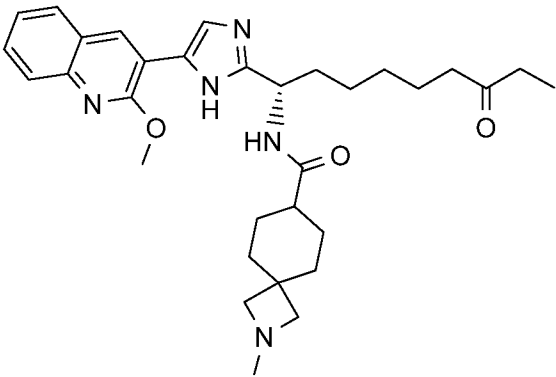
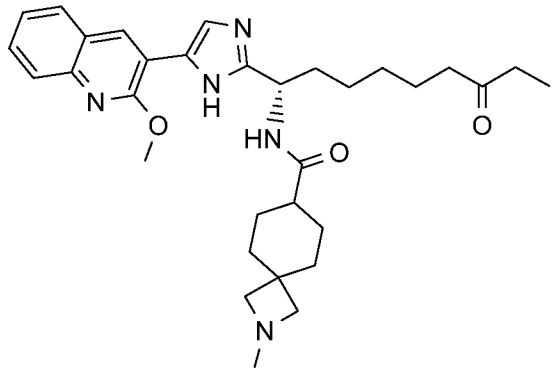
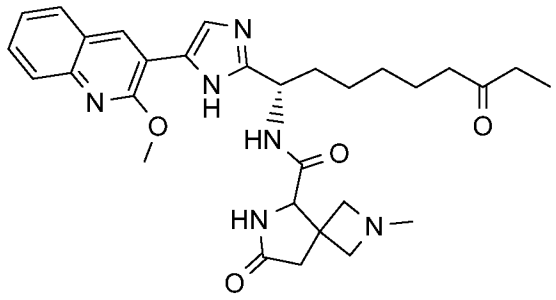
274		546.5
275		546.4
276		533.4
277		546.5

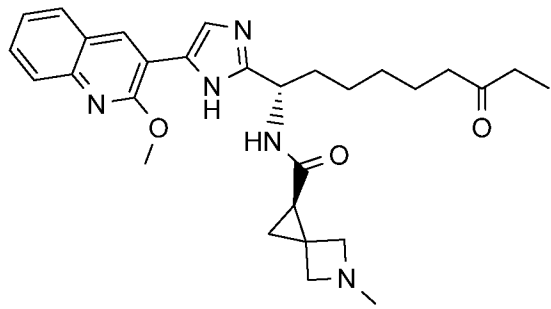
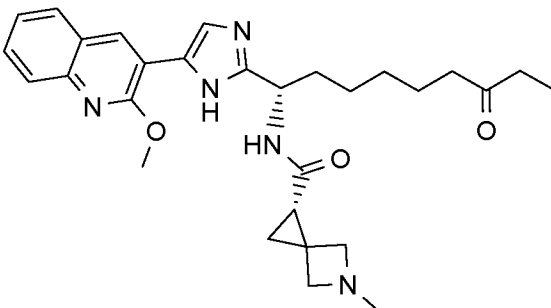
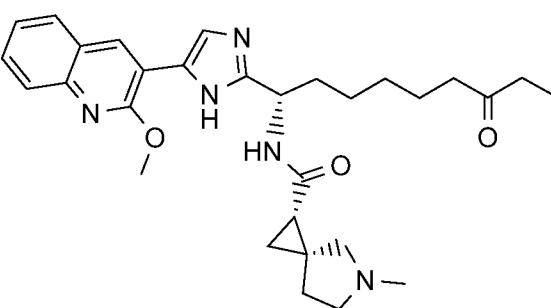
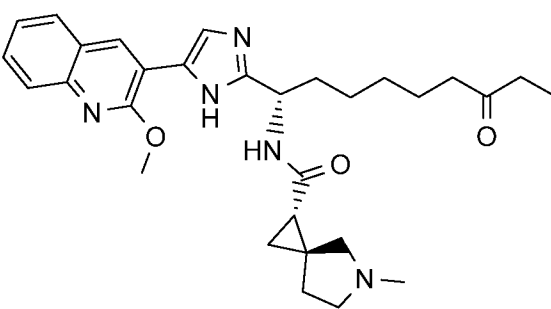
278		560.5
279		532.5
285		532.4
286		532.4

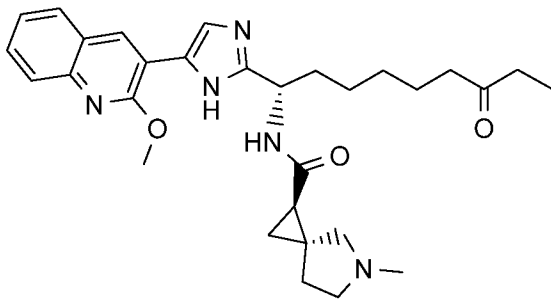
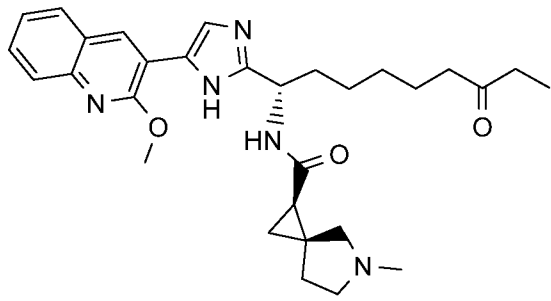
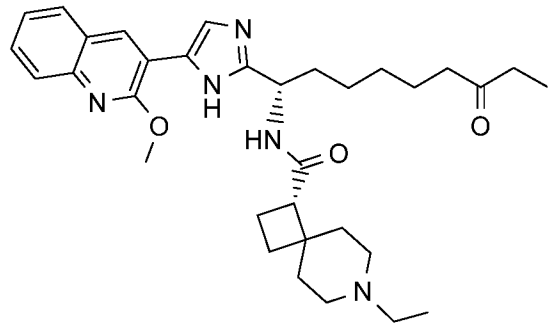
287		532.4
288		532.4
302		635.5
303		520.4

304	 <chem>CCCCCCCC(=O)C[C@H](C(=O)N1CC2CCNCC2C1=O)C(=O)Oc3cc4ccccc4nc3</chem>	535.4
305	 <chem>CCCCCCCC(=O)C[C@H](C(=O)N1CC2CCN(C)CC2C1=O)C(=O)Oc3cc4ccccc4nc3</chem>	534.4
306	 <chem>CCCCCCCC(=O)C[C@@H](C(=O)N1CC2CCN(C)CC2C1=O)C(=O)Oc3cc4ccccc4nc3</chem>	534.4
308	 <chem>CCCCCCCC(=O)C[C@H](C(=O)N1CC2CCN(C)CC2C1=O)C(=O)Oc3cc4ccccc4nc3</chem>	534.4

309		549.3
311		518.4
312		504.4
313		532.4

314		532.1
315		546.4
316		
317		547.2

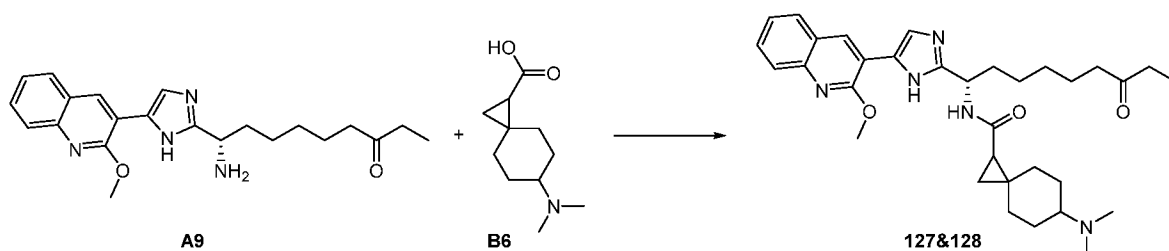
322		504.3
323		504.3
327		518.4
328		518.3

329		518.4
330		518.4
338		560.2

Example 63

6-(dimethylamino)-*N*-{(1*S*)-1-[5-(2-methoxyquinolin-3-yl)-1*H*-imidazol-2-yl]-7-oxononyl}spiro[2.5]octane-1-carboxamide (127&128)

5



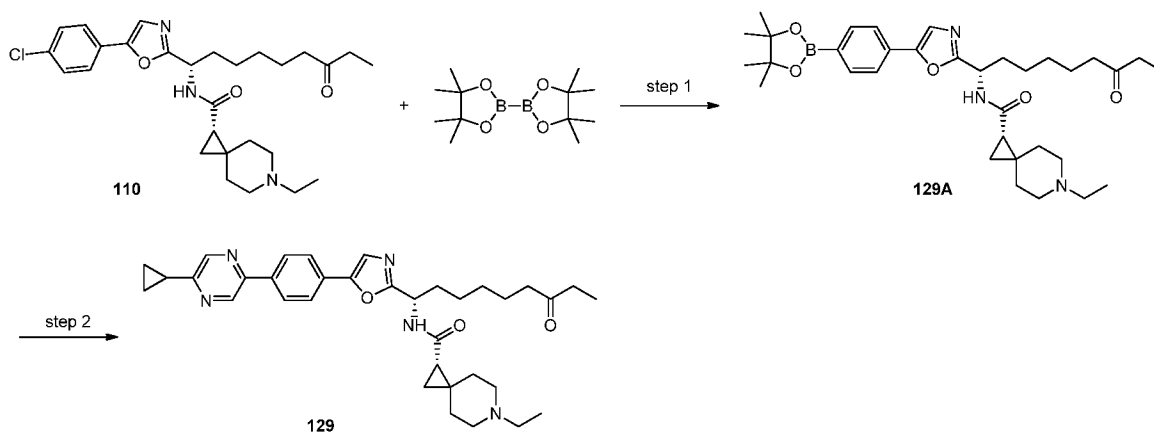
Step 5: Preparation of 6-(dimethylamino)-*N*-((*S*)-1-(5-(2-methoxyquinolin-3-yl)-1*H*-imidazol-2-yl)-7-oxononyl)spiro[2.5]octane-1-carboxamide (127 & 128): (*S*)-9-amino-9-(5-(2-methoxyquinolin-3-yl)-1*H*-imidazol-2-yl)nonan-3-one (**A9**, 174 mg, 0.456 mmol) was added to

the stirred mixture of DIPEA (0.159 mL, 0.912 mmol), T₃P (435 mg, 0.684 mmol) and 6-(dimethylamino)spiro[2.5]octane-1-carboxylic acid (**B6**, 90 mg, 0.456 mmol) in DMF (1.5 mL), and the resultant mixture was stirred at 20°C for 2 h. The mixture was quenched with water (10 mL), and the mixture was extracted with ethyl acetate (2 x 20 mL). The combined organic fractions were washed with brine (saturated, 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by preparative TLC on silica gel, eluting with DCM / MeOH =10:1 (with 2% NH₄OH) to give 6-(dimethylamino)-*N*-((*S*)-1-(5-(2-methoxyquinolin-3-yl)-1*H*-imidazol-2-yl)-7-oxononyl)spiro[2.5]octane-1-carboxamide (mixture of 4 isomers). LCMS (ESI) calc'd for C₃₃H₄₅N₃O₃ [M+H]⁺: 560.4, found: 560.4. The mixture was further separated by Chiral SFC on Chiralpak AD column, eluent with 5% to 40% ethanol in CO₂ (0.05% DEA) to give the title compounds **127** (first eluent, contained second eluent) and **128** (the third eluent, contained the fourth eluent).

For **127**, ¹H NMR (400 MHz, MeOD) δ 8.50-8.67 (m, 1H), 7.73-7.85 (m, 2H), 7.51-7.64 (m, 2H), 7.33-7.44 (m, 1H), 5.03-5.16 (m, 1H), 4.16 (s, 3H), 2.74 (brs, 1H), 2.42 (q, *J* = 7.04 Hz, 4H), 2.29 (brs, 1H), 1.90-2.10 (m, 7H), 1.68-1.85 (m, 3H), 1.30-1.63 (m, 11H), 1.08-1.19 (m, 1H), 0.92-1.03 (m, 4H), 0.65-0.88 (m, 2H). For **128**, ¹H NMR (400 MHz, MeOD) δ 8.40-8.83 (m, 1H), 7.79 (t, *J* = 7.24 Hz, 2H), 7.49-7.66 (m, 2H), 7.38 (t, *J* = 7.43 Hz, 1H), 4.99-5.14 (m, 1H), 4.10-4.24 (m, 3H), 3.01-3.16 (m, 1H), 2.26-2.49 (m, 9H), 1.71-2.08 (m, 6H), 1.25-1.65 (m, 9H), 0.72-1.22 (m, 7H).

Example 64

(1*S*)-*N*-[(1*S*)-1-{5-[4-(5-cyclopropylpyrazin-2-yl)phenyl]-1,3-oxazol-2-yl}-7-oxononyl]-6-ethyl-6-azaspiro[2.5]octane-1-carboxamide (**129**)



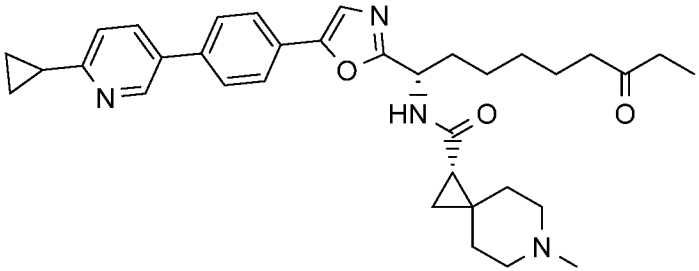
Step 1: Preparation of (S)-6-ethyl-N-((S)-7-oxo-1-(5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxazol-2-yl)nonyl)-6-azaspiro[2.5]octane-1-carboxamide (**129A**): Potassium acetate (40 mg, 0.408 mmol) and Pd₂(dba)₃ (8 mg, 8.74 μmol) was added to the mixture of BPD (76 mg,

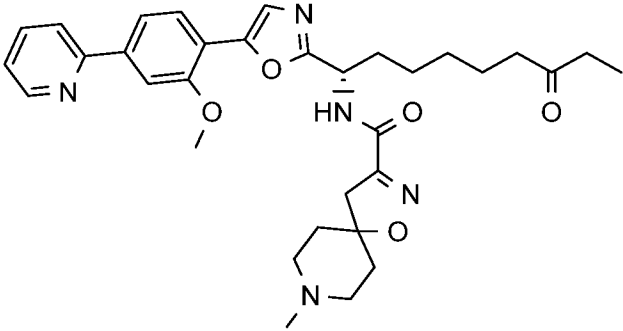
0.300 mmol) and XPhos (20 mg, 0.042 mmol) and (*S*)-*N*-((*S*)-1-(5-(4-chlorophenyl)oxazol-2-yl)-7-oxononyl)-6-ethyl-6-azaspiro[2.5]octane-1-carboxamide (**110**, 100 mg, 0.200 mmol) in dioxane (1.5 mL). The resultant mixture was stirred at 80°C under N₂ overnight. The mixture was concentrated *in vacuo*. The residue was combined with a same reaction from 100 mg of chloride and purified by silica gel flash chromatography (ISCORF75; Sepa flash column), eluting with DCM / MeOH/NH₃(Aq.) = 10: 1.5: 0.02 to give (*S*)-6-ethyl-*N*-((*S*)-7-oxo-1-(5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxazol-2-yl)nonyl)-6-azaspiro[2.5]octane-1-carboxamide (**129A**). LCMS (ESI) calc'd for C₃₄H₅₀BN₃O₅ [M+H]⁺: 592.4, found: 592.4

Step 2: Preparation of (*S*)-*N*-((*S*)-1-(5-(4-(5-cyclopropylpyrazin-2-yl)phenyl)oxazol-2-yl)-7-

oxononyl)-6-ethyl-6-azaspiro[2.5]octane-1-carboxamide (**129**): K₂CO₃ (98 mg, 0.710 mmol) and PdCl₂(DTBPF) (20 mg, 0.031 mmol) was added to the solution of (*S*)-6-ethyl-*N*-((*S*)-7-oxo-1-(5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxazol-2-yl)nonyl)-6-azaspiro[2.5]octane-1-carboxamide (**129A**, 210 mg, 0.355 mmol) and 2-bromo-5-cyclopropylpyrazine (75 mg, 0.377 mmol) in dioxane (2 mL) and water (0.3 mL), and the resultant mixture was stirred at 70°C for 16 h. The mixture was filtered and the filter cake was washed with MeOH (10 mL). The filtrate was concentrated to dryness. The residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile / water + 0.1% TFA, to give (*S*)-*N*-((*S*)-1-(5-(4-(5-cyclopropylpyrazin-2-yl)phenyl)oxazol-2-yl)-7-oxononyl)-6-ethyl-6-azaspiro[2.5]octane-1-carboxamide hydrochloride (**129**). LCMS (ESI) calc'd for C₃₅H₄₅N₅O₃ [M+H]⁺: 584.4, found: 584.4. ¹H NMR (400 MHz, MeOD) δ 9.06-9.18 (m, 1H), 8.82 (s, 1H), 8.14-8.28 (m, 2H), 7.90 (d, *J* = 7.94 Hz, 2H), 7.60-7.74 (m, 1H), 5.07-5.20 (m, 1H), 3.48-3.65 (m, 1H), 3.35 (m, 1H), 2.77-3.25 (m, 4H), 2.21-2.53 (m, 5H), 1.78-2.13 (m, 5H), 1.16-1.66 (m, 16H), 0.75-1.10 (m, 4H).

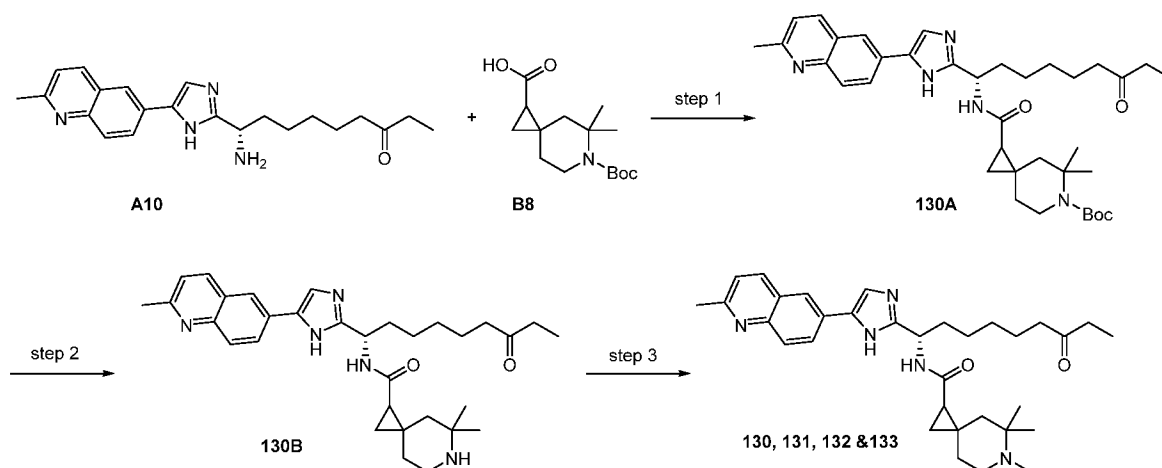
The following compounds were prepared using similar procedures as described for compound **129**.

ID	Structure	Observed [M+H] ⁺
143		569.3

391		588.1
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Example 65

5,5,6-trimethyl-*N*-{[(1*S*)-1-[5-(2-methylquinolin-6-yl)-1*H*-imidazol-2-yl]-7-oxononyl]-6-azaspiro[2.5]octane-1-carboxamide (130, 131, 132 & 133)



Step 1: Preparation of tert-butyl 5,5-dimethyl-1-(((*S*)-1-(5-(2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (130A**):** T₃P (404 mg, 0.635 mmol) was added to a stirred mixture of (*S*)-9-amino-9-(5-(2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)nonan-3-one (**A10**, 127 mg, 0.349 mmol), 6-(tert-butoxycarbonyl)-5,5-dimethyl-6-azaspiro[2.5]octane-1-carboxylic acid (**B8**, 90 mg, 0.318 mmol) and DIPEA (0.166 mL, 0.953 mmol) in DMF (2.0 mL) at room temperature and the mixture was stirred at rt for 3 h. The mixture was cooled, diluted with ethyl acetate (20 mL) and H₂O (8 mL), washed with brine (saturated, 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by preparative TLC on silica gel, eluting with DCM : MeOH = 10:1 to give tert-butyl 5,5-dimethyl-1-(((*S*)-1-(5-(2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**130A**). LCMS (ESI) calc'd for C₃₇H₅₁N₅O₄ [M+H]⁺: 630.4, found: 630.4

Step 2: Preparation of 5,5-dimethyl-N-((S)-1-(5-(2-methylquinolin-6-yl)-1H-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (130B): TFA (0.5 mL, 6.49 mmol) was added to a stirred mixture of tert-butyl 5,5-dimethyl-1-(((S)-1-(5-(2-methylquinolin-6-yl)-1H-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**130A**, 135 mg, 0.214 mmol) in DCM (2.0 mL) at room temperature and the mixture was stirred at rt for 2 h. The mixture was concentrated to afford 5,5-dimethyl-N-((S)-1-(5-(2-methylquinolin-6-yl)-1H-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**130B**) without further purification. LCMS (ESI) calc'd for C₃₂H₄₃N₅O₂ [M+H]⁺: 530.3, found: 530.4

Step 3: Preparation of 5,5,6-trimethyl-N-((S)-1-(5-(2-methylquinolin-6-yl)-1H-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (130, 131, 132, 133): HCHO solution (0.1 mL) was added to a stirred mixture of 5,5-dimethyl-N-((S)-1-(5-(2-methylquinolin-6-yl)-1H-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**130B**, 110 mg, 0.208 mmol) in MeOH (3.0 mL) at room temperature and the mixture was stirred at rt for 18 h. NaBH(OAc)₃ (440 mg, 2.077 mmol) was added to the above mixture solution, and it was stirred at rt for 2 h, and then concentrated. The residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.1% TFA and then separated by chiral SFC on Chiralpak AD column, eluent 5% to 40% ethanol in CO₂ (0.05% DEA) to afford the title compounds.

130. Fast eluent on HPLC and second eluent on SFC, LCMS (ESI) calc'd for C₃₃H₄₅N₅O₂ [M+H]⁺: 544.4, found: 544.4, ¹H NMR (400 MHz, MeOD) δ 8.88 (d, *J* = 8.60 Hz, 1H), 8.60 (d, *J* = 5.73 Hz, 1H), 8.36-8.45 (m, 1H), 8.22 (d, *J* = 9.04 Hz, 1H), 8.06 (s, 1H), 7.91 (d, *J* = 8.60 Hz, 1H), 5.14-5.26 (m, 1H), 3.33-3.42 (m, 2H), 3.01-3.10 (m, 1H), 2.98 (s, 3H), 2.79-2.88 (m, 3H), 2.41-2.51 (m, 4H), 1.71-2.32 (m, 6H), 1.71-1.78 (m, 1H), 1.22-1.64 (m, 16H), 1.04-1.15 (m, 1H), 0.99 (t, *J* = 7.28 Hz, 3H).

131. Second eluent on HPLC and second eluent on SFC, LCMS (ESI) calc'd for C₃₃H₄₅N₅O₂ [M+H]⁺: 544.4, found: 544.4, ¹H NMR (400 MHz, MeOD) δ 8.91 (d, *J* = 8.60 Hz, 1H), 8.57-8.68 (m, 1H), 8.41 (d, *J* = 8.60 Hz, 1H), 8.24 (d, *J* = 8.82 Hz, 1H), 8.04-8.12 (m, 1H), 7.93 (d, *J* = 8.60 Hz, 1H), 5.10 (t, *J* = 7.50 Hz, 1H), 3.32-3.44 (m, 1H), 3.11-3.29 (m, 2H), 2.99 (s, 3H), 2.71-2.86 (m, 3H), 2.22-2.58 (m, 5H), 1.77-2.21 (m, 5H), 1.05-1.74 (m, 16H), 0.75-1.03 (m, 3H).

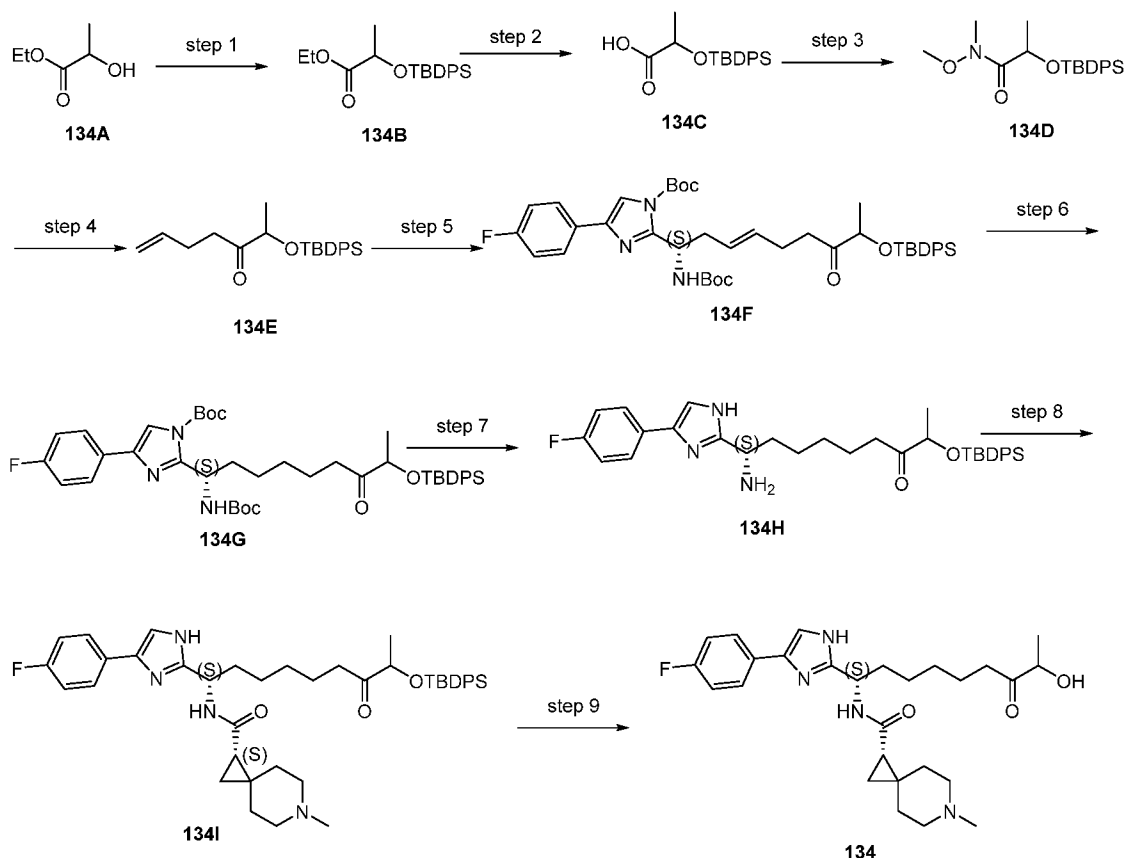
132. Fast eluent on HPLC and first eluent on SFC, LCMS (ESI) calc'd for C₃₃H₄₅N₅O₂ [M+H]⁺: 544.4, found: 544.4, ¹H NMR (400 MHz, MeOD) δ 8.81 (dd, *J* = 2.32, 8.49 Hz, 1H), 8.55 (brs, 1H), 8.36 (d, *J* = 8.82 Hz, 1H), 8.19 (d, *J* = 8.82 Hz, 1H), 8.03 (s, 1H), 7.86 (d, *J* = 8.60 Hz, 1H), 5.05-5.24 (m, 1H), 3.32-3.56 (m, 3H), 2.95 (s, 3H), 2.84 (d, *J* = 8.60 Hz, 3H), 2.40-2.54 (m, 4H), 1.65-2.37 (m, 6H), 1.22-1.63 (m, 15H), 0.87-1.19 (m, 4H).

133. Second eluent on HPLC and first eluent on SFC, LCMS (ESI) calc'd for C₃₃H₄₅N₅O₂

[M+H]⁺: 544.4, found: 544.4, ¹H NMR (400 MHz, MeOD) δ 8.80 (d, *J* = 8.60 Hz, 1H), 8.55 (d, *J* = 9.92 Hz, 1H), 8.30-8.41 (m, 1H), 8.18 (d, *J* = 8.82 Hz, 1H), 8.01 (d, *J* = 4.85 Hz, 1H), 7.85 (d, *J* = 8.60 Hz, 1H), 5.02-5.18 (m, 1H), 3.21-3.29 (m, 1H), 2.94 (s, 3H), 2.66-2.81 (m, 3H), 2.40-2.52 (m, 4H), 1.68-2.32 (m, 7H), 1.20-1.63 (m, 14H), 0.84-1.19 (m, 6H).

Example 66

(1*S*)-*N*-{(1*S*)-1-[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]-8-hydroxy-7-oxononyl}-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (134)



- 10 **Step 1: Preparation of ethyl 2-((tert-butyldiphenylsilyl)oxy)propanoate (134B):** TBDPSCl (3.3 mL, 12.85 mmol) and imidazole (0.576 g, 8.47 mmol) were added to a stirred mixture of ethyl 2-hydroxypropanoate (134A, 1 g, 8.47 mmol) in THF (10 mL) at 0°C and the mixture was stirred at rt for 18 h. The mixture was extracted with ethyl acetate (100 mL*2). The combined organic fractions were washed with water (50 mL), dried (Na₂SO₄), filtered and the solvent was
- 15 evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 0-30% to give ethyl 2-((tert-butyldiphenylsilyl)oxy) propanoate (134B). ¹H NMR (400 MHz, CDCl₃) δ 7.69 (t, *J* = 7.94 Hz,

4H), 7.30-7.52 (m, 6H), 4.28 (q, $J = 6.84$ Hz, 1H), 4.03 (q, $J = 6.98$ Hz, 2H), 1.38 (d, $J = 6.62$ Hz, 3H), 1.16 (t, $J = 7.06$ Hz, 3H), 1.11 (s, 9H).

Step 2: Preparation of 2-((tert-butyl)diphenylsilyl)oxy)propanoic acid (134C): Lithium

hydroxide hydrate (0.377 g, 8.98 mmol) was added to a stirred mixture of ethyl 2-((tert-butyl)diphenylsilyl)oxy)propanoate (**134B**, 1.6 g, 4.49 mmol) in THF (5 mL), MeOH (5 mL),
5 water (2 mL) at 25°C and the mixture was stirred at 25°C for 1 h. The mixture was acidified by 1 M HCl to pH=5-6 then extracted with ethyl acetate (50 mL*2). The combined organic fractions were washed with water (20 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure to afford 2-((tert-butyl)diphenylsilyl)oxy) propanoic acid
10 (**134C**) which was used to next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.59-7.69 (m, 5H), 7.33-7.45 (m, 7H), 4.34 (q, $J = 6.84$ Hz, 1H), 1.32 (d, $J = 6.84$ Hz, 3H), 1.13 (s, 9H).

Step 3: Preparation of 2-((tert-butyl)diphenylsilyl)oxy)-N-methoxy-N-methyl propanamide

(134D): Oxalyl dichloride (0.3 mL, 3.42 mmol) was added to a stirred mixture of 2-((tert-butyl)diphenylsilyl)oxy)propanoic acid (**134C**, 1 g, 3.04 mmol) in DCM (10 mL) at 25°C and
15 followed by *N,N*-dimethylformamide (two drops), and the mixture was stirred at 25°C for 1 h. The mixture was added to a stirred mixture of *N,O*-dimethylhydroxylamine hydrochloride (1.45 g, 15.3 mmol) in water (20 mL) which was basified by NaHCO₃ (0.25 g, 3.05 mmol) to pH=7-8 at 0°C and the mixture was stirred at 0°C for 1 h. The mixture was extracted with DCM (25
20 mL*2), and washed with water (20 mL). The combined organic fractions were dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure to afford 2-((tert-butyl)diphenylsilyl)oxy)-*N*-methoxy-*N*-methyl propanamide (**134D**) which was used to next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.71 (d, $J = 6.26$ Hz, 4H), 7.31-7.48 (m, 6H), 4.53 (q, $J = 6.65$ Hz, 1H), 2.95-3.20 (m, 6H), 1.38 (d, $J = 6.26$ Hz, 3H), 1.09 (s, 9H).

Step 4: Preparation of 2-((tert-butyl)diphenylsilyl)oxy)hept-6-en-3-one (134E): I₂ (164 mg,

0.646 mmol) and magnesium (314 mg, 12.92 mmol) were added to a stirred mixture of 4-bromobut-1-ene (872 mg, 6.46 mmol) in THF (5 mL) at 25°C under N₂ atmosphere. The exothermic reaction was complete when the temperature returned to room temperature. The mixture was used into next step without further purification. But-3-en-1-ylmagnesium bromide
25 solution was added to a stirred mixture of 2-((tert-butyl)diphenylsilyl)oxy)-*N*-methoxy-*N*-methylpropanamide (**134D**, 800 mg, 2.153 mmol) in THF (5 mL) at 0°C and the mixture was stirred at 0°C for 3 h. The mixture was quenched with NH₄Cl aq and the mixture was extracted with ethyl acetate (50 mL*2) and washed with water. The combined organic fractions were evaporated under reduced pressure. The residue was purified by silica gel column flash
30

chromatography, eluting with petroleum ether/EtOAc = 0-30% to give 2-((tert-butylidiphenylsilyl)oxy)hept-6-en-3-one (**134E**). ¹H NMR (400 MHz, CDCl₃) δ 7.59-7.70 (m, 4H), 7.33-7.49 (m, 6H), 5.78 (m, 1H), 4.91-5.06 (m, 2H), 4.22 (q, *J* = 6.91 Hz, 1H), 2.66 (dt, *J* = 2.74, 7.24 Hz, 2H), 2.24 (q, *J* = 7.04 Hz, 2H), 1.20 (d, *J* = 6.65 Hz, 3H), 1.12 (s, 9H).

- 5 Step 5: Preparation of tert-butyl 4-(4-fluorophenyl)-2-((12*S,E*)-2,2,5,16,16-penta methyl-6,14-dioxo-3,3-diphenyl-4,15-dioxo-13-aza-3-silaheptadec-9-en-12-yl)-1*H*-imidazole-1-carboxylate (**134F**): (1,3-dimesitylimidazolidin-2-ylidene)(5-(*N,N*-dimethylsulfamoyl)-2-isopropoxybenzylidene)ruthenium(VI) chloride (17 mg, 0.023 mmol) and 2-((tert-butylidiphenylsilyl)oxy)hept-6-en-3-one (**134E**, 187 mg, 0.510 mmol) were added to a stirred
- 10 mixture of (*S*)-tert-butyl 2-(1-((tert-butoxycarbonyl)amino)but-3-en-1-yl)-4-(4-fluorophenyl)-1*H*-imidazole-1-carboxylate (200 mg, 0.463 mmol) in toluene (5 mL) at 25°C and the mixture was stirred at 60°C for 15 h under N₂ atmosphere. The mixture was cooled, diluted with ethyl acetate (30 mL*2), washed with water (10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash
- 15 chromatography, eluting with petroleum ether / EtOAc = 0-30% to give tert-butyl 4-(4-fluorophenyl)-2-((12*S,E*)-2,2,5,16,16-pentamethyl-6,14-dioxo-3,3-diphenyl-4,15-dioxo-13-aza-3-silaheptadec-9-en-12-yl)-1*H*-imidazole-1-carboxylate (**134F**). LCMS (ESI) calc'd for C₄₄H₅₆FN₃O₆Si [M+H]⁺: 770.3, found: 670.4
- 20 Step 6: Preparation of tert-butyl 4-(4-fluorophenyl)-2-((12*S*)-2,2,5,16,16-penta methyl-6,14-dioxo-3,3-diphenyl-4,15-dioxo-13-aza-3-silaheptadecan-12-yl)-1*H*-imidazole-1-carboxylate (**134G**): Pd/C (10%, 10 mg, 0.094 mmol) was added to a stirred mixture of tert-butyl 4-(4-fluorophenyl)-2-((12*S,E*)-2,2,5,16,16-pentamethyl-6,14-dioxo-3,3-diphenyl-4,15-dioxo-13-aza-3-silaheptadec-9-en-12-yl)-1*H*-imidazole-1-carboxylate (**134F**, 100 mg, 0.130 mmol) in MeOH (1 mL) at 25°C and the mixture was stirred at 25°C under H₂ at 1 atm for 3 h. The mixture was
- 25 filtered through Celite and the filter cake was washed with MeOH (2 x 20 mL). The filtrate was concentrated to dryness to give tert-butyl 4-(4-fluorophenyl)-2-((12*S*)-2,2,5,16,16-pentamethyl-6,14-dioxo-3,3-diphenyl-4,15-dioxo-13-aza-3-silaheptadecan-12-yl)-1*H*-imidazole-1-carboxylate (**134G**). LCMS showed the target was de-Boc. LCMS (ESI) calc'd for C₄₄H₅₈FN₃O₆Si [M+H]⁺: 772.4, found: 672.1
- 30 Step 7: Preparation of (9*S*)-9-amino-2-((tert-butylidiphenylsilyl)oxy)-9-(4-(4-fluorophenyl)-1*H*-imidazol-2-yl)nonan-3-one (**134H**): TFA (0.1 mL, 1.298 mmol) was added to a stirred mixture of tert-butyl 4-(4-flu orophenyl)-2-((12*S*)-2,2,5,16,16-pentamethyl-6,14-dioxo-3,3-diphenyl-4,15-dioxo-13-aza-3-silaheptadecan-12-yl)-1*H*-imidazole-1-carboxylate (**134G**, 90 mg, 0.117 mmol) in DCM (2 mL) at 25°C and the mixture was stirred at 25°C for 3 h. The mixture was

evaporated under reduced pressure to give (9*S*)-9-amino-2-((tert-butylidiphenylsilyl)oxy)-9-(4-(4-fluorophenyl)-1*H*-imidazol-2-yl)nonan-3-one (**134H**) which was used to the next step without further purification. LCMS (ESI) calc'd for C₃₄H₄₂FN₃O₂Si [M+H]⁺: 572.3, found: 572.3

Step 8: Preparation of (1*S*)-*N*-((1*S*)-8-((tert-butylidiphenylsilyl)oxy)-1-(4-(4-fluorophenyl)-1*H*-

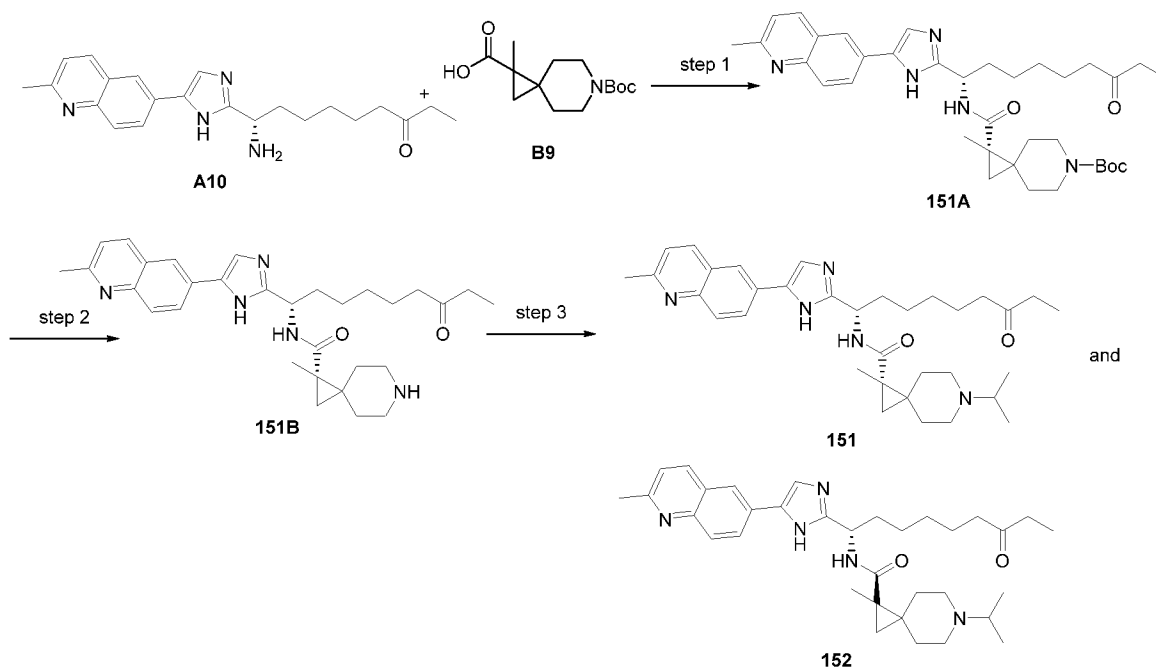
imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**134I**): HATU (33 mg, 0.087 mmol), triethylamine (0.1 mL, 0.717 mmol), (5*S*)-6-(tert-butoxycarbonyl)-6-azaspiro[2.5]octane-1-carboxylic acid (**B3**, 23 mg, 0.090 mmol) were added to a stirred mixture of (9*S*)-9-amino-2-((tert-butylidiphenylsilyl)oxy)-9-(4-(4-fluorophenyl)-1*H*-imidazol-2-yl)nonan-3-one (**134H**, 50 mg, 0.087 mmol) in DCM (2 mL) at 25°C and the mixture was stirred at 25°C for 6 h. The mixture was extracted with ethyl acetate (5 mL) and washed with water (2 mL). The organic fractions were filtered and the solvent was evaporated under reduced pressure. The residue was purified by preparative TLC on silica gel, eluting with petroleum ether / EtOAc = 2:1 to give (1*S*)-tert-butyl 1-(((1*S*)-8-((tert-butylidiphenylsilyl)oxy)-1-(4-(4-fluorophenyl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**134I**). LCMS (ESI) calc'd for C₄₃H₅₅FN₄O₃Si [M+H]⁺: 809.4, found: 809.5

Step 9: Preparation of (1*S*)-*N*-((1*S*)-1-(4-(4-fluorophenyl)-1*H*-imidazol-2-yl)-8-hydroxy-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**134**): TBAF (3 mg, 0.011 mmol)

was added to a stirred mixture of (1*R*)-*N*-((1*S*)-8-((tert-butylidiphenylsilyl)oxy)-1-(4-(4-fluorophenyl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**134I**, 5 mg, 6.92 μmol) in THF (2 mL) at 30°C and the mixture was stirred at rt for 18 h. The mixture was evaporated under pressure and purified by HPLC to get (1*R*)-*N*-((1*S*)-1-(4-(4-fluorophenyl)-1*H*-imidazol-2-yl)-8-hydroxy-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide hydrochloride (**134**). LCMS (ESI) calc'd for C₂₇H₃₇FN₄O₃ [M+H]⁺: 485.3, found: 485.3. ¹H NMR (400 MHz, MeOD) δ 7.74 (dd, *J* = 5.28, 10.76 Hz, 2H), 7.67 (d, *J* = 7.43 Hz, 1H), 7.42-7.48 (m, 1H), 7.29-7.37 (m, 2H), 7.22 (d, *J* = 4.70 Hz, 2H), 4.99 (t, *J* = 7.43 Hz, 1H), 4.14 (q, *J* = 6.78 Hz, 1H), 2.83 (d, *J* = 5.87 Hz, 3H), 2.55 (t, *J* = 7.04 Hz, 2H), 2.11-2.34 (m, 1H), 1.92-2.07 (m, 3H), 1.74-1.92 (m, 3H), 1.49-1.66 (m, 3H), 1.35 (brs, 4H), 1.26 (d, *J* = 7.04 Hz, 5H), 0.82-1.07 (m, 1H).

Example 67

(1*S* or 1*R*)-1-methyl-6-(1-methylethyl)-*N*-{(1*S*)-1-[5-(2-methylquinolin-6-yl)-1*H*-imidazol-2-yl]-7-oxononyl}-6-azaspiro[2.5]octane-1-carboxamide (151 & 152)



Step 1: Preparation of (*R*)-tert-butyl 1-methyl-1-(((*S*)-1-(5-(2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**151A**):

HATU (313 mg, 0.823 mmol) was added to a stirred mixture of 6-(tert-butoxycarbonyl)-1-methyl-6-azaspiro[2.5]octane-1-carboxylic acid (**B9**, 122 mg, 0.453 mmol) and Et₃N (0.172 mL, 1.235 mmol) in DMF (2 mL) at 18°C, and the mixture was stirred at 18°C for 30 min. Then (*S*)-9-amino-9-(5-(2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)nonan-3-one (**A10**, 150 mg, 0.412 mmol) was added, and the resulting mixture was stirred at 18°C until LCMS showed completion of the reaction. The mixture was quenched with water (10 mL), extracted with EtOAc (10 mL*3), the combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated. The crude was purified by prep-HPLC (TFA) to give tert-butyl 1-methyl-1-(((*S*)-1-(5-(2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**151A**) which was further separated by chiral SFC on AD column to afford two single isomers. LCMS (ESI) calc'd for C₃₆H₄₉N₅O₄ [M+H]⁺: 616.4, found: 616.4.

(first peak); LCMS (ESI) calc'd for C₃₆H₄₉N₅O₄ [M+H]⁺: 616.4, found: 616.4. (second peak).

Step 2: Preparation of (*R*)-tert-butyl 1-methyl-1-(((*S*)-1-(5-(2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**151B**):

HCl / MeOH (2 mL, 8.00 mmol) was added to a stirred mixture of tert-butyl 1-methyl-1-(((*S*)-1-(5-(2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**151A**, first peak in SFC) in MeOH (1 mL) at 15°C and the mixture was stirred at 15°C for 4 h. The mixture was quenched with NaHCO₃ (10 mL), extracted with EtOAc (10 mL*3), the combined organic layers were washed with brine (10 mL), dried over Na₂SO₄,

filtered and concentrated to get 1-methyl-*N*-((*S*)-1-(5-(2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**151B**) which was used in the next step directly without purification. LCMS (ESI) calc'd for C₃₁H₄₁N₅O₂ [M+H]⁺: 516.3, found: 516.3.

Step 3: Preparation of (*R*)-tert-butyl 1-methyl-1-(((*S*)-1-(5-(2-methylquinolin-6-yl)-1*H*-

imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**151**): A mixture of

1-methyl-*N*-((*S*)-1-(5-(2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**151B**, 21 mg, 0.041 mmol) in acetone (3 mL) was heated at 50°C for 1 h, then sodium triacetoxymethylborohydride (104 mg, 0.489 mmol) was added to the mixture. The mixture was stirred at the same temperature for 48 h. The mixture was quenched

with NaHCO₃ (10 mL), extracted with EtOAc (10 mL*3), the combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated. The crude was

purified by prep-HPLC (TFA) to give 6-isopropyl-1-methyl-*N*-((*S*)-1-(5-(2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**151**). HCl (10 µL,

0.122 mmol) was added to a mixture of 6-isopropyl-1-methyl-*N*-((*S*)-1-(5-(2-methylquinolin-6-

yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**151**, 15 mg, 0.027 mmol) in MeCN (5 mL) and water (5 mL) at rt, then the mixture was stirred at rt for 30 min, and the resulting mixture was lyophilized to give 6-isopropyl-1-methyl-*N*-((*S*)-1-(5-(2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide hydrochloride. LCMS (ESI) calc'd for C₃₄H₄₇N₅O₂ [M+H]⁺: 558.4, found: 558.5. ¹H NMR (400

MHz, MeOD-*d*) δ 9.12 (d, *J* = 8.8 Hz, 1H), 8.76 (d, *J* = 8.8 Hz, 1H), 8.51 (d, *J* = 8.4 Hz, 1H), 8.28 (d, *J* = 10.0 Hz, 1H), 8.7 (s, 1H), 8.2 (d, *J* = 8.4 Hz, 1H), 5.3 (t, 1H), 3.2 (m, 4H), 3.1 (s, 5H), 2.5 (m, 4H), 2.3 (m, 4H), 1.5 (m, 5H), 1.4 (s, 3H), 1.3 (m, 13H), 1.0 (t, 3H), 0.6 (s, 1H).

152 was prepared using a similar method as **151** from the second peak from step 1; the absolute configuration was not confirmed. LCMS (ESI) calc'd for C₃₄H₄₇N₅O₂ [M+H]⁺: 558.4, found:

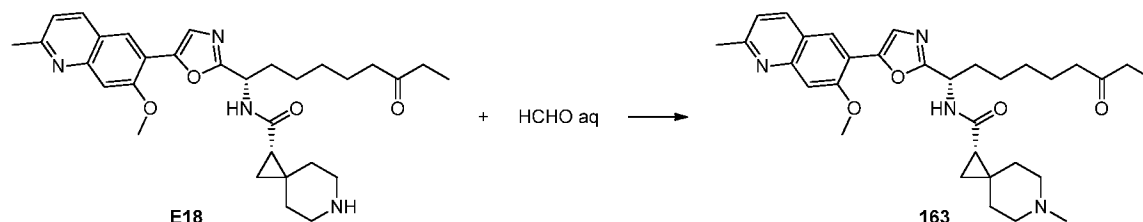
558.5.

The following compounds were prepared using similar procedures as described for compounds **151** and **152**.

ID	Structure	Observed [M+H] ⁺
272		574.6
273		560.4

Example 68

(1*S*)-*N*-{(1*S*)-1-[5-(7-methoxy-2-methylquinolin-6-yl)-1,3-oxazol-2-yl]-7-oxononyl}-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (163)



Formaldehyde (0.1 mL, 1.232 mmol) was added to a stirred mixture of (*S*)-*N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**E18**, 250 mg, 0.469 mmol) in MeOH (3 mL) at room temperature and the mixture was stirred at rt for 23 h. Then triacetoxyhydroborate (532 mg, 2.82 mmol) was added into the mixture at room temperature and the mixture was stirred at rt for 3 h. The mixture was extracted with ethyl acetate (100 mLx2) and washed with water (100 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column

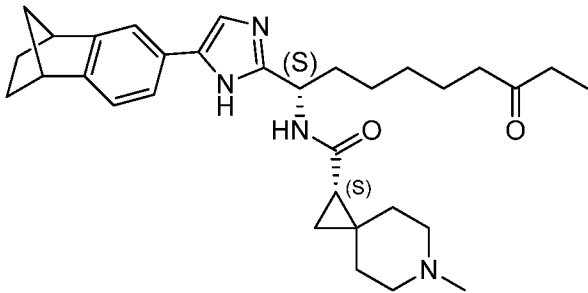
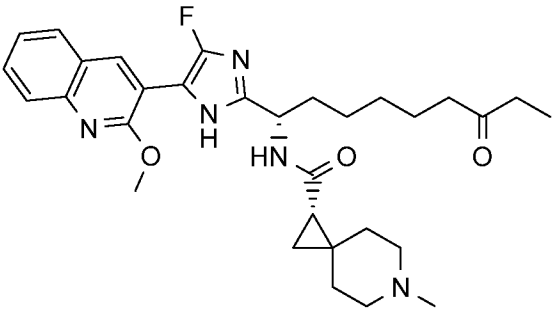
10

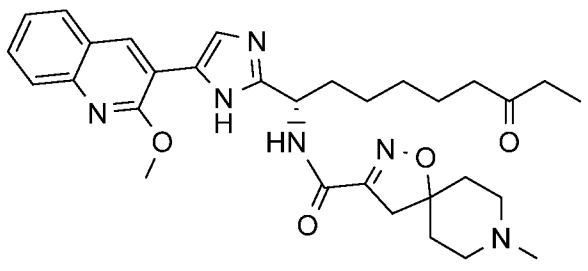
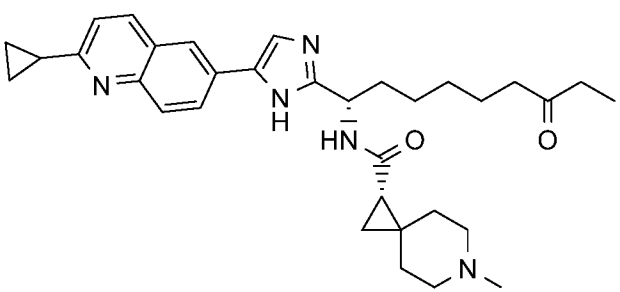
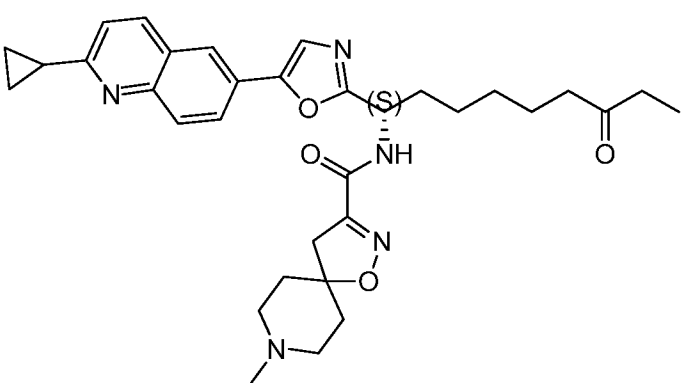
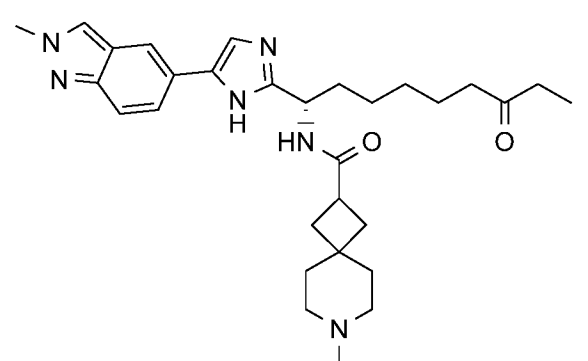
flash chromatography, eluting with DCM/MeOH = 0-10% to give (*S*)-*N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**163**).

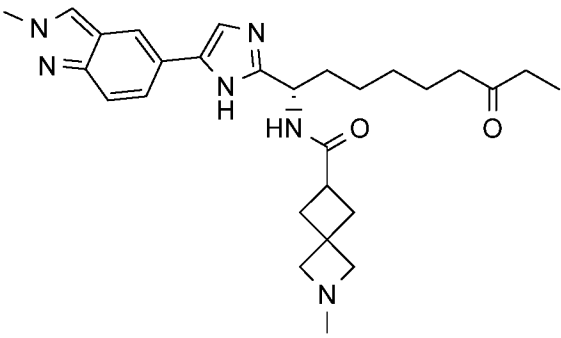
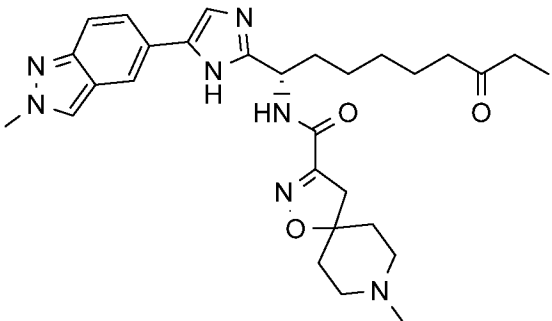
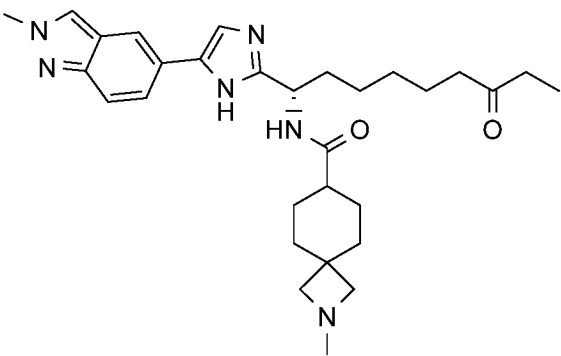
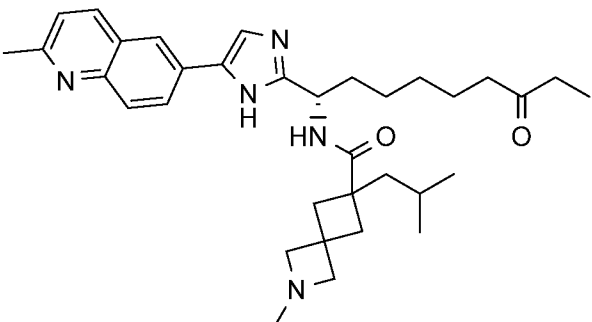
L-(+)-tartaric acid (55 mg, 0.366 mmol) was added to a stirred mixture of (*S*)-*N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**163**, 200 mg, 0.366 mmol) in MeCN (2 mL)/water (2 mL) at room temperature and the mixture was dried to give (*S*)-*N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (2*R*,3*R*)-2,3-

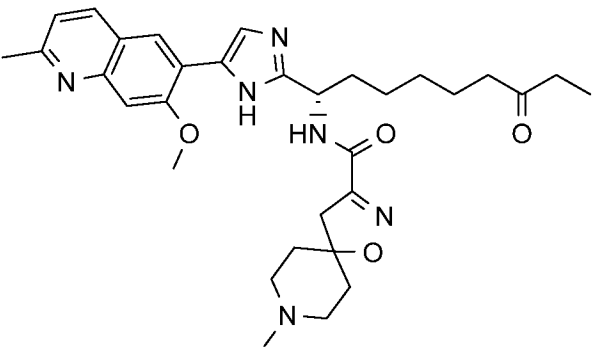
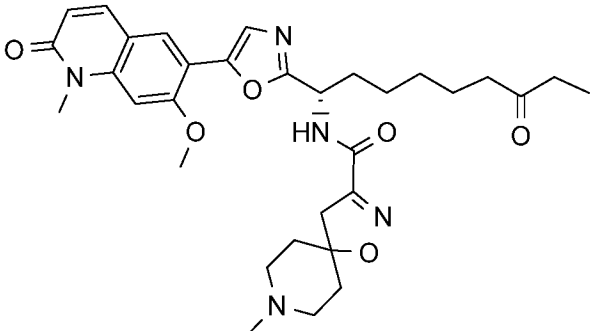
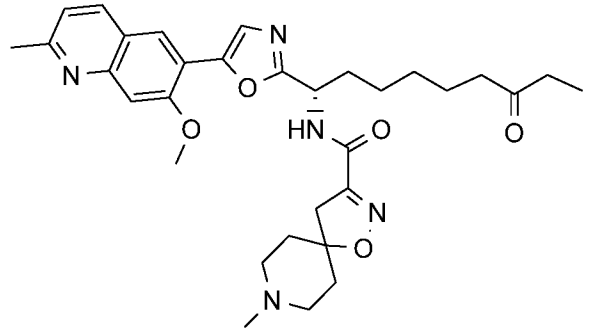
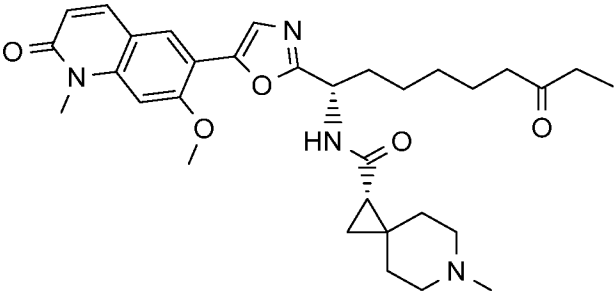
dihydroxysuccinate. LCMS (ESI) calc'd for C₃₂H₄₂N₄O₄ [M+H]⁺: 547.3, found: 547.3. ¹H NMR (400 MHz, MeOD) δ 8.62 (d, *J* = 8.22 Hz, 1H), 8.39-8.47 (m, 1H), 7.68 (brs, 1H), 7.53-7.59 (m, 2H), 5.17 (dd, *J* = 5.87, 8.61 Hz, 1H), 4.54 (s, 3H), 4.19 (s, 2H), 4.16-4.21 (m, 1H), 3.42-3.62 (m, 1H), 2.93-3.15 (m, 1H), 2.88 (s, 3H), 2.84 (s, 3H), 2.42-2.50 (m, 4H), 2.28 (brs, 1H), 1.90-2.14 (m, 4H), 1.83 (brs, 1H), 1.60 (brs, 2H), 1.35-1.54 (m, 4H), 1.18-1.33 (m, 3H), 0.96-1.10 (m, 4H).

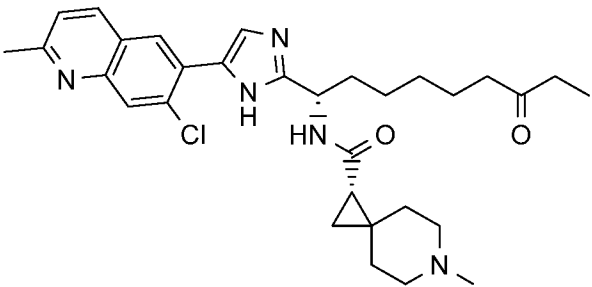
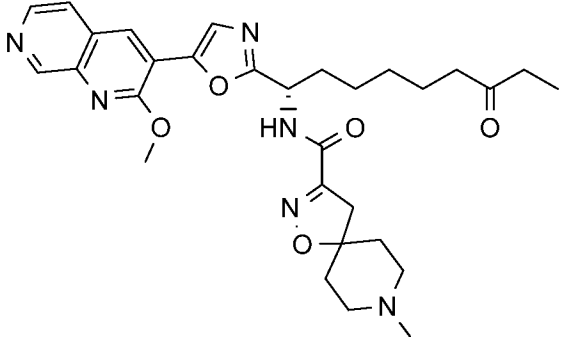
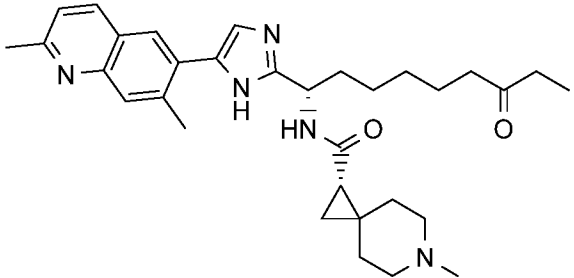
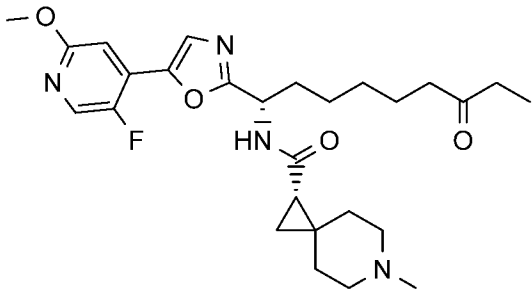
The following compounds were prepared using similar procedures as described for compound **163**.

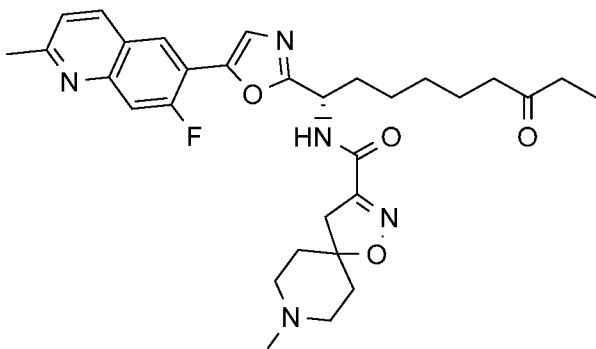
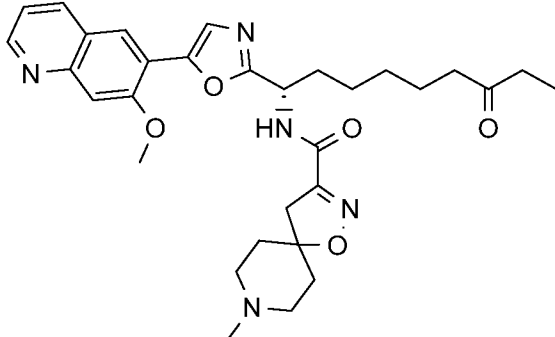
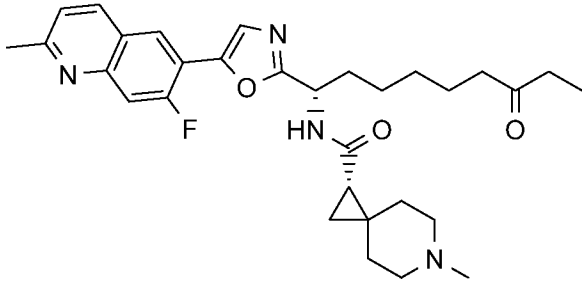
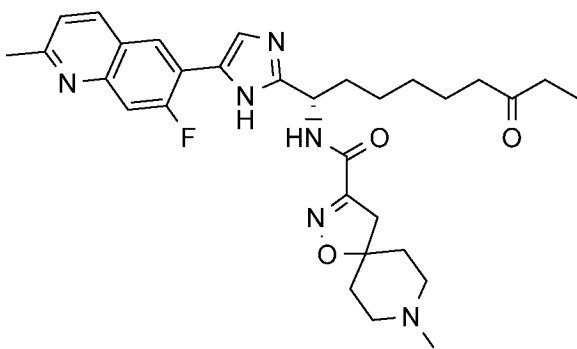
ID	Structure	Observed [M+H] ⁺
74		517.3
75		550.1

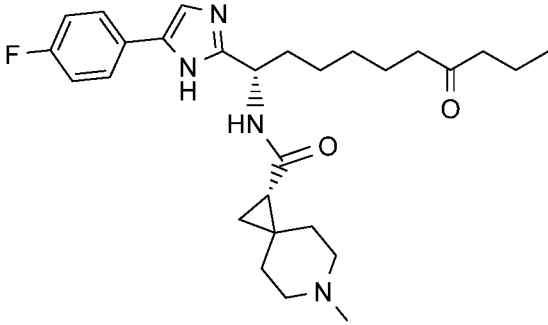
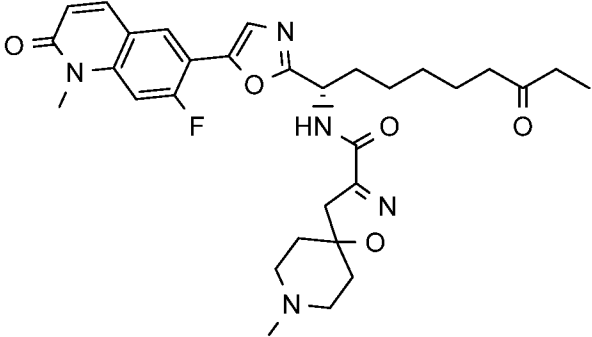
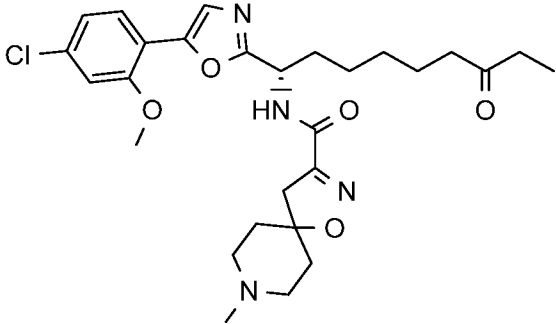
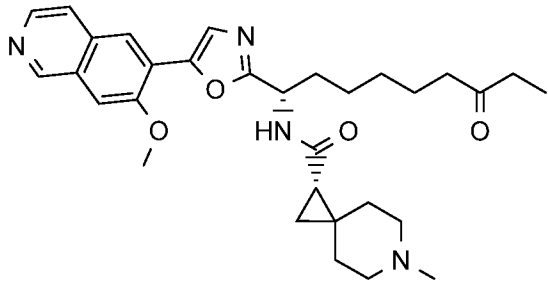
105		561.3
112		542.2
135		572.2
145		519.4

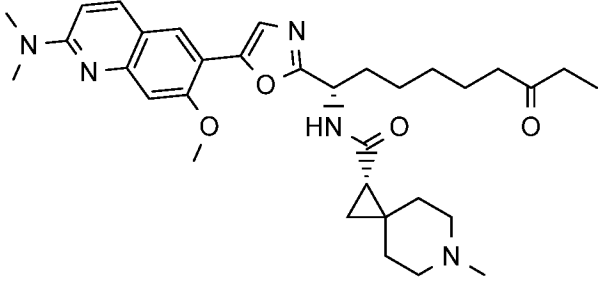
147		491.4
154		534.3
156		519.4
157		558.3

188		561.4
193		592.1
196		576.3
198		563.1

200		550.1
216		563.0
218		530.2
220		501.1

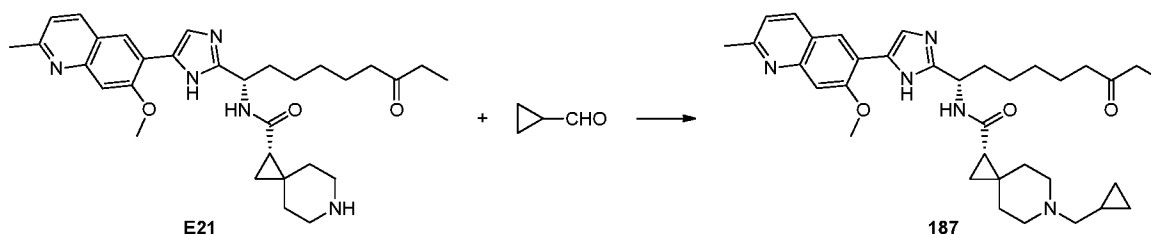
221		564.0
223		562.0
226		535.1
232		563.0

239		483.4
386		580.3
390		545.1
405		533.1

406		576.1
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Example 69

(1*S*)-6-(cyclopropylmethyl)-*N*-{(1*S*)-1-[5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl]-7-oxononyl}-6-azaspiro[2.5]octane-1-carboxamide (**187**)

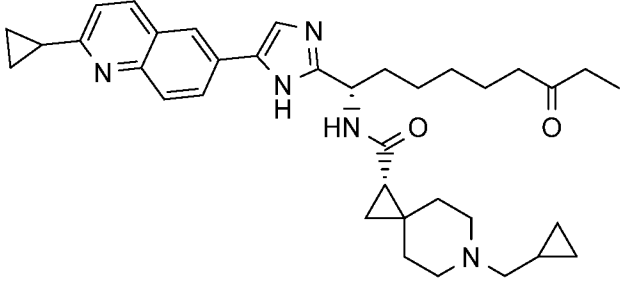
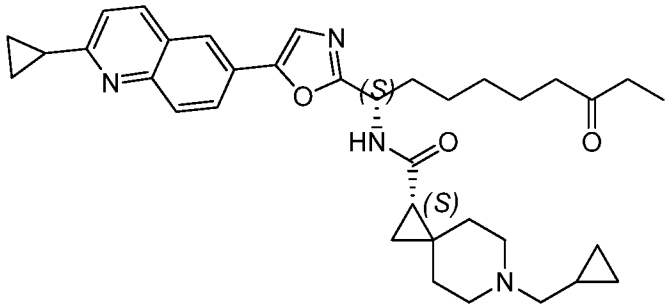
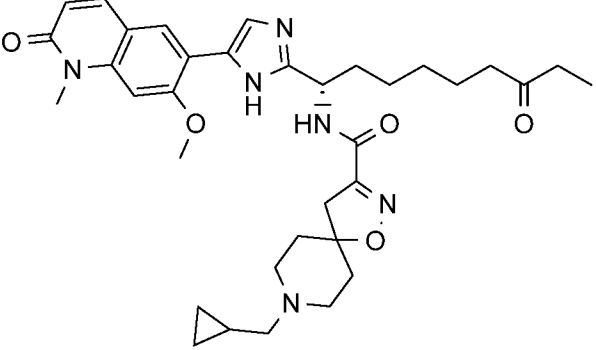


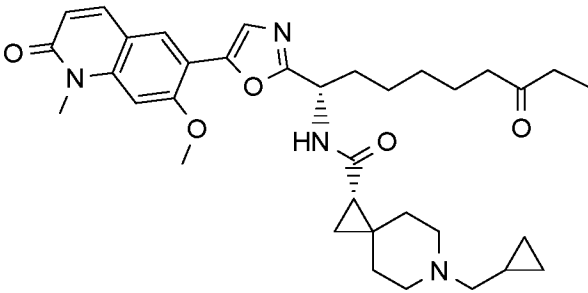
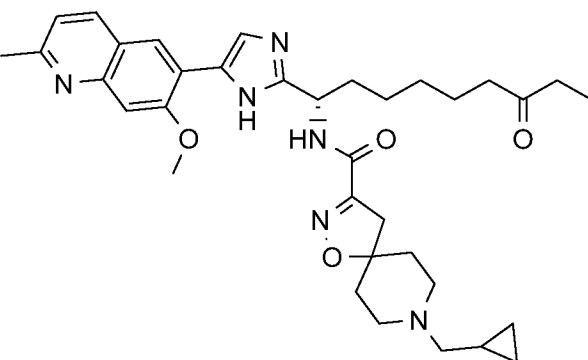
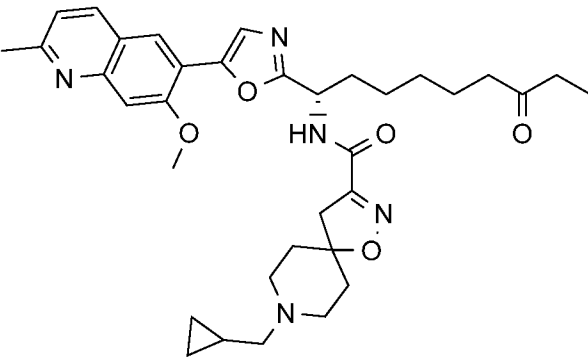
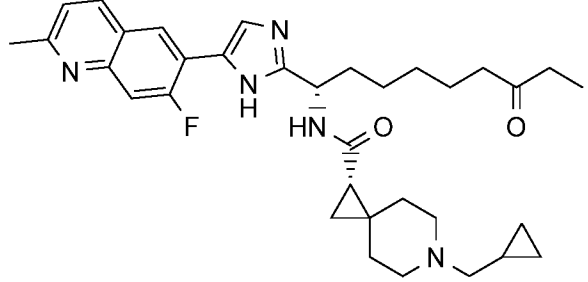
Cyclopropanecarbaldehyde (25 mg, 0.357 mmol) was added to a stirred mixture of (*S*)-*N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide 2,2,2-trifluoroacetate (**E21**, 125 mg, 0.194 mmol) in MeOH (2 mL) and the mixture was stirred at room temperature for 1 h. Then, NaBH(OAc)₃ (123 mg, 0.581 mmol) was added and it was stirred at rt for 24 h. Water (5 mL) was added and the mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic fractions were washed with aqueous NaHCO₃ (saturated, 1 x 5 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile / water + 0.05% NH₃·H₂O, to give (*S*)-6-(cyclopropylmethyl)-*N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**187**).

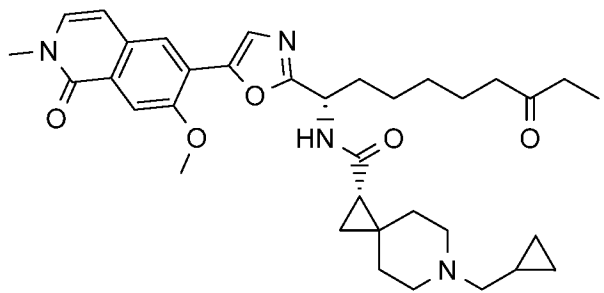
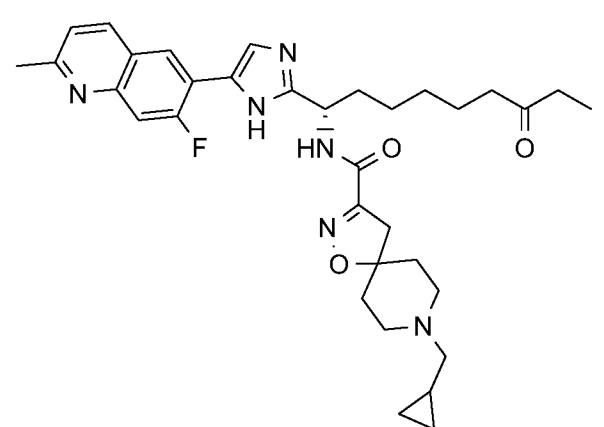
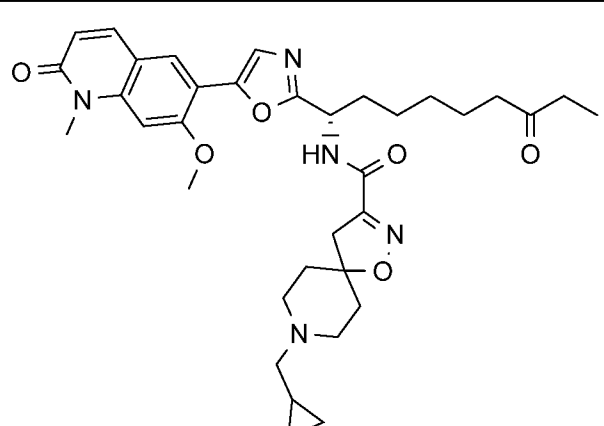
L-(+)-tartaric acid (10 mg, 0.067 mmol) was added to a stirred mixture of (*S*)-6-(cyclopropylmethyl)-*N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**187**, 50 mg, 0.085 mmol) in acetonitrile (2 mL) and water (2 mL) at room temperature and the mixture was made dry by lyophilization to give (*S*)-6-(cyclopropylmethyl)-*N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (2*R*,3*R*)-2,3-dihydroxysuccinate. LCMS (ESI) calc'd for C₃₅H₄₇N₅O₃ [M+H]⁺: 586.4, found: 586.1. ¹H NMR (400 MHz, MeOD) δ 8.40

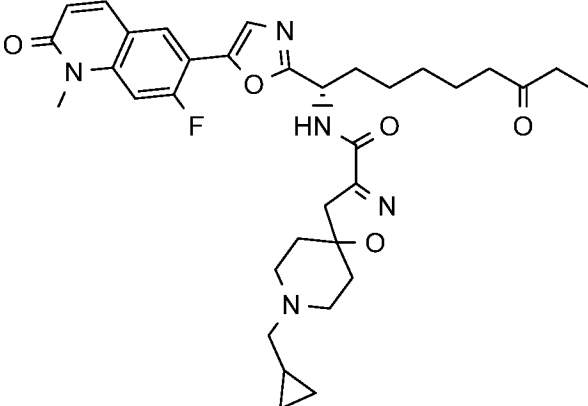
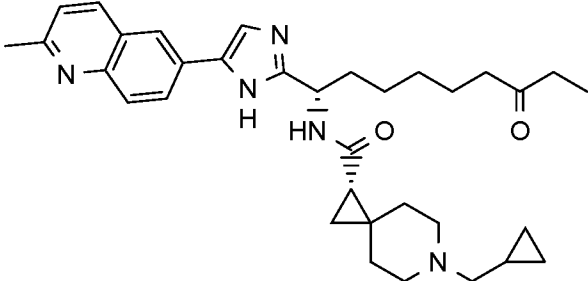
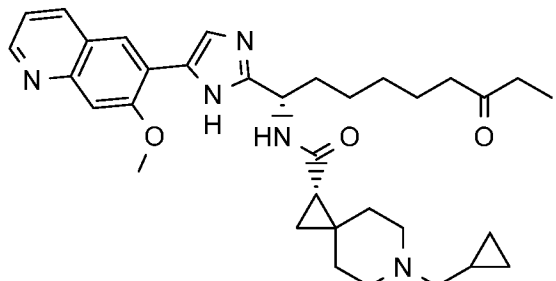
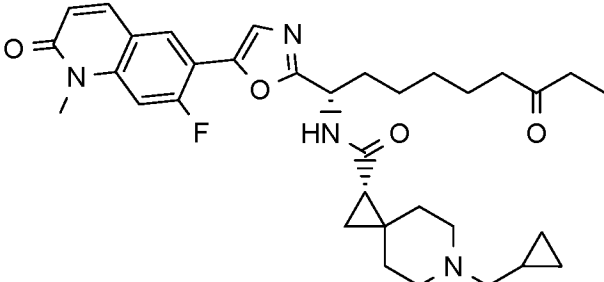
(brs, 1H), 8.23 (d, $J = 8.2$ Hz, 1H), 7.65 (s, 1H), 7.43 (s, 1H), 7.34 (d, $J = 8.2$ Hz, 1H), 5.07 (t, $J = 7.6$ Hz, 1H), 4.45 (s, 2H), 4.10 (s, 3H), 3.50 (brs, 3H), 3.13 (brs, 2H), 2.71 (s, 4H), 2.38-2.50 (m, 4H), 1.73-2.35 (m, 6H), 1.08-1.68 (m, 9H), 0.98 (t, $J = 7.2$ Hz, 4H), 0.72 (brs, 1H), 0.43 (brs, 2H), -0.03 (br s, 1H).

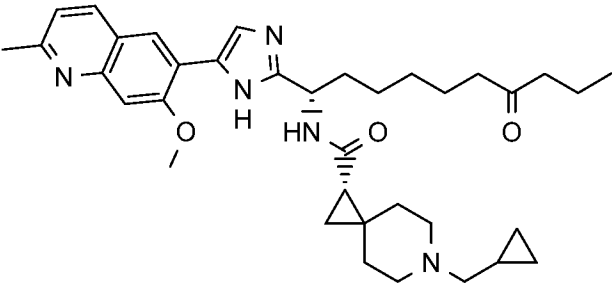
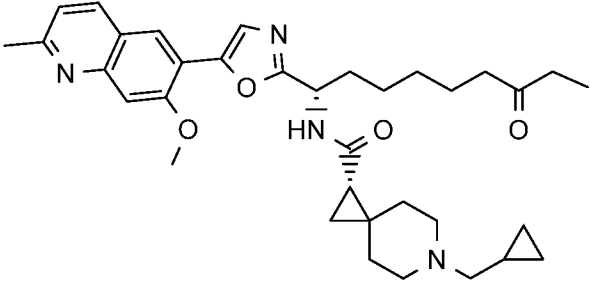
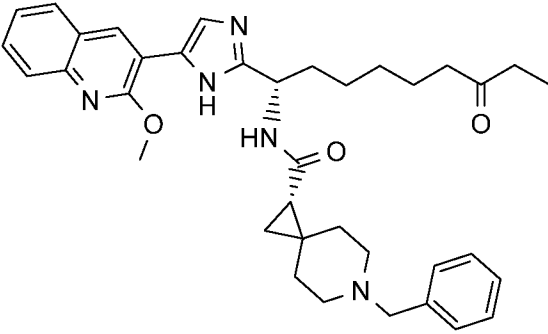
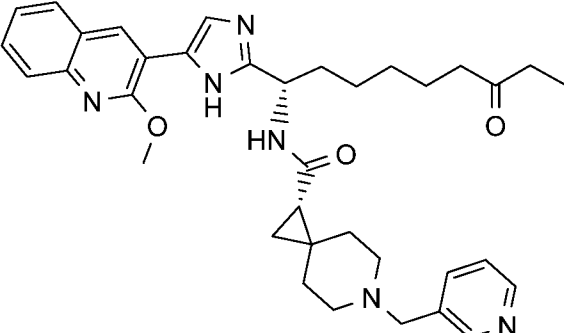
- 5 The following compounds were prepared using similar procedures as described for compound **187**.

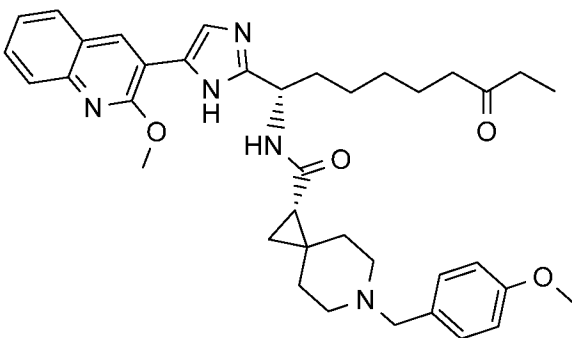
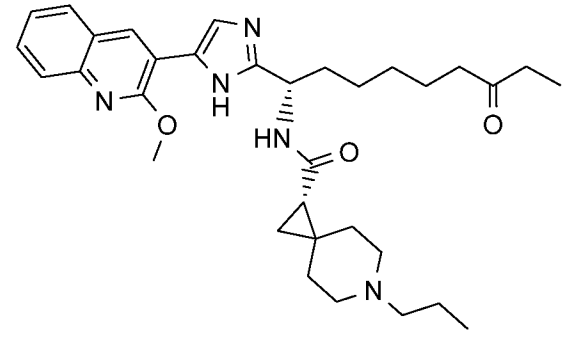
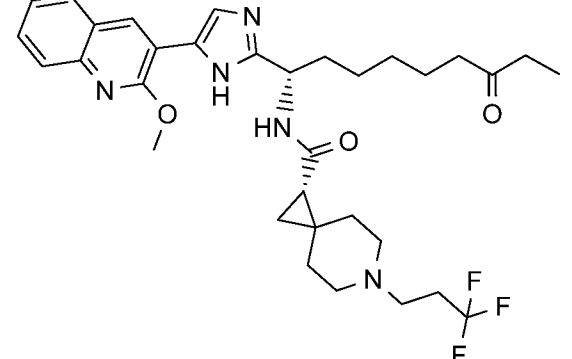
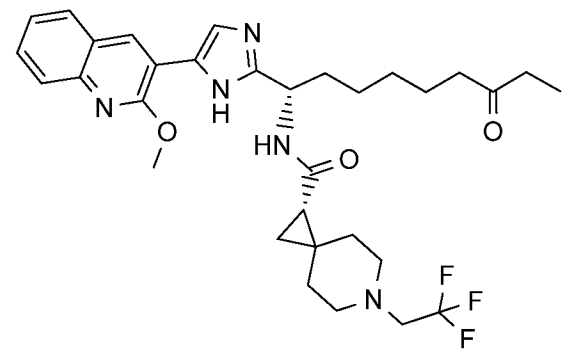
ID	Structure	Observed $[M+H]^+$
104		582.3
115		583.3
192		577.4

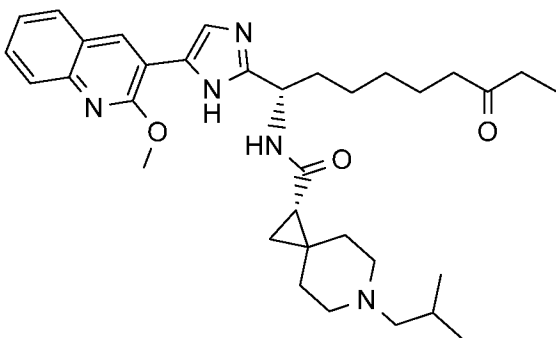
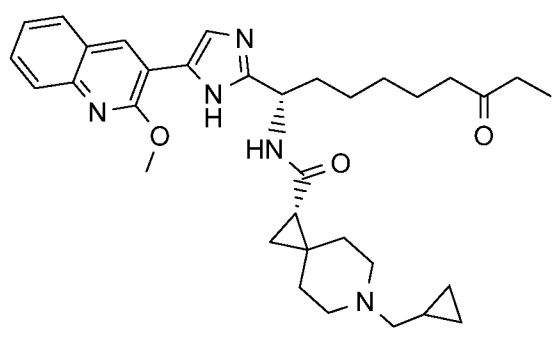
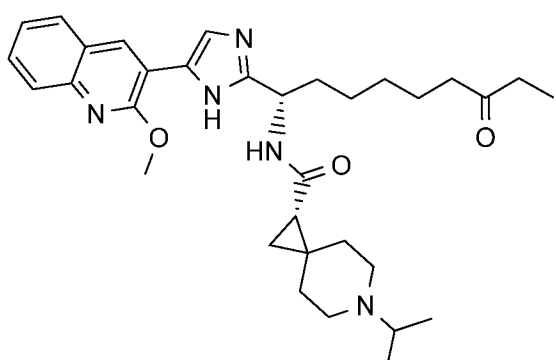
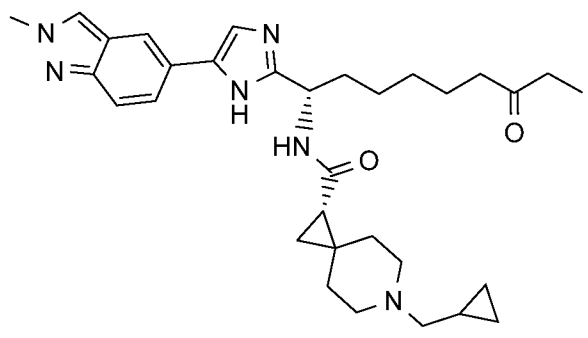
199		603.1
219		615.1
225		616.4
228		574.1

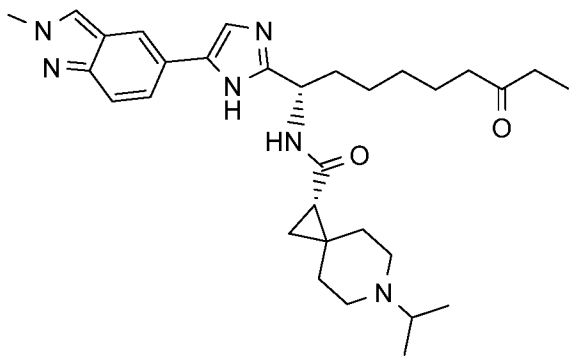
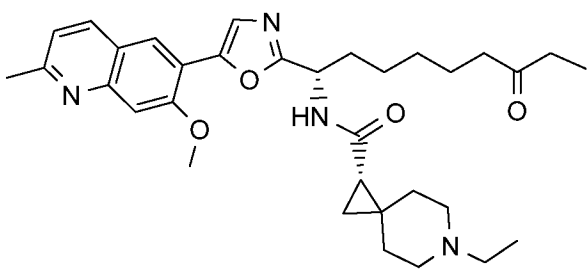
229		603.2
234		603.1
236		632.1

387		620.1
393		556.1
394		572.2
400		591.1

416		600.4
422		587.1
293		608.4
294		609.4

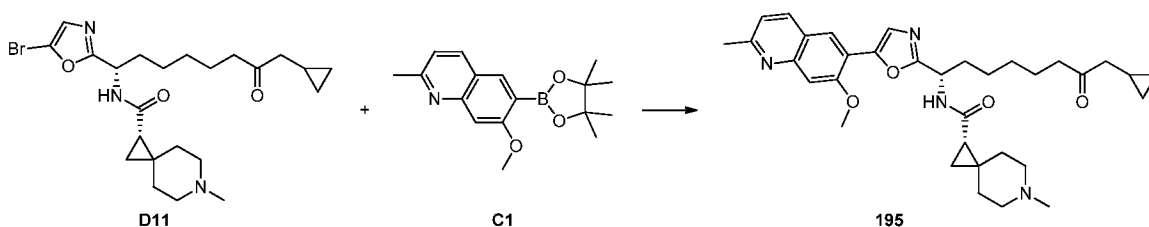
295		638.5
331		560.5
332		614.4
333		600.5

335		574.5
336		572.5
337		560.2
359		359

360		360
361		361

Example 70

(1*S*)-*N*-{(1*S*)-8-cyclopropyl-1-[5-(7-methoxy-2-methylquinolin-6-yl)-1,3-oxazol-2-yl]-7-oxooctyl}-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (195)

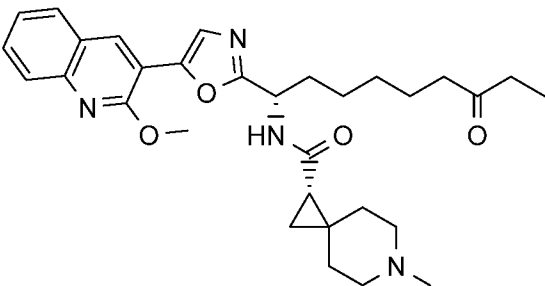
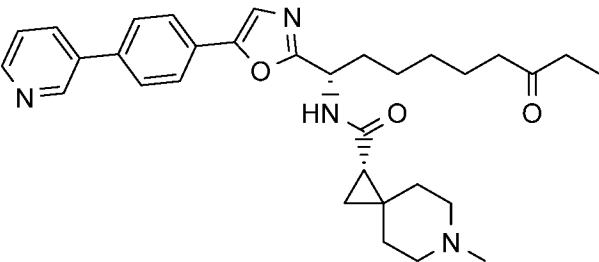
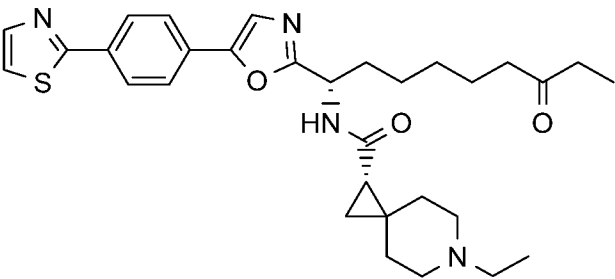
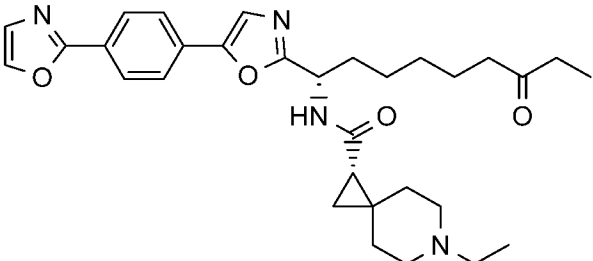


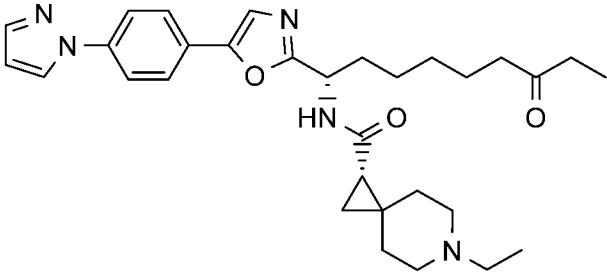
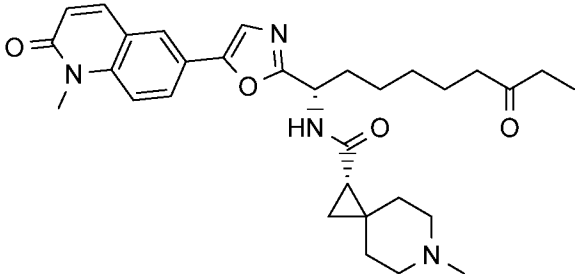
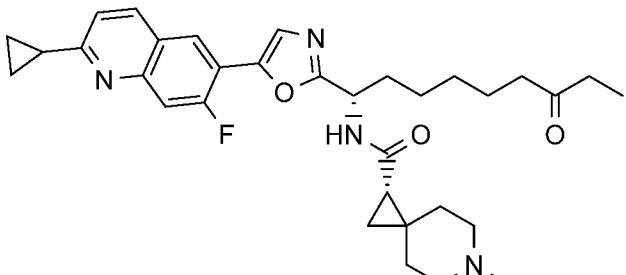
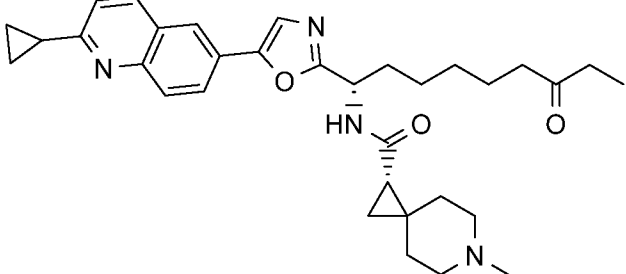
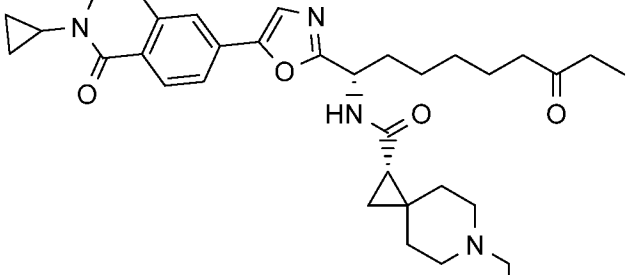
Potassium phosphate tribasic (60 mg, 0.283 mmol) and PdCl₂(DTBPF) (10 mg, 0.015 mmol) was added to the solution of (*S*)-*N*-((*S*)-1-(5-bromooxazol-2-yl)-8-cyclopropyl-7-oxooctyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**D11**, 60 mg, 0.125 mmol) and 7-methoxy-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (**C1**, 50 mg, 0.167 mmol) in THF (1.5 mL) and water (0.1 mL), and the resultant mixture was stirred at 70 °C for 2 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.05% NH₃·H₂O, to give (*S*)-*N*-((*S*)-8-cyclopropyl-1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxooctyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**195**).

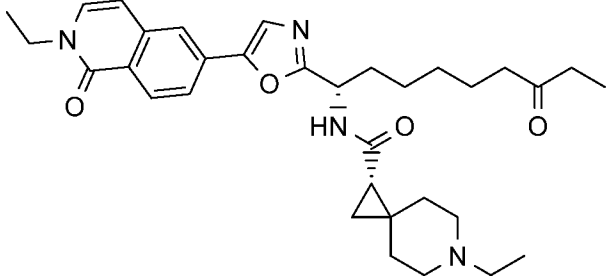
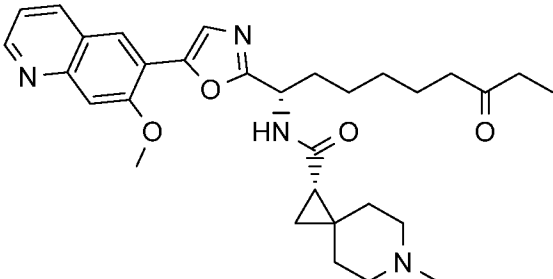
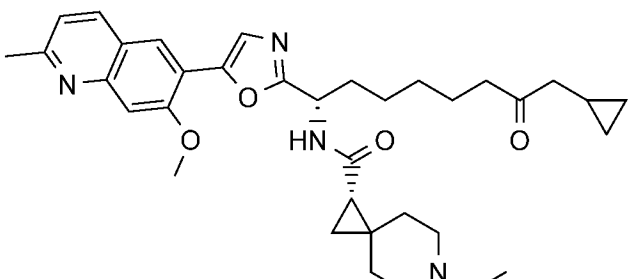
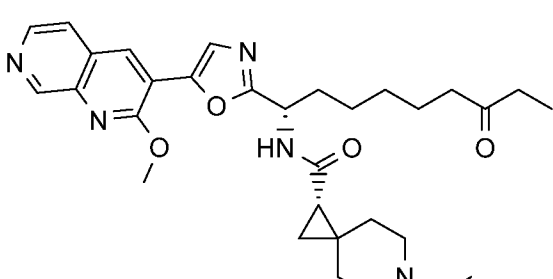
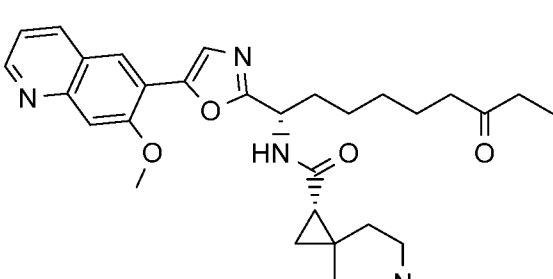
The free base was dissolved in water (2 mL) and MeCN (1 mL), L-tartaric acid (7 mg) was added to the solution and the resultant mixture was lyophilized to give the tartaric salt.

LCMS (ESI) calc'd for $C_{34}H_{44}N_4O_4$ $[M+H]^+$: 573.3, found: 573.1. ^1H NMR (400 MHz, MeOD) δ 8.15-8.28 (m, 2H), 7.55 (s, 1H), 7.40 (s, 1H), 7.30 (d, $J = 8.41$ Hz, 1H), 5.05-5.17 (m, 1H), 5.05-5.16 (m, 1H), 4.41 (s, 4H), 4.07 (s, 3H), 2.78 (brs, 3H), 2.66 (s, 3H), 2.46 (t, $J = 7.04$ Hz, 2H), 2.23 (d, $J = 7.04$ Hz, 2H), 1.70-2.08 (m, 6H), 1.12-1.62 (m, 10H), 0.78-1.04 (m, 3H), 0.37-0.50 (m, 2H), -0.11-0.08 (m, 3H).

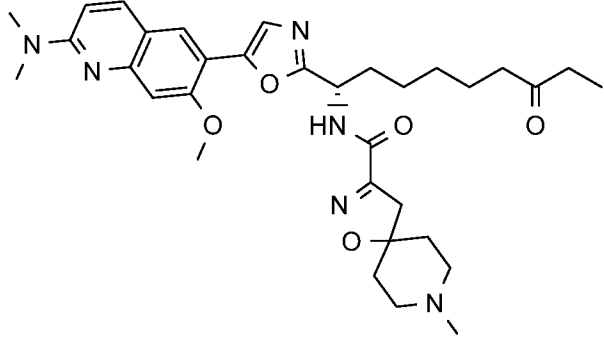
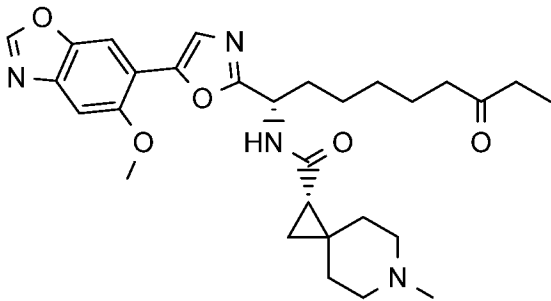
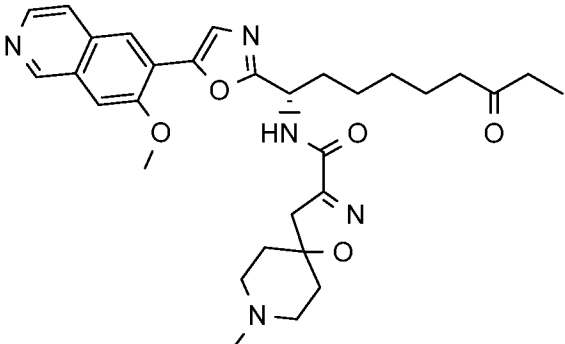
The following compounds were prepared using similar procedures as described for compound **195**.

ID	Structure	Observed $[M+H]^+$
77		533.3
79		529.3
93		549.3
94		533.3

95		532.3
109		533.3
111		561.3
121		543.3
153		573.4

162		561.4
164		533.1
167		587.3
168		548.1
169		547.4

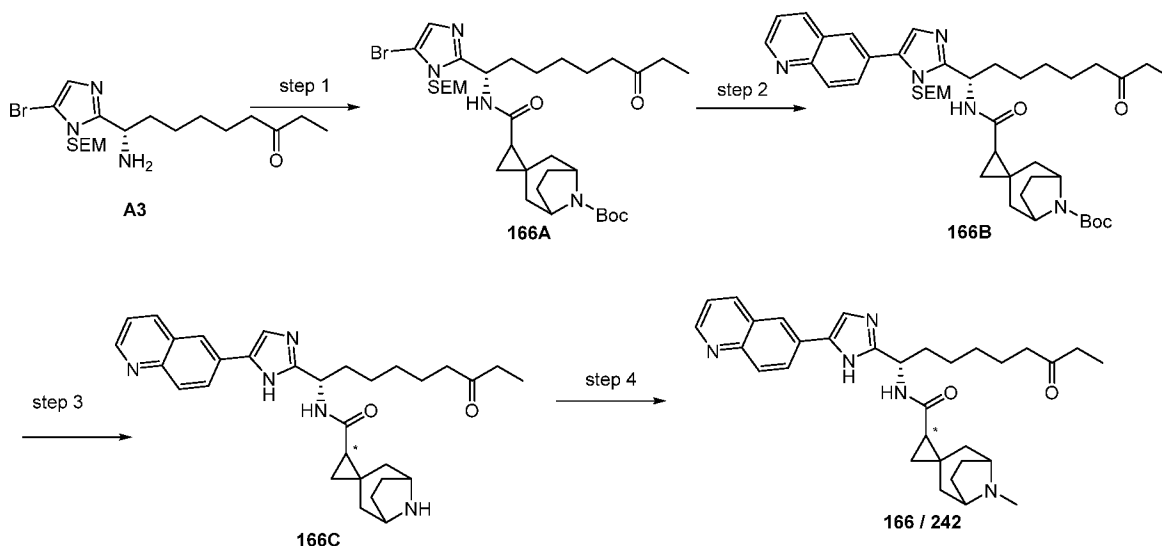
171	 <chem>CC(=O)CCCC[C@H](NC(=O)[C@H]1C2CCN(CC)CC2C1)C(=O)Nc3cc(OC)c4cc5c(c3)cnc45C6=CC=CC=C6N7C(=O)C=CC=C7N7C</chem>	577.3
173	 <chem>CC(=O)CCCC[C@H](NC(=O)[C@H]1C2CCN(CC)CC2C1)C(=O)Nc3cc(OC)c4cc5c(c3)cnc45C6=CC=CC=C6N7C(=O)C=CC=C7N7CC</chem>	591.2
189	 <chem>CC(=O)CCCC[C@H](NC(=O)[C@H]1C2CCN(CC)CC2C1)C(=O)Nc3cc(OC)c4cc5c(c3)cnc45C6=CC=CC=C6N7C(=O)C=CC=C7N7C</chem>	550.1
389	 <chem>CC(=O)CCCC[C@H](NC(=O)[C@H]1C2CCN(C)CC2C1)C(=O)Nc3cc(F)c4cc5c(c3)cnc45C6=CC=CC=C6N7C(=O)C=CC=C7N7C</chem>	511.2

397		605.1
408		523.1
415		562.1

Example 71

8-methyl-N-[(1*S*)-7-oxo-1-(5-quinolin-6-yl-1*H*-imidazol-2-yl)nonyl]-8-azaspiro[bicyclo[3.2.1]octane-3,1'-cyclopropane]-2'-carboxamide (166 & 242)

5



Step 1: Preparation of tert-butyl 2'-(((S)-1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-7-oxononyl)carbamoyl)-8-azaspiro[bicyclo[3.2.1]octane-3,1'-cyclopropane]-8-carboxylate (166A):

T₃P (3.70 g, 5.82 mmol) was added to a stirred mixture of (S)-9-amino-9-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)nonan-3-one (**A3**, 1.677 g, 3.88 mmol), DIPEA (2.0 mL, 11.45 mmol), and 8-(tert-butoxycarbonyl)-8-azaspiro[bicyclo[3.2.1]octane-3,1'-cyclopropane]-2'-carboxylic acid (**B7**, 1.091 g, 3.88 mmol) in DMF (10 mL) at room temperature and the mixture was stirred at room temperature for 12 h. The mixture was diluted with ethyl acetate (20 mL), washed with brine (saturated, 3 x 20 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with EtOAc/petroleum ether = 0-50% to give tert-butyl 2'-(((S)-1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-7-oxononyl)carbamoyl)-8-azaspiro[bicyclo[3.2.1]octane-3,1'-cyclopropane]-8-carboxylate (**166A**). LCMS (ESI) calc'd for C₃₃H₅₅BrN₄O₅Si [M+H]⁺: 695.3, found: 697.4. ¹H NMR (400 MHz, CDCl₃) δ 6.90 (d, *J* = 5.5 Hz, 1H), 5.50-5.71 (m, 2H), 5.03-5.15 (m, 2H), 4.26 (brs, 2H), 3.42-3.61 (m, 3H), 2.30-2.53 (m, 5H), 1.71-1.99 (m, 7H), 1.55 (brs, 2H), 1.46 (d, *J* = 13.3 Hz, 8H), 1.27 (t, *J* = 7.2 Hz, 5H), 1.04 (t, *J* = 7.2 Hz, 4H), 0.72-0.96 (m, 4H), -0.13-0.09 (m, 9H).

Step 2: Preparation of tert-butyl 2'-(((S)-7-oxo-1-(5-(quinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)nonyl)carbamoyl)-8-

azaspiro[bicyclo[3.2.1]octane-3,1'-cyclopropane]-8-carboxylate (166B): PdCl₂(DTBPF) (0.141 g, 0.216 mmol) was added to a stirred mixture of K₃PO₄ (1.373 g, 6.47 mmol), 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (0.6 g, 2.352 mmol), and tert-butyl 2'-(((S)-1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-7-oxononyl)carbamoyl)-8-azaspiro[bicyclo[3.2.1]octane-3,1'-cyclopropane]-8-carboxylate (**166A**, 1.5 g, 2.156 mmol) in

water (2 mL) / THF (10 mL) at room temperature and the mixture was stirred at 70°C for 8 h under N₂. The mixture was cooled, diluted with ethyl acetate (20 mL), washed with brine (saturated, 3 x 15 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by preparative HPLC, eluting with acetonitrile/water + 0.1% TFA, to give tert-butyl 2'-(((*S*)-7-oxo-1-(5-(quinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)nonyl)carbamoyl)-8-azaspiro[bicyclo[3.2.1]octane-3,1'-cyclopropane]-8-

carboxylate (**166B**). LCMS (ESI) calc'd for C₄₂H₆₁N₅O₅Si [M+H]⁺: 744.4, found: 744.4
Step 3: Preparation of *N*-((*S*)-7-oxo-1-(5-(quinolin-6-yl)-1*H*-imidazol-2-yl)nonyl)-8-azaspiro[bicyclo[3.2.1]octane-3,1'-cyclopropane]-2'-carboxamide (**166C**): TFA (5 mL, 64.9

mmol) was added to a stirred mixture of tert-butyl 2'-(((*S*)-7-oxo-1-(5-(quinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)nonyl)carbamoyl)-8-azaspiro[bicyclo[3.2.1]octane-3,1'-cyclopropane]-8-carboxylate (**166B**, 1.05 g, 1.411 mmol) in DCM (5 mL) at room temperature and the mixture was stirred at room temperature for 13 h. Most of the DCM was removed, and the residue was purified by preparative HPLC, eluting with acetonitrile / water + 0.1% TFA, to give *N*-((*S*)-7-oxo-1-(5-(quinolin-6-yl)-1*H*-imidazol-2-yl)nonyl)-8-azaspiro[bicyclo[3.2.1]octane-3,1'-cyclopropane]-2'-carboxamide (**166C**, two isomers). LCMS (ESI) calc'd for C₃₇H₅₃N₅O₃Si [M+H]⁺: 514.3, found: 514.4.

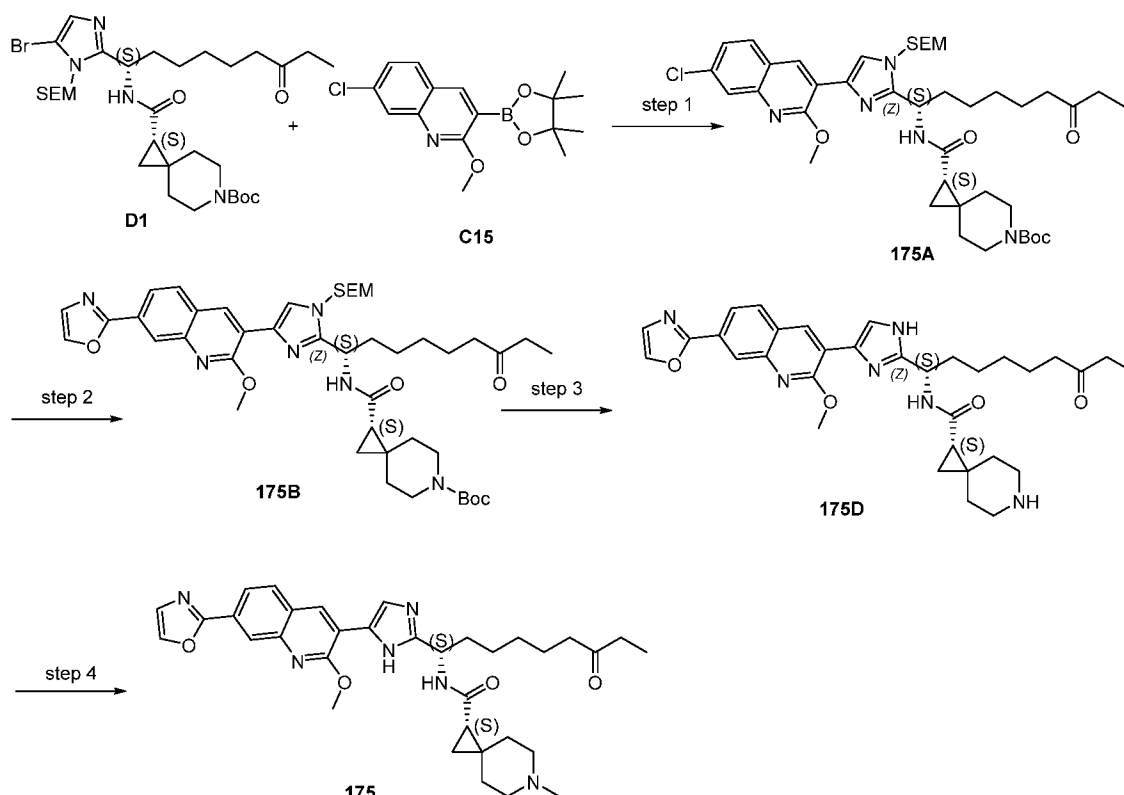
Step 4: Preparation of 8-methyl-*N*-((*S*)-7-oxo-1-(5-(quinolin-6-yl)-1*H*-imidazol-2-yl)nonyl)-8-azaspiro[bicyclo[3.2.1]octane-3,1'-cyclopropane]-2'-carboxamide (**166**): Formaldehyde (1.0 mL,

13.43 mmol) was added to the solution of *N*-((*S*)-7-oxo-1-(5-(quinolin-6-yl)-1*H*-imidazol-2-yl)nonyl)-8-azaspiro[bicyclo[3.2.1]octane-3,1'-cyclopropane]-2'-carboxamide (**166C**, second peak on HPLC, 190 mg, 0.370 mmol) in MeOH (5 mL) and stirred at 20°C for 2 h, then sodium triacetoxyborohydride (78 mg, 0.370 mmol) was added to the reaction mixture, stirred at 20°C for 1 h. The mixture was quenched with aqueous NaHCO₃ (saturated, 20 mL), and the mixture was extracted with ethyl acetate (2 x 30 mL). The combined organic fractions were washed with brine (saturated, 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.05% NH₃·H₂O, to give 8-methyl-*N*-((*S*)-7-oxo-1-(5-(quinolin-6-yl)-1*H*-imidazol-2-yl)nonyl)-8-azaspiro[bicyclo[3.2.1]octane-3,1'-cyclopropane]-2'-carboxamide (**166**). ¹H NMR (400 MHz, MeOD) δ 8.74-8.81 (m, 1H), 8.77 (brs, 1H), 8.77 (dd, *J* = 1.65, 4.30 Hz, 1H), 8.37 (d, *J* = 7.94 Hz, 1H), 8.32-8.41 (m, 1H), 8.24 (s, 1H), 8.14 (dd, *J* = 1.76, 8.82 Hz, 1H), 8.01 (d, *J* = 8.82 Hz, 1H), 7.49-7.57 (m, 2H), 5.02 (t, *J* = 7.50 Hz, 1H), 3.22 (brs, 2H), 2.36-2.47 (m, 2H), 2.28 (s, 3H), 1.71-2.09 (m, 6H), 1.50-1.61 (m, 2H), 1.24-1.47 (m, 6H), 0.87-1.11 (m, 4H).

Compound **242** was prepared using the same procedures as above, but using the compound from first peak in HPLC. ¹H NMR (400 MHz, MeOD) δ 8.77 (d, J = 2.87 Hz, 1H), 8.36 (d, J = 8.16 Hz, 1H), 8.25 (s, 1H), 8.13 (d, J = 9.04 Hz, 1H), 8.00 (d, J = 8.82 Hz, 1H), 7.48-7.58 (m, 2H), 5.04 (t, J = 7.39 Hz, 1H), 3.48-3.68 (m, 1H), 3.14-3.25 (m, 1H), 2.44 (tt, J = 3.64, 7.28 Hz, 4H), 2.31 (s, 3H), 1.78-2.12 (m, 7H), 1.57 (t, J = 6.84 Hz, 2H), 1.27-1.50 (m, 7H), 0.90-1.08 (m, 5H).

Example 72

(1*S*)-*N*-[(1*S*)-1-{5-[2-methoxy-7-(1,3-oxazol-2-yl)quinolin-3-yl]-1*H*-imidazol-2-yl}-7-oxononyl]-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**175**)



Step 1: Preparation of (S)-tert-butyl 1-(((S)-1-(4-(7-chloro-2-methoxyquinolin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (175A**):** A mixture of Pd(DTBPF)Cl₂ (0.109 g, 2.06 mmol), K₃PO₄ (0.996 g, 4.70 mmol), 7-chloro-2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (**C15**, 0.900 g, 2.82 mmol) and (S)-tert-butyl 1-(((S)-1-(4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**D1**, 1.380 g, 2.06 mmol) in toluene/water was degassed and backfilled with N₂. The mixture was heated to 80°C and stirred for 3 h. The precipitate was filtered off, the filtrate was concentrated, and the residue was purified by chromatography on

silica gel with petroleum ether / EtOAc = 5:1 to obtain (*S*)-tert-butyl 1-(((*S*)-1-(4-(7-chloro-2-methoxyquinolin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**175A**). LCMS (ESI) calc'd for C₄₁H₆₀ClN₅O₆Si [M+H]⁺: 782.5, found: 782.5

- 5 Step 2: Preparation of (*S*)-tert-butyl 1-(((*S*)-1-(5-(2-methoxy-7-(oxazol-2-yl)quinolin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**175B**): A mixture of (*S*)-tert-butyl 1-(((*S*)-1-(4-(7-chloro-2-methoxyquinolin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**175A**, 300 mg, 0.383 mmol), 2-(tributylstannyl)oxazole (165 mg, 0.460 mmol), K₃PO₄ (163 mg, 0.767 mmol) and XPhos- Pd-G2 (31 mg, 0.039 mmol) in toluene (4 mL) was degassed and backfilled with N₂ three times. The mixture was heated at 85°C for 18 h. The mixture was filtered and the filter cake was washed with ethyl acetate (20 mL). The filtrate was concentrated to dryness. The residue was purified by silica gel flash chromatography (ISCORF75; Sepa flash column), eluting with DCM / MeOH = 100:1 - 9:1 to give (*S*)-tert-butyl 1-(((*S*)-1-(5-(2-methoxy-7-(oxazol-2-yl)quinolin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**175B**). LCMS (ESI) calc'd for C₄₄H₆₂N₆O₇Si [M+H]⁺: 815.4, found: 815.5
- 10
- 15

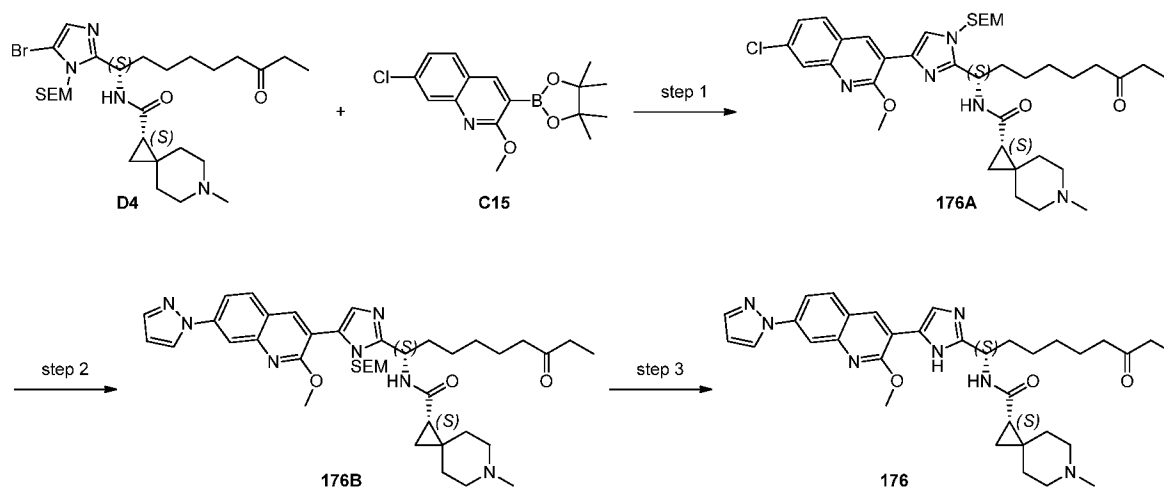
- Step 3: Preparation of (*S*)-*N*-(((*S*)-1-(4-(2-methoxy-7-(oxazol-2-yl)quinolin-3-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**175C**): A mixture of (*S*)-tert-butyl 1-(((*S*)-1-(4-(2-methoxy-7-(oxazol-2-yl)quinolin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**175B**, 100 mg, 0.123 mmol) in TFA (2 mL, 26.9 mmol) at rt was stirred at room temperature for 1 h. The mixture was concentrated to give (*S*)-*N*-(((*S*)-1-(4-(2-methoxy-7-(oxazol-2-yl)quinolin-3-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**175C**) which was used directly to next step. LCMS (ESI) calc'd for C₃₃H₄₀N₆O₄ [M+H]⁺: 585.3, found: 585.4
- 20
- 25

- Step 4: Preparation of (*S*)-*N*-(((*S*)-1-(5-(2-methoxy-7-(oxazol-2-yl)quinolin-3-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**175**): Formaldehyde (103 mg, 1.368 mmol) was added to a stirred mixture of (*S*)-*N*-(((*S*)-1-(4-(2-methoxy-7-(oxazol-2-yl)quinolin-3-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**175C**, 80 mg, 0.137 mmol) in MeOH (5 mL) at rt and the mixture was stirred at room temperature for 10 min. Then, sodium triacetoxhydroborate (87 mg, 0.410 mmol) was added. The mixture was stirred at rt for 30 min. Aqueous NaHCO₃ (saturated, 2 mL) was added and the mixture was extracted with ethyl acetate (3 x 3 mL). The combined organic fractions were washed with brine
- 30

(saturated, 1 x 3 mL), dried (Na₂SO₄), filtered and the residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.1% TFA, to give (*S*)-*N*-((*S*)-1-(5-(2-methoxy-7-(oxazol-2-yl)quinolin-3-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**175**). LCMS (ESI) calc'd for C₃₄H₄₂N₆O₄ [M+H]⁺: 599.3, found: 599.4. ¹H NMR (400 MHz, MeOD) δ 8.59-8.77 (m, 1H), 8.42-8.51 (m, 1H), 8.03-8.15 (m, 2H), 7.88-8.02 (m, 2H), 7.36-7.42 (m, 1H), 4.98-5.19 (m, 1H), 4.19-4.28 (m, 3H), 3.37-3.55 (m, 2H), 2.98-3.26 (m, 3H), 2.71-2.88 (m, 1H), 2.71-2.88 (m, 3H), 2.35-2.51 (m, 4H), 1.97-2.27 (m, 3H), 1.74-1.95 (m, 3H), 1.49-1.62 (m, 3H), 1.15-1.42 (m, 5H), 0.93-1.06 (m, 4H).

Example 73

(*S*)-*N*-[(*S*)-1-{5-[2-methoxy-7-(1*H*-pyrazol-1-yl)quinolin-3-yl]-1*H*-imidazol-2-yl}-7-oxononyl]-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**176**)



Step 1: Preparation of (*S*)-*N*-((*S*)-1-(4-(7-chloro-2-methoxyquinolin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide

(176A): A mixture of 7-chloro-2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (**C15**, 600 mg, 1.877 mmol), (*S*)-*N*-((*S*)-1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5] octane-1-carboxamide (**D4**, 1.205 g, 2.065 mmol), K₃PO₄ (996 mg, 4.69 mmol) and PdCl₂(DTBPF) (122 mg, 0.188 mmol) in THF (5 mL) and water (0.5 mL) was degassed and backfilled with N₂ three times. The mixture was heated at 80°C for 10 h. The mixture was cooled to rt, water (10 mL) was added and the mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic fractions were washed with brine (saturated, 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.1% TFA, to give (*S*)-*N*-((*S*)-1-(4-(7-chloro-2-methoxyquinolin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-

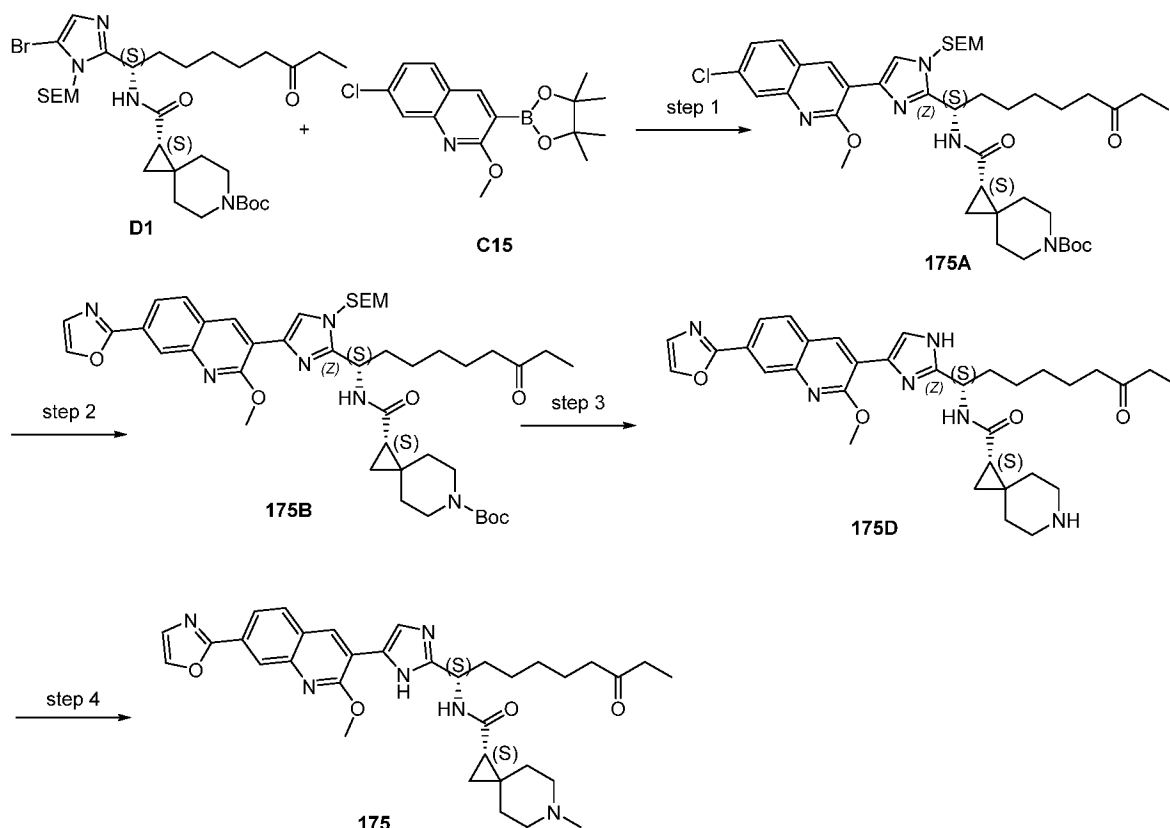
oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**176A**). LCMS (ESI) calc'd for $C_{37}H_{54}ClN_5O_4Si$ $[M+H]^+$: 696.3, found: 696.1. ^1H NMR (400 MHz, $CDCl_3$) δ 9.06-9.25 (m, 1H), 7.77-7.89 (m, 1H), 7.69-7.77 (m, 1H), 7.60-7.69 (m, 1H), 7.35-7.42 (m, 1H), 5.89-6.02 (m, 1H), 5.34-5.43 (m, 1H), 4.95-5.07 (m, 1H), 4.14-4.27 (m, 3H), 3.61-3.72 (m, 2H), 3.22-3.32 (m, 1H), 2.69-2.79 (m, 1H), 2.28-2.46 (m, 6H), 2.16-2.28 (m, 3H), 1.91-2.04 (m, 2H), 1.50-1.69 (m, 1H), 1.18-1.43 (m, 6H), 0.86-1.09 (m, 8H), -0.01-0.02 (m, 9H).

Step 2: Preparation of (S)-N-((S)-1-(4-(2-methoxy-7-(1H-pyrazol-1-yl)quinolin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (176B): A mixture of (S)-N-((S)-1-(4-(7-chloro-2-methoxyquinolin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**176A**, 110 mg, 0.158 mmol), tBuXPhos-Pd-G1 (10.85 mg, 0.016 mmol), Cs_2CO_3 (154 mg, 0.474 mmol) and 1H-pyrazole (22 mg, 0.323 mmol) in dioxane (2 mL) was degassed and backfilled with N_2 three times. The mixture was heated at 100°C for 22 h. The residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.1% TFA, to give (S)-N-((S)-1-(4-(2-methoxy-7-(1H-pyrazol-1-yl)quinolin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**176B**). LCMS (ESI) calc'd for $C_{40}H_{57}N_7O_4Si$ $[M+H]^+$: 728.4, found: 728.3

Step 3: Preparation of (S)-N-((S)-1-(5-(2-methoxy-7-(1H-pyrazol-1-yl)quinolin-3-yl)-1H-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (176): A stirred mixture of (S)-N-((S)-1-(5-(2-methoxy-7-(1H-pyrazol-1-yl)quinolin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**176B**, 20 mg, 0.027 mmol) in TFA (1 mL) was stirred at room temperature for 1 h. The residue was concentrated and purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.1% TFA, to give (S)-N-((S)-1-(5-(2-methoxy-7-(1H-pyrazol-1-yl)quinolin-3-yl)-1H-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**176**). LCMS (ESI) calc'd for $C_{34}H_{43}N_7O_3$ $[M+H]^+$: 598.3, found: 598.4. ^1H NMR (400 MHz, MeOD) δ 8.57-8.73 (m, 1H), 8.40-8.51 (m, 1H), 8.10-8.24 (m, 1H), 7.87-8.01 (m, 3H), 7.75-7.82 (m, 1H), 6.54-6.63 (m, 1H), 5.03-5.14 (m, 1H), 4.16-4.30 (m, 3H), 3.37-3.53 (m, 2H), 2.98-3.26 (m, 3H), 2.72-2.89 (m, 3H), 2.36-2.49 (m, 4H), 1.97-2.28 (m, 3H), 1.76-1.94 (m, 3H), 1.51-1.63 (m, 3H), 1.18-1.40 (m, 5H), 0.92-1.09 (m, 4H).

Example 74

(1S)-N-((1S)-7-oxo-1-[5-(9-prop-2-en-1-yl)-1,2,3,4-tetrahydro-1,4-epiminonaphthalen-6-yl)-1H-imidazol-2-yl]nonyl)-6-prop-2-en-1-yl-6-azaspiro[2.5]octane-1-carboxamide (**179**)



Step 1: Preparation of tert-butyl 6-(2-((*S*)-1-((*S*)-6-(tert-butoxycarbonyl)-6-azaspiro[2.5]octane-1-carboxamido)-7-oxononyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)-1,2,3,4-tetrahydro-1,4-epiminonaphthalene-9-carboxylate (**179A**): PdCl₂(DTBPF) (36.0 mg, 0.055

- 5 mmol) was added to a stirred mixture of (*S*)-tert-butyl 1-(((*S*)-1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**D1**, 370 mg, 0.552 mmol), tert-butyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,4-epiminonaphthalene-9-carboxylate (**C29**, 220 mg, 0.593 mmol) and K₂CO₃ (229 mg, 1.657 mmol) in THF (5.0 mL) and water (0.5 mL) at
- 10 room temperature under N₂ atmosphere and the mixture was stirred at 65°C for 16 h, then cooled to room temperature and concentrated. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether: EtOAc = 1.5:1 to give tert-butyl 6-(2-((*S*)-1-((*S*)-6-(tert-butoxycarbonyl)-6-azaspiro[2.5]octane-1-carboxamido)-7-oxononyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)-1,2,3,4-tetrahydro-1,4-epiminonaphthalene-9-
- 15 carboxylate (**179A**). LCMS (ESI) calc'd for C₄₆H₇₁N₅O₇Si [M+H]⁺: 834.5, found: 834.7

Step 2: Preparation of (1*S*)-*N*-((1*S*)-7-oxo-1-(5-(1,2,3,4-tetrahydro-1,4-epiminonaphthalen-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)nonyl)-6-azaspiro[2.5]octane-1-carboxamide (**179B**): HCl/MeOH (2.0 mL, 8.00 mmol) was added to a stirred mixture of tert-

butyl 6-(2-((*S*)-1-((*S*)-6-(tert-butoxycarbonyl)-6-azaspiro[2.5]octane-1-carboxamido)-7-oxononyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)-1,2,3,4-tetrahydro-1,4-epiminonaphthalene-9-carboxylate (**179A**, 380 mg, 0.456 mmol) in MeOH (5.0 mL) at room temperature and the mixture was stirred at rt for 1 h. Then the mixture was concentrated at room temperature, adjusted to pH 9 with NaHCO₃ solution, and the mixture was extracted with ethyl acetate (2 x 20 mL). The combined organic fractions were washed with brine (saturated, 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure to give (*S*)-*N*-((*S*)-7-oxo-1-(5-(1,2,3,4-tetrahydro-1,4-epiminonaphthalen-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)nonyl)-6-azaspiro[2.5]octane-1-carboxamide (**179B**). LCMS (ESI) calc'd for C₃₆H₅₅N₅O₃Si [M+H]⁺: 634.4, found: 634.5

Step 3: Preparation of (*S*)-6-allyl-*N*-((*S*)-1-(5-(9-allyl-1,2,3,4-tetrahydro-1,4-epiminonaphthalen-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**179C**): DIEA (0.207 mL, 1.183 mmol) was added to a stirred mixture of (*S*)-*N*-((*S*)-7-oxo-1-(5-(1,2,3,4-tetrahydro-1,4-epiminonaphthalen-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)nonyl)-6-azaspiro[2.5]octane-1-carboxamide (**179B**, 250 mg, 0.394 mmol) and 3-bromoprop-1-ene (95 mg, 0.789 mmol) in acetonitrile (10 mL) at room temperature and the mixture was stirred at rt for 2 h, then water (10 mL) was added and the mixture was extracted with ethyl acetate (20 mL). The combined organic fractions were washed with brine (saturated, 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by preparative TLC on silica gel, eluting with DCM / MeOH = 10:1 to give (*S*)-6-allyl-*N*-((*S*)-1-(5-(9-allyl-1,2,3,4-tetrahydro-1,4-epiminonaphthalen-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**179C**). LCMS (ESI) calc'd for C₄₂H₆₃N₅O₃Si [M+H]⁺: 714.5, found: 714.5.

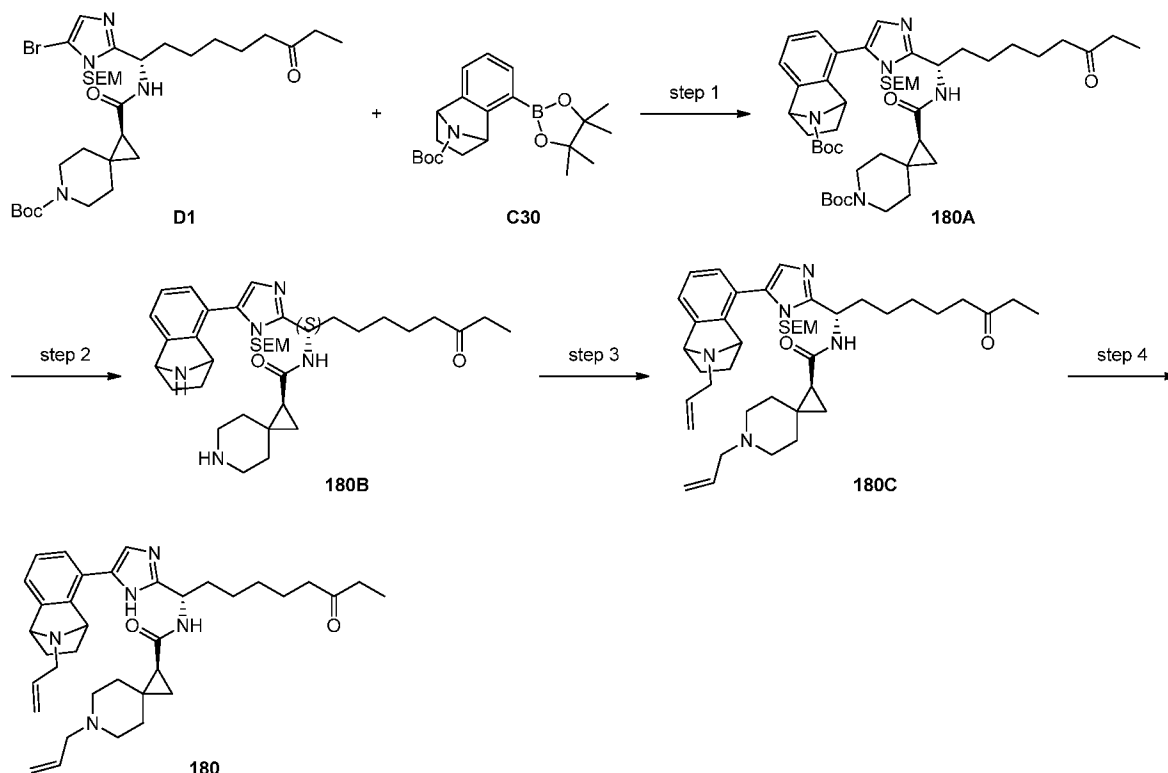
Step 4: Preparation of (*S*)-6-allyl-*N*-((*S*)-1-(5-(9-allyl-1,2,3,4-tetrahydro-1,4-epiminonaphthalen-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**179**): TFA (1.0 mL, 12.98 mmol) was added to a stirred mixture of (*S*)-6-allyl-*N*-((*S*)-1-(5-(9-allyl-1,2,3,4-tetrahydro-1,4-epiminonaphthalen-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**179C**, 10 mg, 0.014 mmol) in DCM (1.0 mL) under N₂ atmosphere at room temperature and the mixture was stirred at rt for 2 h, then left to stand overnight. The mixture was concentrated and the residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.1% TFA, to give (*S*)-6-allyl-*N*-((*S*)-1-(5-(9-allyl-1,2,3,4-tetrahydro-1,4-epiminonaphthalen-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**179**). LCMS (ESI)

calc'd for C₃₆H₄₉N₅O₂ [M+H]⁺: 584.4, found: 584.1. ¹H NMR (400 MHz, MeOD) δ 7.73-7.98 (m, 3H), 7.57-7.69 (m, 1H), 5.78-6.06 (m, 2H), 5.42-5.72 (m, 3H), 5.16-5.38 (m, 2H), 5.06 (brs, 1H), 3.62-3.84 (m, 3H), 3.51 (brs, 1H), 3.42 (d, *J* = 7.06 Hz, 1H), 2.94-3.23 (m, 2H), 2.37-2.60 (m, 6H), 2.13-2.36 (m, 1H), 1.74-2.12 (m, 5H), 1.13-1.73 (m, 11H), 0.99 (t, *J* = 7.39 Hz, 4H).

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Example 75

(1*S*)-*N*-{(1*S*)-7-oxo-1-[5-(9-prop-2-en-1-yl)-1,2,3,4-tetrahydro-1,4-epiminonaphthalen-5-yl]-1*H*-imidazol-2-yl]nonyl}-6-prop-2-en-1-yl-6-azaspiro[2.5]octane-1-carboxamide (180)



Step 1: Preparation of tert-butyl 5-(2-((*S*)-1-((*S*)-6-(tert-butoxycarbonyl)-6-azaspiro[2.5]octane-

1-carboxamido)-7-oxononyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)-1,2,3,4-tetrahydro-1,4-epiminonaphthalene-9-carboxylate (180A): PdCl₂(DTBPF) (15 mg, 0.023 mmol) was added to a stirred mixture of (*S*)-tert-butyl 1-(((*S*)-1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**D1**, 250 mg, 0.373 mmol), tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro-1,4-epiminonaphthalene-9-carboxylate (**C30**, 150 mg, 0.404 mmol) and K₂CO₃ (155 mg, 1.120 mmol) in THF (5.0 mL) and water (0.5 mL) at room temperature under N₂ atmosphere and the mixture was stirred at 60°C for 16 h, then cooled to room temperature and concentrated. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether : EtOAc = 1.5:1 to give tert-butyl 5-(2-((*S*)-1-((*S*)-

6-(tert-butoxycarbonyl)-6-azaspiro[2.5]octane-1-carboxamido)-7-oxononyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)-1,2,3,4-tetrahydro-1,4-epiminonaphthalene-9-carboxylate (**180A**). LCMS (ESI) calc'd for C₄₆H₇₁N₅O₇Si [M+H]⁺: 834.5, found: 834.6

Step 2: Preparation of (1*S*)-*N*-((1*S*)-7-oxo-1-(5-(1,2,3,4-tetrahydro-1,4-epiminonaphthalen-5-yl)-

1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)nonyl)-6-azaspiro[2.5]octane-1-carboxamide (**180B**): HCl/MeOH (2.0 mL, 8.00 mmol) was added to a stirred mixture of tert-butyl 5-(2-((*S*)-1-((*S*)-6-(tert-butoxycarbonyl)-6-azaspiro[2.5]octane-1-carboxamido)-7-oxononyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)-1,2,3,4-tetrahydro-1,4-epiminonaphthalene-9-carboxylate (**180A**, 250 mg, 0.300 mmol) in MeOH (5.0 mL) at room temperature and the mixture was stirred at rt for 4 h, then adjusted to pH 8 with NaHCO₃ solution, extracted with EtOAc (10 mL*2), washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated to afford (1*S*)-*N*-((1*S*)-7-oxo-1-(5-(1,2,3,4-tetrahydro-1,4-epiminonaphthalen-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)nonyl)-6-azaspiro[2.5]octane-1-carboxamide (**180B**) without further purification. LCMS (ESI) calc'd for C₃₆H₅₅N₅O₃Si [M+H]⁺: 634.4, found: 634.4

Step 3: Preparation of (1*S*)-6-allyl-*N*-((1*S*)-1-(5-(9-allyl-1,2,3,4-tetrahydro-1,4-epiminonaphthalen-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-

azaspiro[2.5]octane-1-carboxamide (**180C**): 3-bromoprop-1-ene (67 mg, 0.554 mmol) was added to a stirred mixture of (1*S*)-*N*-((1*S*)-7-oxo-1-(5-(1,2,3,4-tetrahydro-1,4-epiminonaphthalen-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)nonyl)-6-azaspiro[2.5]octane-1-carboxamide (**180B**, 170 mg, 0.268 mmol) and DIPEA (0.141 mL, 0.804 mmol) in MeCN (3.0 mL) at room temperature and the mixture was stirred at rt for 4 h. The mixture was diluted with ethyl acetate (10 mL), washed with brine (saturated, 5 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by preparative TLC on silica gel, eluting with DCM: MeOH = 10: 1 to give (1*S*)-6-allyl-*N*-((1*S*)-1-(5-(9-allyl-1,2,3,4-tetrahydro-1,4-epiminonaphthalen-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**180C**). LCMS (ESI) calc'd for C₄₂H₆₃N₅O₃Si [M+H]⁺: 714.5, found: 714.5

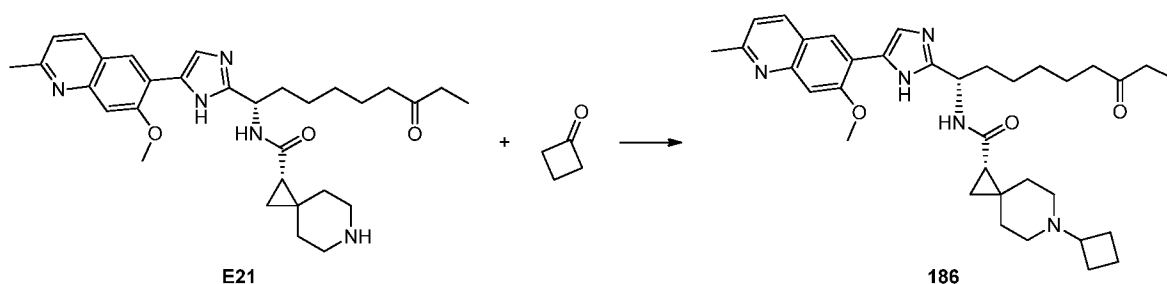
Step 4: Preparation of (1*S*)-6-allyl-*N*-((1*S*)-1-(5-(9-allyl-1,2,3,4-tetrahydro-1,4-

epiminonaphthalen-5-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**180**): TFA (1.0 mL, 12.98 mmol) was added to a stirred mixture of (1*S*)-6-allyl-*N*-((1*S*)-1-(5-(9-allyl-1,2,3,4-tetrahydro-1,4-epiminonaphthalen-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**180C**, 10 mg, 0.014 mmol) in DCM (0.2 mL) under N₂ atmosphere at room temperature and the mixture was stirred

at rt for 2 h, then left to stand overnight. The mixture was concentrated. The residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.1% TFA, to give (1*S*)-6-allyl-*N*-((1*S*)-1-(5-(9-allyl-1,2,3,4-tetrahydro-1,4-epiminonaphthalen-5-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**180**). LCMS (ESI) calc'd for C₃₆H₄₉N₅O₂ [M+H]⁺: 584.4, found: 584.1. ¹H NMR (400 MHz, MeOD) δ 7.69 (brs, 1H), 7.38-7.58 (m, 3H), 5.91 (brs, 2H), 5.40-5.71 (m, 4H), 5.15-5.31 (m, 1H), 5.02 (t, *J* = 7.24 Hz, 1H), 3.75 (brs, 3H), 3.37-3.58 (m, 1H), 3.35-3.43 (m, 1H), 2.86-3.20 (m, 2H), 2.38-2.62 (m, 6H), 2.21 (brs, 1H), 1.98 (brs, 4H), 1.65-1.85 (m, 3H), 1.40-1.59 (m, 3H), 1.10-1.39 (m, 6H), 0.98 (t, *J* = 7.34 Hz, 4H).

Example 76

(1*S*)-6-cyclobutyl-*N*-{(1*S*)-1-[5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl]-7-oxononyl}-6-azaspiro[2.5]octane-1-carboxamide (**186**)



Cyclobutanone (25 mg, 0.357 mmol) was added to a stirred mixture of (*S*)-*N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide 2,2,2-trifluoroacetate (**E21**, 125 mg, 0.194 mmol) in MeOH (2 mL) at room temperature for 1 h. Then NaBH(OAc)₃ (123 mg, 0.581 mmol) was added. It was stirred at rt for 24 h. Water (5 mL) was added and the mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic fractions were washed with aqueous NaHCO₃ (saturated, 1 x 5 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.05% NH₃·H₂O, to give (*S*)-6-cyclobutyl-*N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**186**).

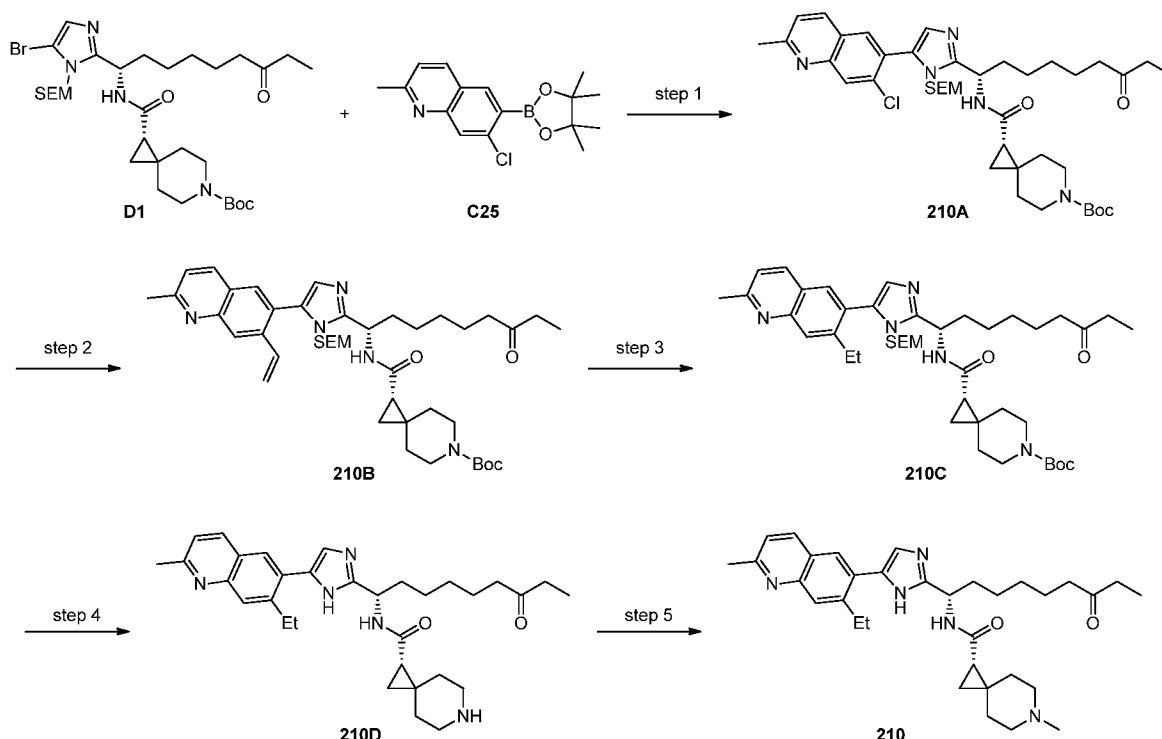
L-(+)-tartaric acid (11 mg, 0.073 mmol) was added to a stirred mixture of (*S*)-6-cyclobutyl-*N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**186**, 40 mg, 0.068 mmol) in acetonitrile (2 mL) and water (2 mL) at room temperature and the mixture was made dry by lyophilization to give (*S*)-6-cyclobutyl-*N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (2*R*,3*R*)-2,3-dihydroxysuccinate. ¹H NMR (400 MHz,

MeOD) δ 8.45-8.59 (m, 1H), 8.25-8.36 (m, 1H), 7.63-7.77 (m, 1H), 7.45 (s, 1H), 7.32-7.41 (m, 1H), 5.01-5.16 (m, 1H), 4.48 (s, 2H), 4.11 (s, 3H), 2.88 (brs, 2H), 2.72 (s, 3H), 2.44 (d, $J = 6.7$ Hz, 5H), 1.67-2.35 (m, 11H), 1.16-1.64 (m, 10H), 0.98 (t, $J = 7.0$ Hz, 5H). LCMS (ESI) calc'd for $C_{27}H_{29}N_5O_4$ $[M+H]^+$: 586.4, found: 586.1

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Example 77

(1*S*)-*N*-{(1*S*)-1-[5-(7-ethyl-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl]-7-oxononyl}-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (210)



Step 1: Preparation of (S)-tert-butyl 1-(((S)-1-(5-(7-chloro-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-

azaspiro[2.5]octane-6-carboxylate (210A): PdCl₂(DTBPF) (52 mg, 0.081 mmol) was added to a stirring mixture of (S)-tert-butyl 1-(((S)-1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**D1**, 600 mg, 0.896 mmol), 7-chloro-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (**C25**, 408 mg, 1.344 mmol) and K₃PO₄ (570 mg, 2.69 mmol) in dioxane (12.0 mL) and water (0.5 mL). Then, the mixture was heated with stirring at 70°C under N₂ atmosphere for 4 h. The combined mixture was cooled to rt and filtered through Celite. The resulting filtrate was concentrated under reduced pressure and the residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc to give (S)-tert-butyl 1-(((S)-1-(5-(7-chloro-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-

oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**210A**). LCMS (ESI) calc'd for $C_{41}H_{60}ClN_5O_5Si$ $[M+H]^+$: 766.4, found: 766.5

Step 2: (S)-tert-butyl 1-(((S)-1-(5-(2-methyl-7-vinylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-

- 5 azaspiro[2.5]octane-6-carboxylate (**210B**): PdCl₂(DTBPF) (33 mg, 0.051 mmol) was added to a mixture of (S)-tert-butyl 1-(((S)-1-(5-(7-chloro-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**210A**, 203 mg, 0.265 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (210 mg, 1.364 mmol) and K₃PO₄ (189 mg, 0.890 mmol) in co-solvents of
- 10 THF (3 mL) and water (0.3 mL) at rt and the mixture was stirred at 80°C for 6 h. To the mixture was added another 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (200 mg), K₃PO₄ (190 mg), PdCl₂(DTBPF) (30 mg) and bubbled with N₂, then it was stirred at 80°C for 9 h. To the mixture was added another 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (180 mg), K₃PO₄ (190 mg), PdCl₂(DTBPF) (33 mg) and it was bubbled with N₂, then stirred at 80°C for another 20 h. The
- 15 mixture was diluted with water (30 mL) and extracted with DCM (3 x 15 mL). The combined organic fractions were washed with brine (saturated, 15 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with MeOH / DCM = 0~10% and then purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.1% TFA, to give (S)-tert-
- 20 butyl 1-(((S)-1-(5-(2-methyl-7-vinylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**210B**). LCMS (ESI) calc'd for $C_{43}H_{63}N_5O_5Si$ $[M+H]^+$: 758.5, found: 758.4

Step 3: (S)-tert-butyl 1-(((S)-1-(5-(7-ethyl-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-

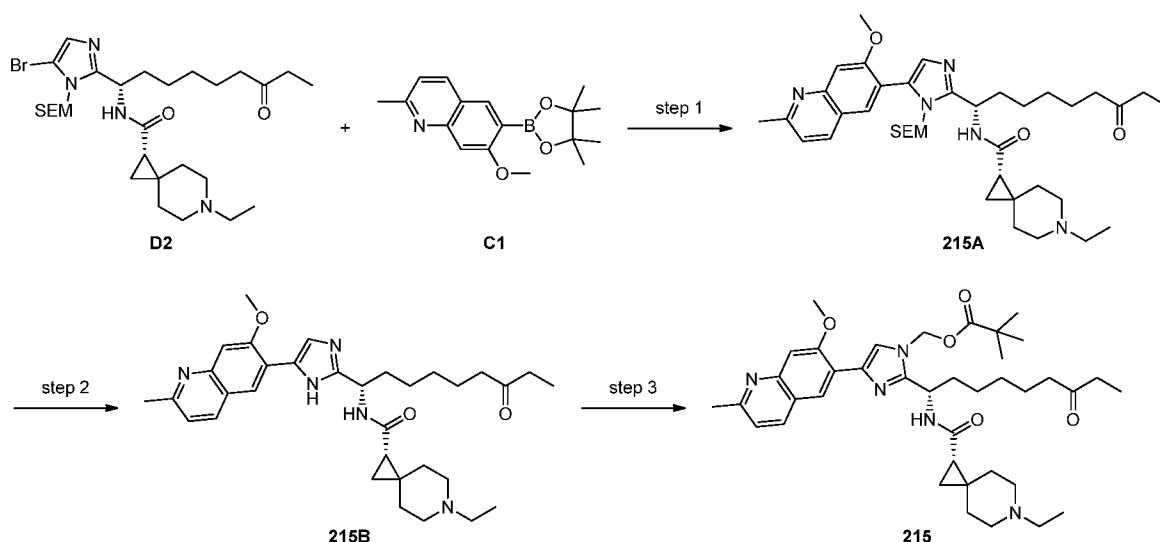
- 25 azaspiro[2.5]octane-6-carboxylate (**210C**): 10% Pd-C (80 mg, 0.075 mmol) was added to a stirred mixture of (S)-tert-butyl 1-(((S)-1-(5-(2-methyl-7-vinylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**210B**, 70 mg, 0.092 mmol) in MeOH (15 mL) at rt and the mixture was stirred at rt for 2 h under H₂ (15 psi). The mixture was filtered and the filter cake
- 30 was washed with MeOH (30 mL). The filtrate was concentrated to give (S)-tert-butyl 1-(((S)-1-(5-(7-ethyl-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**210C**) which was used to the next step without purification. LCMS (ESI) calc'd for $C_{43}H_{65}N_5O_5Si$ $[M+H]^+$: 760.5, found: 760.5

Step 4: (S)-N-((S)-1-(5-(7-ethyl-2-methylquinolin-6-yl)-1H-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (210D): TFA (4 mL, 51.9 mmol) was added to (S)-tert-butyl 1-(((S)-1-(5-(7-ethyl-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-7-oxononyl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (210C, 65 mg, 0.086 mmol) and the mixture was stirred at rt for 3 h. TFA was evaporated under reduced pressure to give (S)-N-((S)-1-(5-(7-ethyl-2-methylquinolin-6-yl)-1H-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (210D) which was used in the next step without purification. LCMS (ESI) calc'd for C₃₂H₄₃N₅O₂ [M+H]⁺: 530.3, found: 530.4

Step 5: (S)-N-((S)-1-(5-(7-ethyl-2-methylquinolin-6-yl)-1H-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (210): A mixture of (S)-N-((S)-1-(5-(7-ethyl-2-methylquinolin-6-yl)-1H-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (210D, 45 mg, 0.085 mmol) and formaldehyde (0.5 mL, 6.72 mmol) in MeOH (2 mL) was stirred at rt for 8 h, then NaBH(OAc) (103 mg, 0.486 mmol) was added portionwise and the mixture was stirred at rt for 1 h. The mixture was diluted with DMF (3 mL). The residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.1% TFA, to give (S)-N-((S)-1-(5-(7-ethyl-2-methylquinolin-6-yl)-1H-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (20 mg). (S)-N-((S)-1-(5-(7-ethyl-2-methylquinolin-6-yl)-1H-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (20 mg, 0.037 mmol) was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.05% NH₃·H₂O, to give (S)-N-((S)-1-(5-(7-ethyl-2-methylquinolin-6-yl)-1H-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (210). LCMS (ESI) calc'd for C₃₃H₄₅N₅O₂ [M+H]⁺: 544.4, found: 544.4. ¹H NMR (400 MHz, MeOD) δ 8.19 (d, *J* = 8.22 Hz, 1H), 7.92 (brs, 1H), 7.85 (s, 1H), 7.37 (d, *J* = 8.61 Hz, 1H), 7.15 (brs, 1H), 5.02 (t, *J* = 7.63 Hz, 1H), 2.98 (d, *J* = 6.65 Hz, 2H), 2.71 (s, 3H), 2.40-2.56 (m, 6H), 2.34 (brs, 1H), 2.17 (s, 3H), 1.88-2.05 (m, 2H), 1.67 (brs, 2H), 1.51-1.62 (m, 4H), 1.43 (d, *J* = 6.26 Hz, 1H), 1.29-1.41 (m, 4H), 1.24 (t, *J* = 7.63 Hz, 3H), 1.11 (t, *J* = 4.89 Hz, 1H), 1.07-1.14 (m, 1H), 0.99 (t, *J* = 7.24 Hz, 3H), 0.79-0.86 (m, 1H), 0.82 (dd, *J* = 4.50, 8.02 Hz, 1H).

Example 78

{2-[(1S)-1-({[(1S)-6-ethyl-6-azaspiro[2.5]oct-1-yl]carbonyl}amino)-7-oxononyl]-4-(7-methoxy-2-methylquinolin-6-yl)-1H-imidazol-1-yl}methyl 2,2-dimethylpropanoate (215)



Step 1: Preparation of (*S*)-6-ethyl-*N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (215A**):** PdCl₂(DTBPF) (27 mg, 0.041 mmol) was added to a mixture of (*S*)-*N*-

((*S*)-1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-ethyl-6-azaspiro[2.5]octane-1-carboxamide (**D2**, 250 mg, 0.418 mmol), 7-methoxy-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (**C1**, 128 mg, 0.427 mmol) and K₃PO₄ (266 mg, 1.255 mmol) in co-solvents of THF (3 mL) and water (0.3 mL) at room temperature and the mixture was stirred at 70°C for 2 h. The mixture was diluted with water (15 mL), and extracted

with ethyl acetate (3 x 10 mL). The combined organic fractions were washed with brine (saturated, 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with DCM / MeOH = 0~30% to give (*S*)-6-ethyl-*N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**215A**). LCMS (ESI) calc'd for C₃₉H₅₉N₅O₄Si [M+H]⁺: 690.4, found: 690.4

Step 2: Preparation of (*S*)-6-ethyl-*N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (215B**):** TFA (4 mL, 51.9 mmol) was

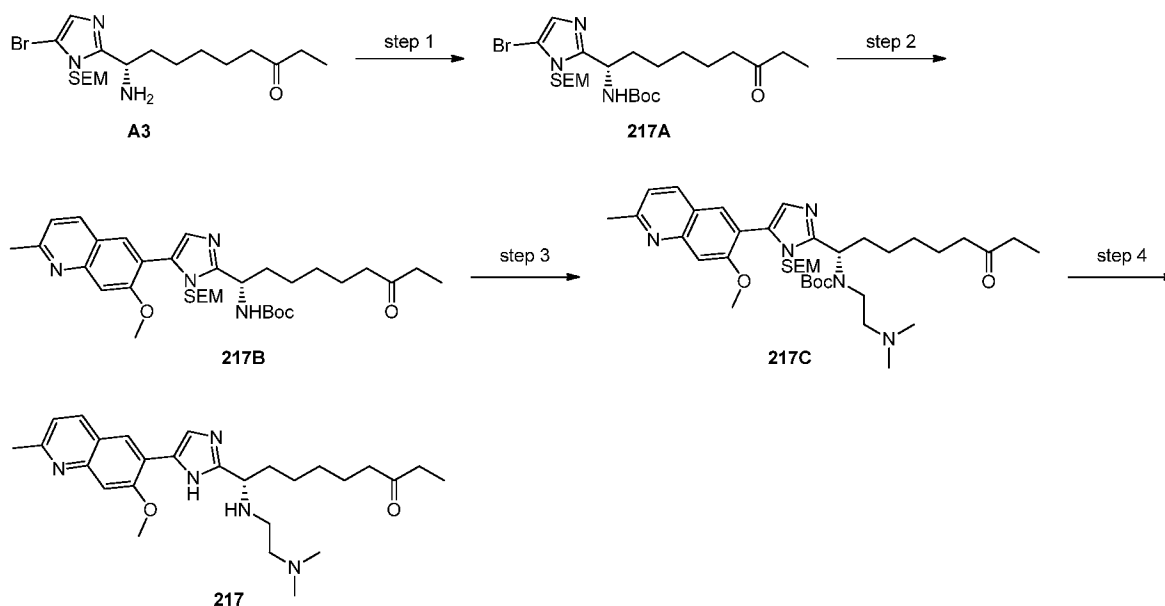
added to a stirred mixture of (*S*)-6-ethyl-*N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**215A**, 250 mg, 0.362 mmol) at room temperature and the mixture was stirred at room temperature for 2 h. All the volatiles were removed by evaporator to give (*S*)-6-ethyl-*N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide (**215B**) which was used to the next step without further purification. LCMS (ESI) calc'd for C₃₃H₄₅N₅O₃ [M+H]⁺: 560.4, found: 560.4

Step 3: Preparation of (2-((*S*)-1-((*S*)-6-ethyl-6-azaspiro[2.5]octane-1-carboxamido)-7-oxononyl)-4-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-1-yl)methyl pivalate (**215**):

Chloromethyl pivalate (89 mg, 0.594 mmol) was added to a stirred mixture of (*S*)-6-ethyl-*N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide 2,2,2-trifluoroacetate (**215B**, 160 mg, 0.237 mmol) and DIPEA (0.25 mL, 1.431 mmol) in DMF (2 mL) at rt and the mixture was stirred at rt for 7 d. The mixture was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.05% NH₃·H₂O, to give (2-((*S*)-1-((*S*)-6-ethyl-6-azaspiro[2.5]octane-1-carboxamido)-7-oxononyl)-4-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-1-yl)methyl pivalate (**215**). LCMS (ESI) calc'd for C₃₉H₅₅N₅O₅ [M+H]⁺: 674.4, found: 674.1. ¹H NMR (400 MHz, MeOD) δ 8.51 (s, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.73 (s, 1H), 7.38 (s, 1H), 7.27 (d, *J* = 8.2 Hz, 1H), 6.35 (d, *J* = 10.9 Hz, 1H), 6.00 (d, *J* = 11.2 Hz, 1H), 5.19 (t, *J* = 7.5 Hz, 1H), 4.08 (s, 3H), 2.67 (s, 3H), 2.62 (brs, 1H), 2.35-2.47 (m, 5H), 2.32 (d, *J* = 6.9 Hz, 1H), 1.95-2.22 (m, 4H), 1.25-1.74 (m, 10H), 1.18 (s, 10H), 1.05-1.12 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H), 0.79 (dd, *J* = 4.5, 7.8 Hz, 1H), 0.64 (brs, 3H).

Example 79

(*9S*)-9-{[2-(dimethylamino)ethyl]amino}-9-[5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl]nonan-3-one (**217**)



Step 1: Preparation of (*S*)-tert-butyl (1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamate (**217A**): To a stirred solution of (*S*)-9-amino-9-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)nonan-3-one (**A3**, 1.00 g, 2.31 mmol) in DCM (10 mL) was added Boc₂O (760 mg, 3.47 mmol) and TEA (702 mg, 6.94 mmol). The resulting mixture was stirred at room temperature

for 16 h. The mixture was diluted with water (50 mL), extracted with DCM (50 mL*2), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the title product (**217A**) which was used to the next step without further purification. LCMS (ESI) calc'd for C₂₃H₄₃BrN₃O₄Si [M+H]⁺: 532.2, found: 532.3

- 5 Step 2: Preparation of (S)-tert-butyl(1-(5-(7-methoxy-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-7-oxononyl)carbamate (**217B**): To a stirred solution of (S)-tert-butyl (1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-7-oxononyl)carbamate (**217A**, 1.10 g, 2.07 mmol) in a mixture of dioxane (12 mL) and H₂O (2 mL) was added 7-methoxy-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (C1, 741 mg, 2.48 mmol), PdCl₂(DTBPF) (135 mg, 0.21 mmol) and K₃PO₄ (1.32 g, 6.20 mmol). The reaction mixture was allowed to stir at 70°C for 2 h under N₂ atmosphere. After it cooled to room temperature, the mixture was diluted with water (40 mL), extracted with EtOAc (50 mL*2), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column flash chromatography, eluting with EtOAc: petroleum ether = 1:2 to give (S)-tert-butyl(1-(5-(7-methoxy-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-7-oxononyl)carbamate (**217B**). LCMS (ESI) calc'd for C₃₄H₅₃N₄O₅Si [M+H]⁺: 625.4, found: 625.4. ¹H NMR (400 MHz, CDCl₃) δ 8.54 (s, 1H), 8.07 (d, *J* = 8.16 Hz, 1H), 7.61 (s, 1H), 7.43 (s, 1H), 7.16 (d, *J* = 8.38 Hz, 1H), 5.57 (d, *J* = 10.58 Hz, 1H), 5.32 (d, *J* = 9.48 Hz, 1H), 5.23 (d, *J* = 11.03 Hz, 1H), 4.93 (q, *J* = 7.94 Hz, 1H), 4.07 (s, 3H), 3.49-3.65 (m, 2H), 2.72 (s, 3H), 2.30-2.44 (m, 4H), 1.90-2.00 (m, 2H), 1.52-1.58 (m, 2H), 1.43 (s, 9H), 1.35 (dd, *J* = 7.28, 14.11 Hz, 3H), 1.01 (t, *J* = 7.28 Hz, 3H), 0.89-0.97 (m, 2H), 0.00 (s, 9H).

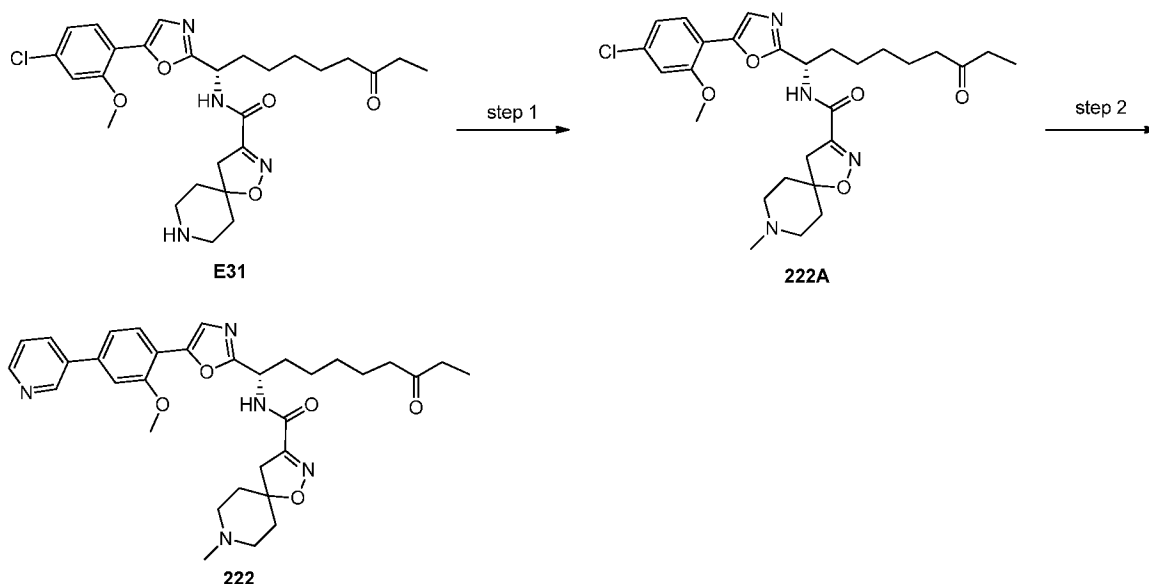
- Step 3: Preparation of (S)-tert-butyl (2-(dimethylamino)ethyl)(1-(5-(7-methoxy-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-7-oxononyl)carbamate (**217C**): NaH (30 mg, 0.750 mmol) was added to a stirred mixture of (S)-tert-butyl (1-(5-(7-methoxy-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-7-oxononyl)carbamate (**217B**, 150 mg, 0.240 mmol) in THF (2 mL), then 2-bromo-*N,N*-dimethylethanamine hydrobromide (80 mg, 0.343 mmol) was added at room temperature and the mixture was stirred at room temperature for 18 h. Water (5 mL) was added and the mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic fractions were washed with brine (saturated, 1 x 5 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure to give (S)-tert-butyl (2-(dimethylamino)ethyl)(1-(5-(7-methoxy-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-7-oxononyl)carbamate (**217C**) which was directly used for next step. LCMS (ESI) calc'd for C₃₈H₆₁N₅O₅Si [M+H]⁺: 696.4, found: 696.5

Step 4: Preparation of *(S)*-9-((2-(dimethylamino)ethyl)amino)-9-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)nonan-3-one (**217**): TFA (2 mL, 26.0 mmol) was added to a stirred mixture of *(S)*-tert-butyl (2-(dimethylamino)ethyl)(1-(5-(7-methoxy-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)carbamate (**217C**, 150 mg, 0.216 mmol) at room temperature and the mixture was stirred at room temperature for 1 h. Most of the TFA was removed by evaporator, then the residue was dissolved in MeOH and neutralized with NaHCO₃ (sat.). The mixture was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.05% NH₃·H₂O, to give *(S)*-9-((2-(dimethylamino)ethyl)amino)-9-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)nonan-3-one (**217**). LCMS (ESI) calc'd for C₂₇H₃₉N₅O₂ [M+H]⁺: 466.3, found: 466.3

L-(+)-tartaric acid (32 mg, 0.213 mmol) was added to a stirred mixture of *(S)*-9-((2-(dimethylamino)ethyl)amino)-9-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)nonan-3-one (**217**, 98 mg, 0.210 mmol) in acetonitrile (2 mL) and water (2 mL) at room temperature and the mixture was made dry by lyophilization to give *(S)*-9-((2-(dimethylamino)ethyl)amino)-9-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)nonan-3-one (2*R*,3*R*)-2,3-dihydroxysuccinate. LCMS (ESI) calc'd for C₂₇H₃₉N₅O₂ [M+H]⁺: 466.3, found: 466.2. ¹H NMR (400 MHz, MeOD) δ 8.39 (s, 1H), 8.25 (d, *J* = 8.2 Hz, 1H), 7.75 (s, 1H), 7.42 (s, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 4.47 (s, 2H), 4.10 (s, 3H), 4.02-4.07 (m, 1H), 2.97-3.27 (m, 3H), 2.83-2.89 (m, 1H), 2.81 (s, 6H), 2.71 (s, 3H), 2.37-2.41 (m, 4H), 1.91-2.02 (m, 2H), 1.52 (q, *J* = 7.3 Hz, 2H), 1.18-1.44 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 3H).

Example 80

N-{(1*S*)-1-[5-(2-methoxy-4-pyridin-3-ylphenyl)-1,3-oxazol-2-yl]-7-oxononyl}-8-methyl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide (**222**)



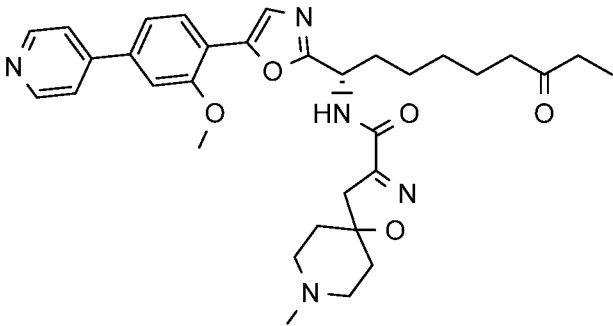
Step 1: Preparation of *(S)*-*N*-(1-(5-(4-chloro-2-methoxyphenyl)oxazol-2-yl)-7-oxononyl)-8-methyl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide (**222A**): Formaldehyde (0.80 mL, 10.75 mmol) was added to a stirred mixture of *(S)*-*N*-(1-(5-(4-chloro-2-methoxyphenyl)oxazol-2-yl)-7-oxononyl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide (**E31**, 589 mg, 1.109 mmol) in methanol (10 mL) at room temperature and the mixture was stirred at room temperature for 30 min. Then NaBH(OAc)₃ (2.351 g, 11.09 mmol) was added and stirred for 1 h. NaHCO₃ (saturated, 30 mL) was added and the mixture was extracted with ethyl acetate (2 x 50 mL). The combined organic fractions were washed with brine (saturated, 50 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure to afford *(S)*-*N*-(1-(5-(4-chloro-2-methoxyphenyl)oxazol-2-yl)-7-oxononyl)-8-methyl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide (**222A**) which was used to the next step without further purification. LCMS (ESI) calc'd for C₂₈H₃₇ClN₄O₅ [M+H]⁺: 545.2, found: 545.3

Step 2: Preparation of compound *(S)*-*N*-(1-(5-(2-methoxy-4-(pyridin-3-yl)phenyl)oxazol-2-yl)-7-oxononyl)-8-methyl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide (**222**): *(S)*-*N*-(1-(5-(4-chloro-2-methoxyphenyl)oxazol-2-yl)-7-oxononyl)-8-methyl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide (**222A**, 100 mg, 0.183 mmol) and K₃PO₄ (117 mg, 0.550 mmol) were added to a stirred mixture of pyridin-3-ylboronic acid (27 mg, 0.220 mmol) in dioxane (2 mL) and water (0.5 mL). The mixture was replaced with N₂. Then, PdCl₂(DTBPF) (12 mg, 0.018 mmol) was added at room temperature and the mixture was heated with stirring at 70°C for 2 h. Then Pd₂(dba)₃ (17 mg, 0.019 mmol) and XPhos (18 mg, 0.038 mmol) were added to the reaction solution and it was heated to 100°C and stirred overnight. The mixture was cooled to room temperature. Water (10 mL) was added and the mixture was extracted with ethyl acetate (2 x 10

mL). The combined organic fractions were washed with brine (2 x 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure and the residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.05% NH₃·H₂O, to give (*S*)-*N*-(1-(5-(2-methoxy-4-(pyridin-3-yl)phenyl)oxazol-2-yl)-7-oxononyl)-8-methyl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide (**222**).

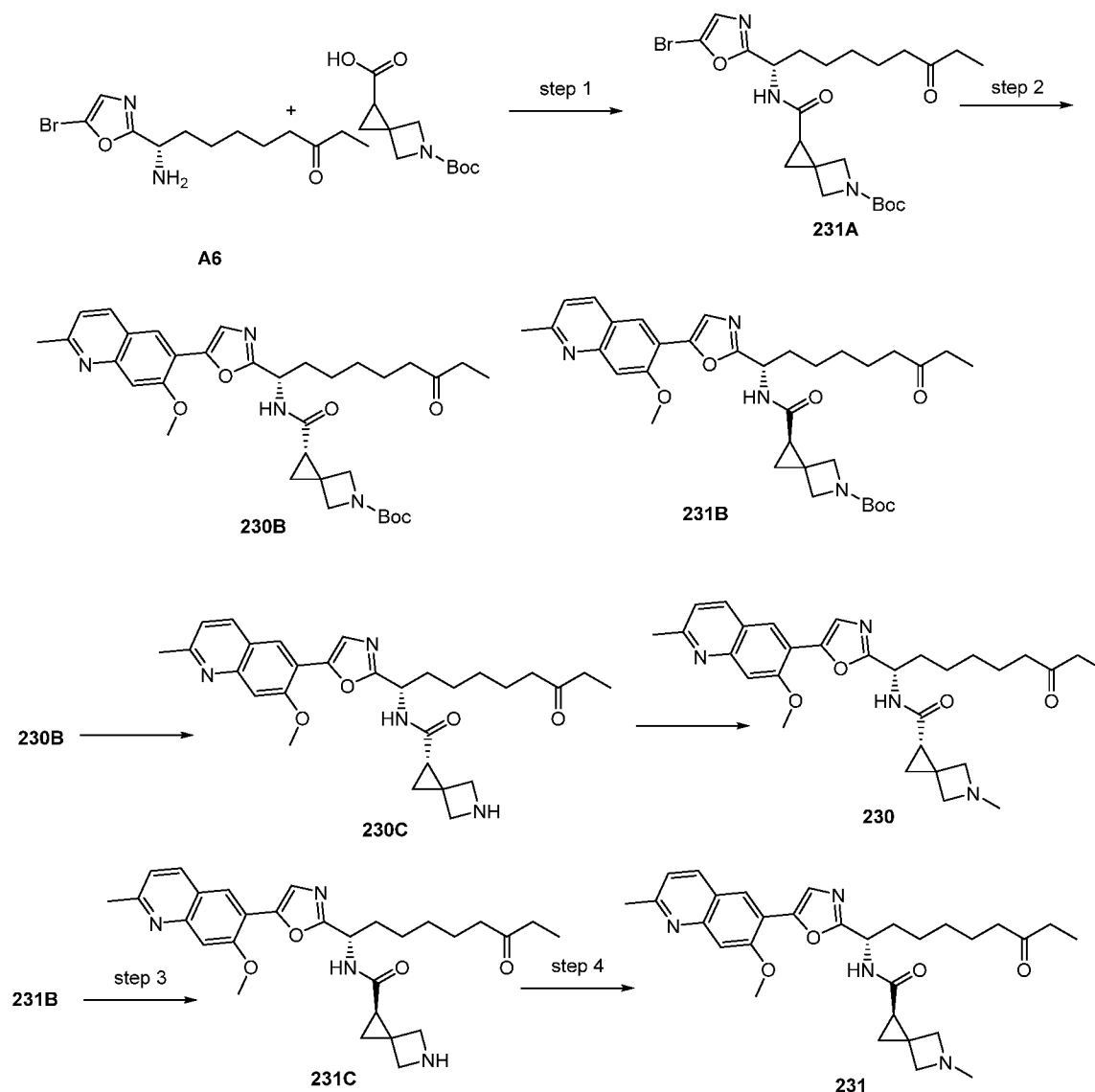
L-(+)-tartaric acid (6 mg, 0.040 mmol) was added to a stirred mixture of (*S*)-*N*-(1-(5-(2-methoxy-4-(pyridin-3-yl)phenyl)oxazol-2-yl)-7-oxononyl)-8-methyl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide (**222**, 23 mg, 0.039 mmol) in acetonitrile (5 mL) and water (2 mL) at room temperature. Then, it was made dry by lyophilization to give (*S*)-*N*-(1-(5-(2-methoxy-4-(pyridin-3-yl)phenyl)oxazol-2-yl)-7-oxononyl)-8-methyl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide (2*R*,3*R*)-2,3-dihydroxysuccinate. LCMS (ESI) calc'd for C₃₃H₄₁N₅O₅ [M+H]⁺: 588.3, found: 588.1. ¹H NMR (400 MHz, MeOD) δ 8.88 (brs, 1H), 8.55 (d, *J* = 2.35 Hz, 1H), 8.18 (d, *J* = 7.83 Hz, 1H), 7.87 (d, *J* = 8.22 Hz, 1H), 7.50-7.58 (m, 2H), 7.34-7.42 (m, 2H), 5.23-5.28 (m, 1H), 4.48 (s, 5H), 4.08 (s, 3H), 3.33-3.51 (m, 4H), 3.16 (s, 2H), 2.90 (s, 3H), 2.42-2.50 (m, 4H), 2.06-2.23 (m, 5H), 2.01 (d, *J* = 9.00 Hz, 1H), 1.52-1.65 (m, 2H), 1.33-1.51 (m, 4H), 0.99 (t, *J* = 7.24 Hz, 3H).

The following compound was prepared using similar procedures as described for compound **222**.

ID	Structure	Observed [M+H] ⁺
395		588.1

Example 81

(*S*)-*N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-5-methyl-5-azaspiro[2.3]hexane-1-carboxamide (230) and (*R*)-*N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-5-methyl-5-azaspiro[2.3]hexane-1-carboxamide (231)



Step 1: Preparation of tert-butyl 1-(((S)-1-(5-bromooxazol-2-yl)-7-oxononyl)carbamoyl)-5-azaspiro[2.3]hexane-5-carboxylate (231A): T3P (4.20 g, 6.60 mmol) was added to a stirred

mixture of (S)-9-amino-9-(5-bromooxazol-2-yl)nonan-3-one (**A6**, 1 g, 3.30 mmol), 5-(tert-butoxycarbonyl)-5-azaspiro[2.3]hexane-1-carboxylic acid (0.899 g, 3.96 mmol) and DIEA (1.8 mL, 10.11 mmol) in DMF (15 mL) at room temperature and the mixture was stirred at room temperature for 18 h. The mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic fractions were washed with brine (saturated, 2 x 50 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column

flash chromatography, eluting with petroleum ether / EtOAc = 1:1 to give tert-butyl 1-(((S)-1-(5-bromooxazol-2-yl)-7-oxononyl)carbamoyl)-5-azaspiro[2.3]hexane-5-carboxylate (**231A**). LCMS (ESI) calc'd for C₂₃H₃₄BrN₃O₅ [M+H]⁺: 512.2, found: 512.2

Step 2: Preparation of tert-butyl 1-(((S)-1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)carbamoyl)-5-azaspiro[2.3]hexane-5-carboxylate (**231B**): PdCl₂(DTBPF) (0.124 g, 0.190 mmol) was added to a stirred mixture of 7-methoxy-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (**C1**, 0.683 g, 2.283 mmol), tert-butyl 1-(((S)-1-(5-bromooxazol-2-yl)-7-oxononyl)carbamoyl)-5-azaspiro[2.3]hexane-5-carboxylate (**231A**, 1.3 g, 1.903 mmol) and K₃PO₄ (1.212 g, 5.71 mmol) in THF (10 mL)/water (2 mL) at room temperature and the mixture was stirred at 70°C for 3 h. The mixture was diluted with ethyl acetate (50 mL), washed with water (20 mL) and brine (saturated 20 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The mixture was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.1% TFA, to give tert-butyl 1-(((S)-1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)carbamoyl)-5-azaspiro[2.3]hexane-5-carboxylate (**231B**, first peak on HPLC). LCMS (ESI) calc'd for C₃₄H₄₄N₄O₆ [M+H]⁺: 605.3, found: 605.3.

tert-butyl 1-(((S)-1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)carbamoyl)-5-azaspiro[2.3]hexane-5-carboxylate (second peak on HPLC). LCMS (ESI) calc'd for C₃₄H₄₄N₄O₆ [M+H]⁺: 605.3, found: 605.4

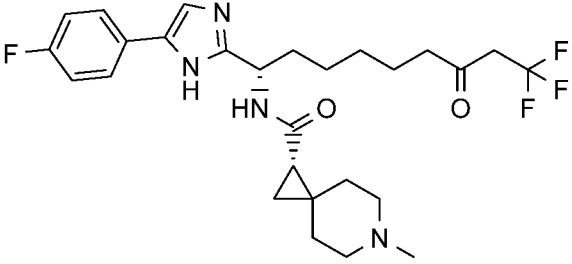
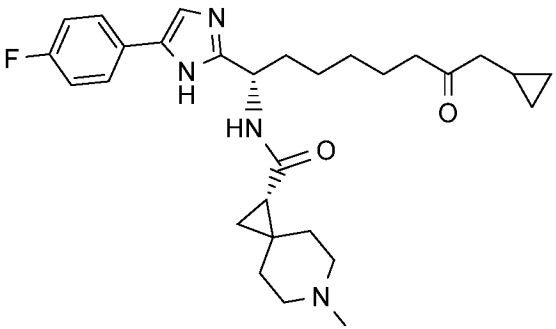
Step 3: Preparation of N-(((S)-1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-5-azaspiro[2.3]hexane-1-carboxamide (**231C**): TFA (0.1 mL, 1.298 mmol) was added to tert-butyl 1-(((S)-1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)carbamoyl)-5-azaspiro[2.3]hexane-5-carboxylate (**231B**, first peak on HPLC, 80 mg, 0.132 mmol) in DCM (1 mL) at room temperature for 1 h. The mixture was evaporated under pressure to remove TFA to give N-(((S)-1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-5-azaspiro[2.3]hexane-1-carboxamide (**231C**) which was used to next step without further purification. LCMS (ESI) calc'd for C₂₉H₃₆N₄O₄ [M+H]⁺: 505.3, found: 505.3

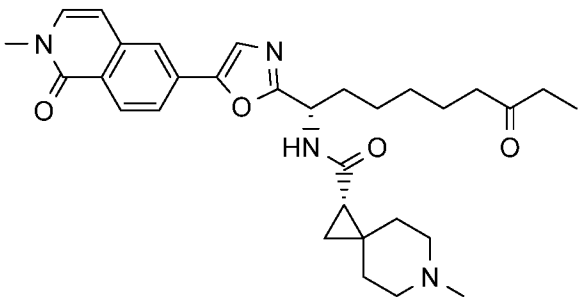
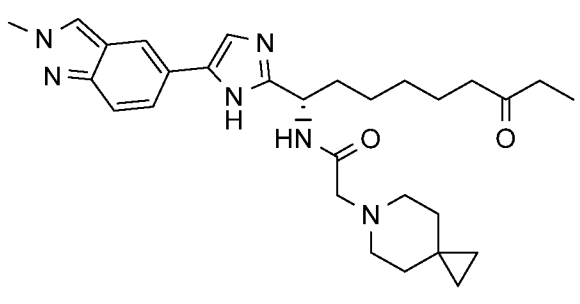
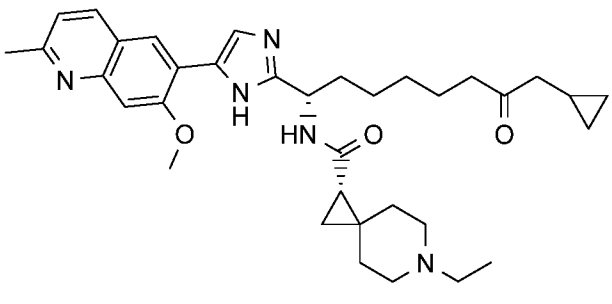
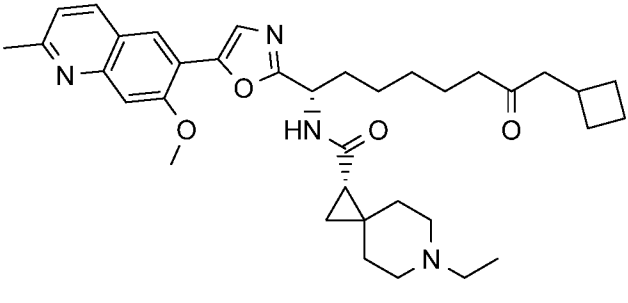
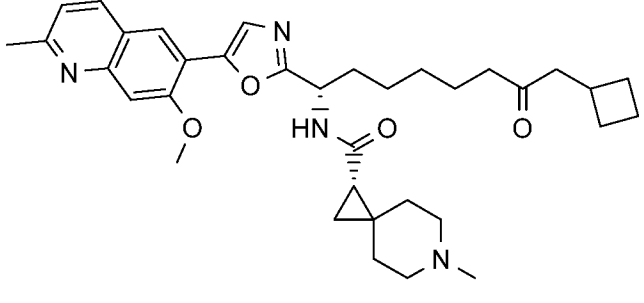
Step 4: Preparation of N-(((S)-1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-5-methyl-5-azaspiro[2.3]hexane-1-carboxamide (**231**): Formaldehyde (22 mg, 0.733 mmol) was added to a stirred mixture of N-(((S)-1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-5-azaspiro[2.3]hexane-1-carboxamide (**231C**, 60 mg, 0.119 mmol) in MeOH (3 mL) at room temperature and the mixture was stirred at room temperature for 1 h. Sodium triacetoxyhydroborate (227 mg, 1.070 mmol) was added into the mixture at room temperature and the mixture was stirred at room temperature for 1 h. The mixture was neutralized by NaHCO₃ (2 mL), extracted with ethyl acetate (2*20 mL) and washed with water (10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water +

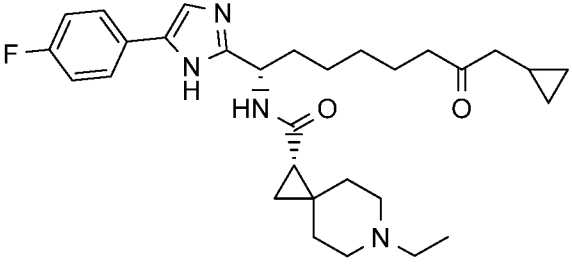
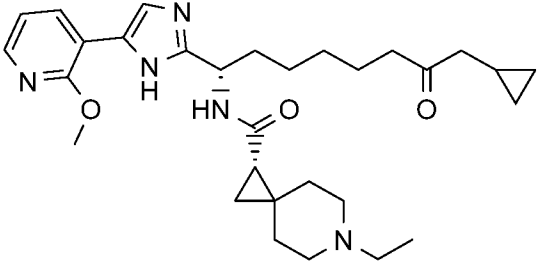
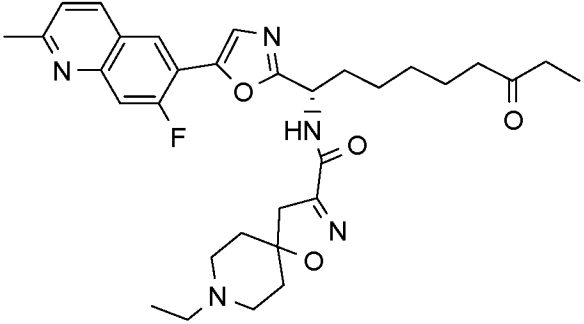
0.05% $\text{NH}_3 \cdot \text{H}_2\text{O}$, to give *N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-5-methyl-5-azaspiro[2.3]hexane-1-carboxamide (**231**). LCMS (ESI) calc'd for $\text{C}_{30}\text{H}_{38}\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$: 519.3, found: 519.1. ^1H NMR (400 MHz, MeOD) δ 8.41 (d, $J = 8.22$ Hz, 1H), 8.32 (s, 1H), 7.62 (s, 1H), 7.41-7.49 (m, 2H), 5.18 (t, $J = 7.43$ Hz, 1H), 4.15 (s, 3H), 3.03 (s, 2H), 2.99-3.09 (m, 1H), 2.77 (s, 3H), 2.42-2.51 (m, 4H), 1.60 (quin, $J = 7.34$ Hz, 2H), 1.27-1.44 (m, 5H), 0.99 (t, $J = 7.24$ Hz, 3H).

Compound **230** was prepared from second peak in step 2. The absolute configuration was not confirmed. LCMS (ESI) calc'd for $\text{C}_{30}\text{H}_{38}\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$: 519.3, found: 519.1. ^1H NMR (400 MHz, MeOD) δ 9.04 (t, $J = 9.00$ Hz, 1H), 8.69 (d, $J = 7.43$ Hz, 1H), 7.74-7.82 (m, 2H), 7.64 (s, 1H), 5.11-5.23 (m, 1H), 4.28 (s, 3H), 2.96-3.03 (m, 6H), 2.46 (q, $J = 7.56$ Hz, 5H), 1.94-2.16 (m, 4H), 1.59 (d, $J = 4.70$ Hz, 4H), 1.29 (brs, 6H), 1.00 (t, $J = 7.43$ Hz, 3H), 0.85-0.93 (m, 2H).

The following compounds were prepared using similar procedures as described for compounds **230** and **231**.

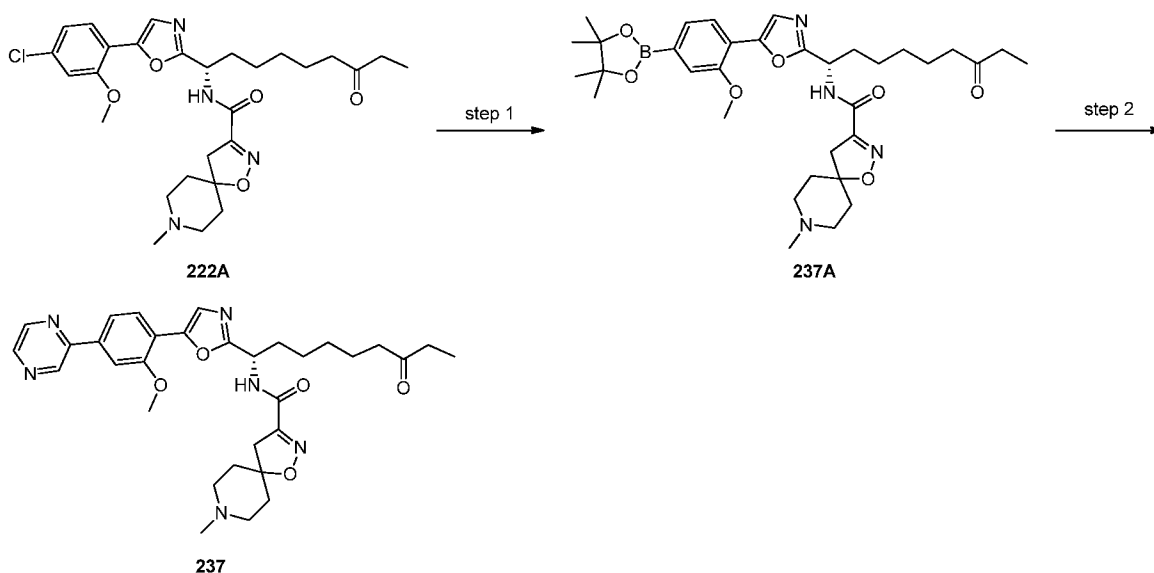
ID	Structure	Observed $[\text{M}+\text{H}]^+$
68		523.2
84		495.1

137		533.3
155		505.3
165		586.1
184		601.2
185		587.2

201		509.1
202		522.2
269		578.4

Example 82

N-{(1*S*)-1-[5-(2-methoxy-4-pyrazin-2-ylphenyl)-1,3-oxazol-2-yl]-7-oxononyl}-8-methyl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide (237)



Step 1: Preparation of (S)-N-(1-(5-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxazol-2-yl)-7-oxononyl)-8-methyl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-

carboxamide (237A): Potassium acetate (45 mg, 0.459 mmol) and Pd₂(dba)₃ (25 mg, 0.027

5 mmol) were added to the mixture of BPD (70 mg, 0.276 mmol) and XPhos (30 mg, 0.063 mmol) and (S)-N-(1-(5-(4-chloro-2-methoxyphenyl)oxazol-2-yl)-7-oxononyl)-8-methyl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide (**222A**, 100 mg, 0.183 mmol) in dioxane (2 mL). The resultant mixture was stirred at 80°C under N₂ for 16 h. The mixture was concentrated *in vacuo*. The residue was purified together with a same reaction from 30 mg **222A** by silica gel flash chromatography (ISCORF75; Sepa flash column), eluting with DCM / MeOH = 30:1-10:1 to give (S)-N-(1-(5-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxazol-2-yl)-7-oxononyl)-8-methyl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide (**237A**). LCMS (ESI) calc'd for C₃₄H₄₉BN₄O₇ [M+H]⁺: 637.4, found: 637.4

Step 2: Preparation of (S)-N-(1-(5-(2-methoxy-4-(pyrazin-2-yl)phenyl)oxazol-2-yl)-7-

15 **oxononyl)-8-methyl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide (237):** Potassium phosphate tribasic (65 mg, 0.306 mmol) and XPhos (22 mg, 0.046 mmol) and Pd₂(dba)₃ (22 mg, 0.024 mmol) were added to the solution of 2-bromopyrazine (40 mg, 0.252 mmol) and (S)-N-(1-(5-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxazol-2-yl)-7-oxononyl)-8-methyl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide (**237A**, 100 mg, 0.157 mmol) in dioxane (2 mL) and water (0.2 mL), the resultant mixture was stirred at 70°C for 4 h. The reaction mixture was extracted with EtOAc (2 * 20 mL) and the combined organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (ISCORF75; Sepa flash column), eluting with DCM / MeOH / NH₃(Aq.) = 20:1:0.01 to give a crude product. The crude product was purified by preparative HPLC (reverse

phase C-18 column), eluting with acetonitrile/water + 0.05% $\text{NH}_3 \cdot \text{H}_2\text{O}$, to give (*S*)-*N*-(1-(5-(2-methoxy-4-(pyrazin-2-yl)phenyl)oxazol-2-yl)-7-oxononyl)-8-methyl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide (**237**).

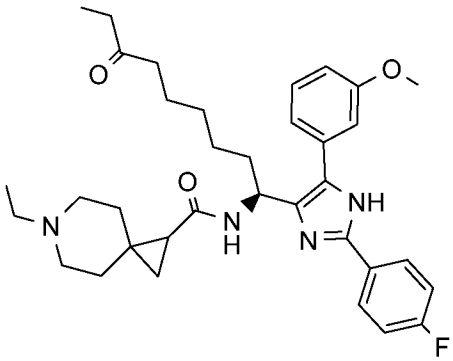
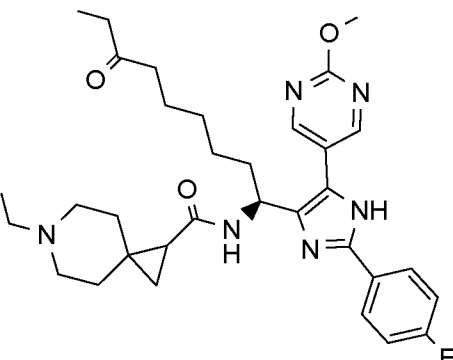
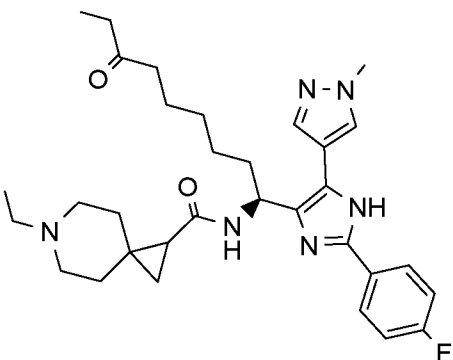
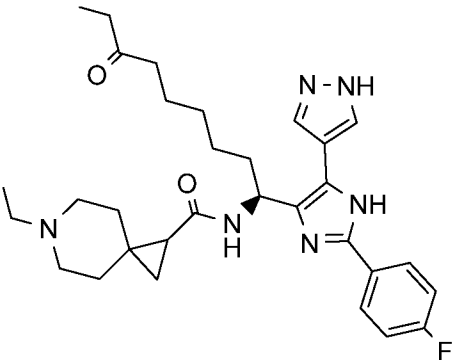
L-(+)-tartaric acid (9 mg, 0.060 mmol) was added to the solution of (*S*)-*N*-(1-(5-(2-methoxy-4-(pyrazin-2-yl)phenyl)oxazol-2-yl)-7-oxononyl)-8-methyl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide (**237**, 32 mg, 0.054 mmol) in MeOH (3 mL) and water (10 mL), and the resultant solution was lyophilized to give (*S*)-*N*-(1-(5-(2-methoxy-4-(pyrazin-2-yl)phenyl)oxazol-2-yl)-7-oxononyl)-8-methyl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide (2*R*,3*R*)-2,3-dihydroxysuccinate. LCMS (ESI) calc'd for $\text{C}_{32}\text{H}_{40}\text{N}_6\text{O}_5$ $[\text{M}+\text{H}]^+$: 589.3, found: 589.1. ^1H NMR (400 MHz, MeOD) δ 9.19 (s, 1H), 8.69 (s, 1H), 8.55 (d, $J = 1.96$ Hz, 1H), 7.75-7.93 (m, 3H), 7.54 (s, 1H), 5.20-5.32 (m, 1H), 4.48 (s, 3H), 4.09 (s, 3H), 3.35-3.52 (m, 1H), 3.34-3.52 (m, 1H), 3.16 (brs, 2H), 2.89 (brs, 3H), 2.40-2.51 (m, 4H), 1.93-2.28 (m, 6H), 1.31-1.64 (m, 6H), 0.99 (t, $J = 7.24$ Hz, 3H).

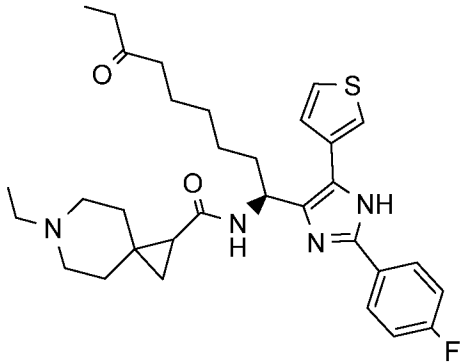
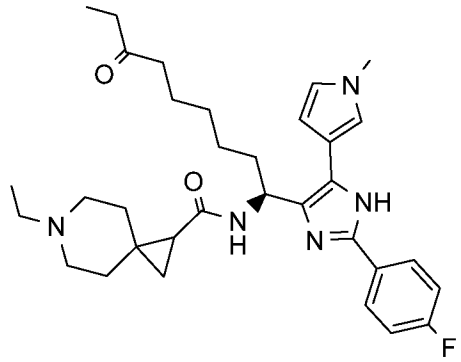
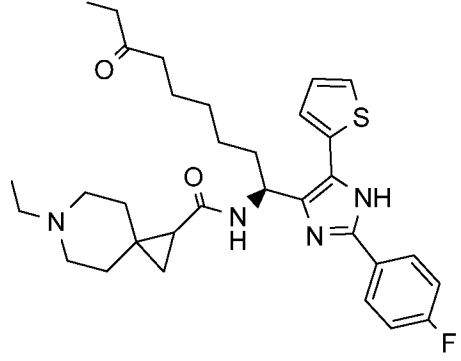
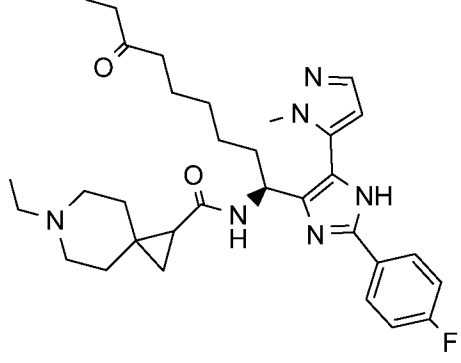
Example 83

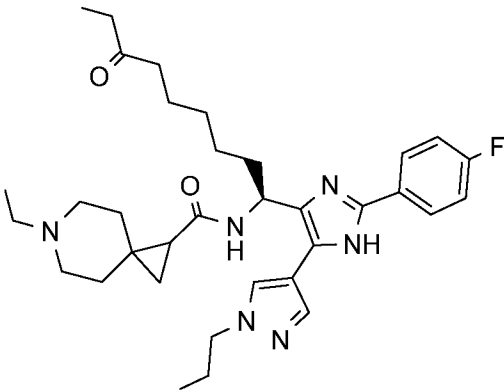
Synthesis of compounds 246 – 254 (library synthesis)

To boronic acid monomer (0.101 mmol) and XPhos Pd G3 (2.447 mg, 2.89 μmol), a solution of (*S*)-*N*-((*S*)-1-(4-bromo-2-(4-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)-7-oxononyl)-6-ethyl-6-azaspiro[2.5]octane-1-carboxamide (40 mg, 0.058 mmol) in dioxane (1.5 ml) at ambient temperature was added, followed by K_3PO_4 (30.7 mg, 0.145 mmol) in water (100 μl). The reaction mixture was heated to 100°C overnight for 16 hr. The reaction mixture was cooled and extracted with DCM and washed by water and brine, and dried by sodium sulfate. The crude was obtained after filtering and concentrating. The resulting residue was assumed to have the corresponding product and was used directly without further purification. The crude was dissolved in DCM (1 ml), and TFA (0.103 ml, 1.334 mmol) was added. The reaction mixture was reacted at 50°C for 2 hr. The reaction mixture was concentrated down via GeneVac. The residue was dissolved in DMSO (1.75 ml) and filtered. The plate was submitted to HTP for further purification and registration.

The following compounds were prepared by the above library synthesis:

ID	Structure	Observed [M+H] ⁺
246		589.308
247		591.308
248		563.308
249		549.308

250		565.308
251		562.308
252		565.308
253		563.308

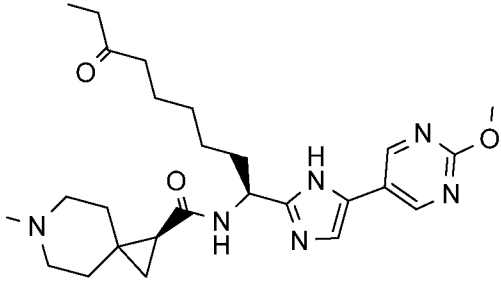
254		591.408
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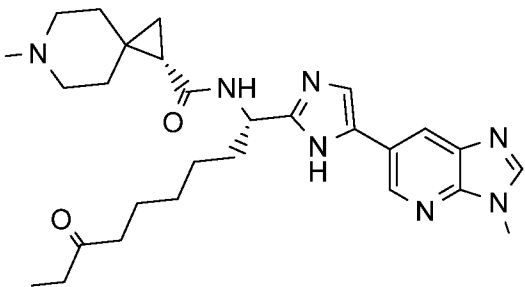
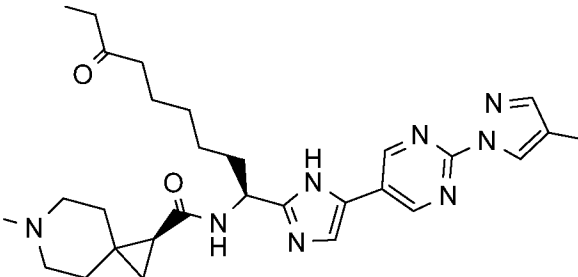
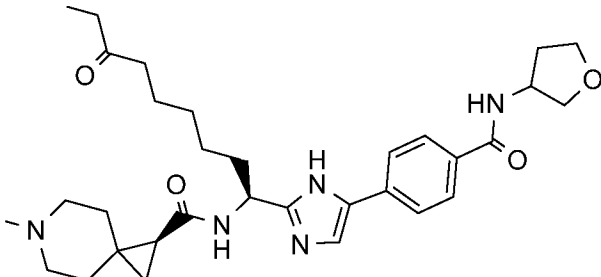
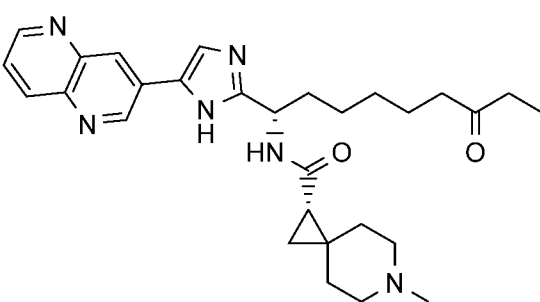
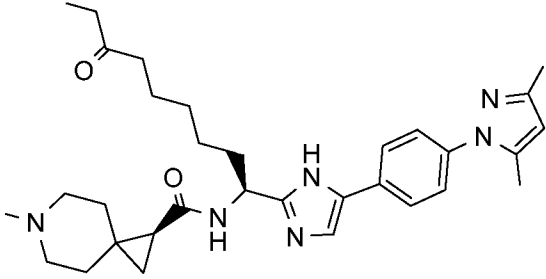
Example 84

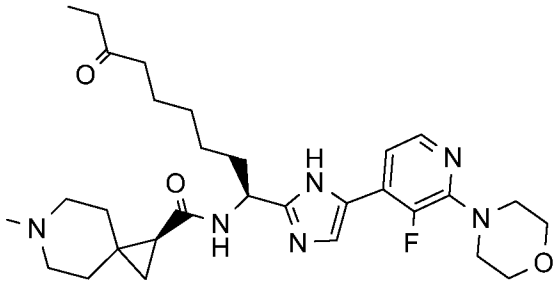
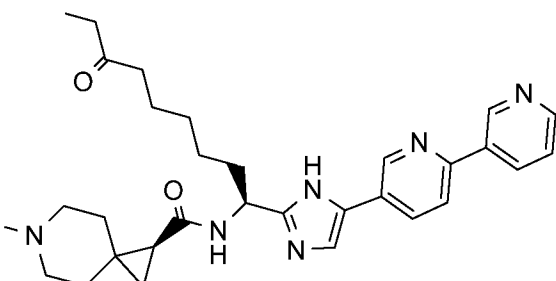
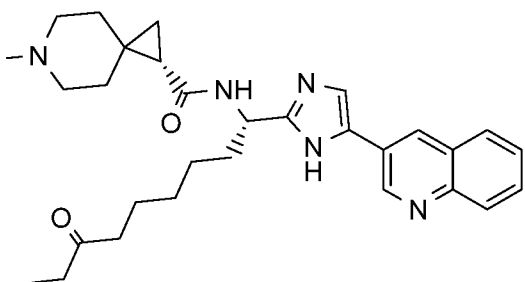
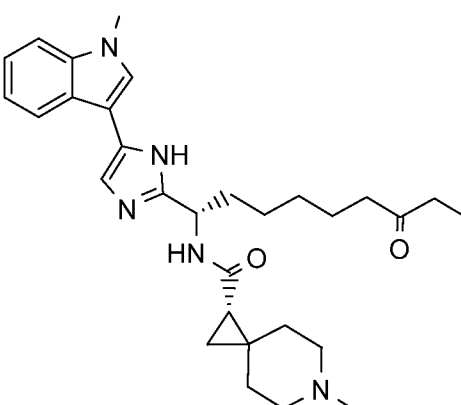
Synthesis of compounds 255 – 268 (library synthesis)

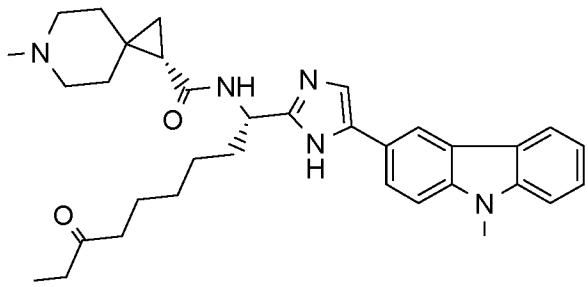
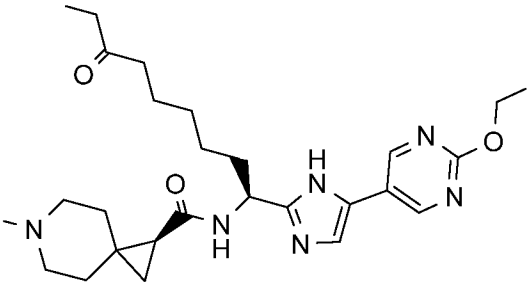
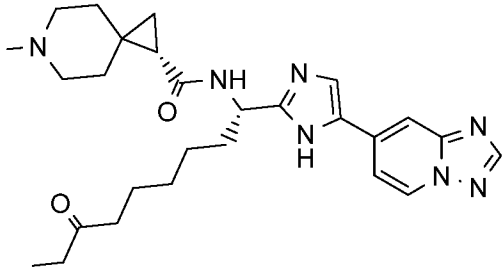
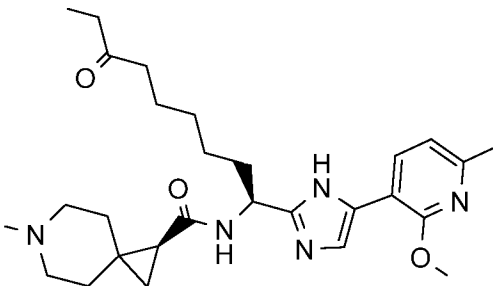
- 5 To a 8 mL pressure vial with a pressure release cap was added PdCl₂(dppf)-CH₂Cl₂Adduct (9.36 mg, 0.011 mmol), (S)-N-((S)-1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide, TFA (40 mg, 0.057 mmol) and the boronic acid monomer (0.100 mmol). The flask was degassed by vacuum and re-filled with N₂. 1,4-Dioxane (1.5 ml) and potassium
- 10 carbonate (0.172 ml, 0.344 mmol) were added. The reaction was stirred at 100°C for 16 hours. The reaction mixture was diluted with EtOAc (4mL) was washed with water. The organic layer was concentrated down via GeneVac. The resulting crude was dissolved in DCM (2 ml), and treated with TFA (0.439 ml, 5.70 mmol). The reaction was stirred at 50°C for 3 hours. The reaction mixture was reacted at 50°C for 2 hr. The reaction mixture was concentrated down via
- 15 GeneVac. The residue was dissolved in DMSO (1.75 ml) and filtered. The plate was submitted to HTP for further purification and registration.

The following compounds were prepared by the above library synthesis:

ID	Structure	Observed [M+H] ⁺
255		482.30

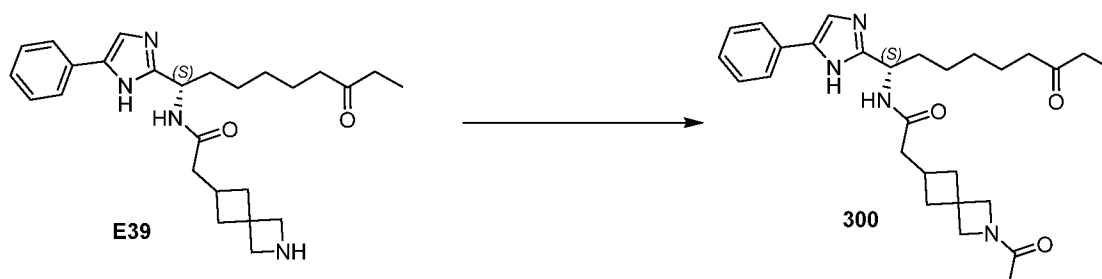
256		506.14
257		533.3349
258		564.3549
259		503.3139
260		545.3609

261		555.3459
262		529.3289
263		502.3179
264		504.3339

265		554.3499
266		497.3239
267		492.3089
268		496.3289

Example 85

(S)-2-(2-acetyl-2-azaspiro[3.3]heptan-6-yl)-N-(7-oxo-1-(5-phenyl-1H-imidazol-2-yl)nonyl)acetamide (300)



To a 4 mL pressure vial with pressure release cap (S)-N-(7-oxo-1-(5-phenyl-1H-imidazol-2-yl)nonyl)-2-(2-azaspiro[3.3]heptan-6-yl)acetamide (**E39**, 12 mg, 0.027 mmol), acetic acid (3.30 mg, 0.055 mmol), HATU (15.68 mg, 0.041 mmol), DMF (275 μ l), and DIPEA (48.0 μ l, 0.275 mmol) were added. The reaction was stirred with DMF (275 μ l) for 2 hours. The product was purified by C18 HPLC (Gilson, CH₃CN in water with 0.1% TFA: 0% to 70%) to give (S)-2-(2-acetyl-2-azaspiro[3.3]heptan-6-yl)-N-(7-oxo-1-(5-phenyl-1H-imidazol-2-yl)nonyl)acetamide, TFA (**300**) LCMS (ESI) calc'd for C₂₈H₃₉N₄O₃ [M+H]⁺: 479.3, found: 479.3.

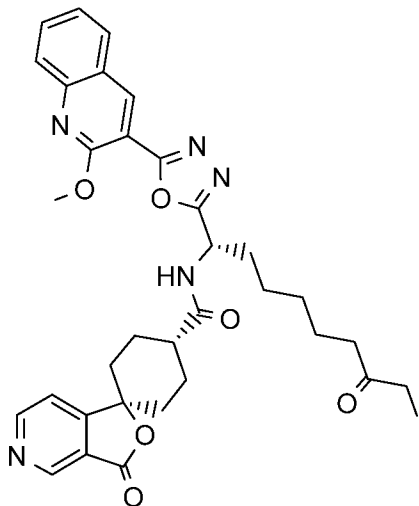
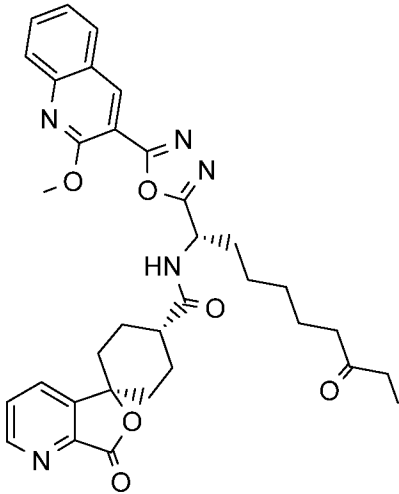
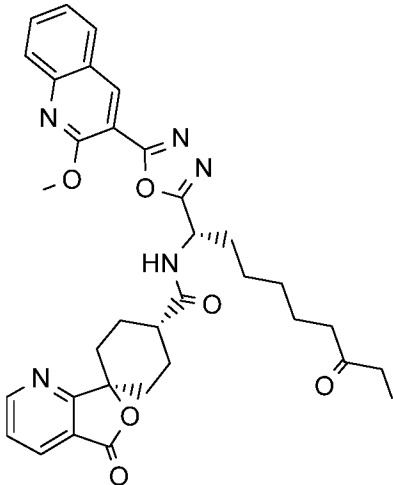
Example 86

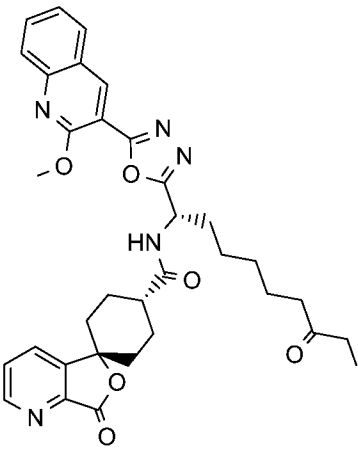
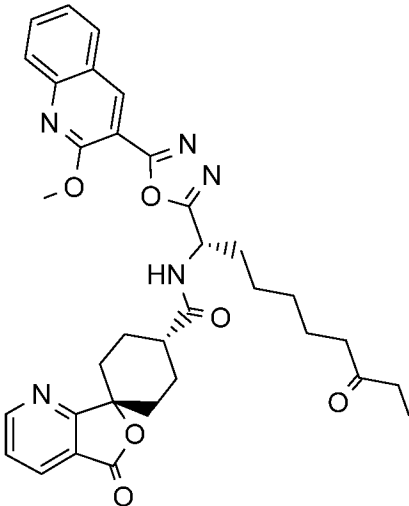
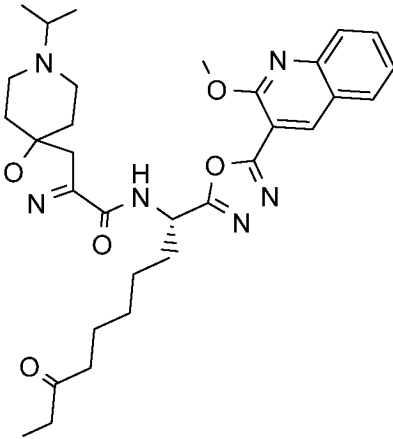
Synthesis of compounds 363 – 384 (library synthesis)

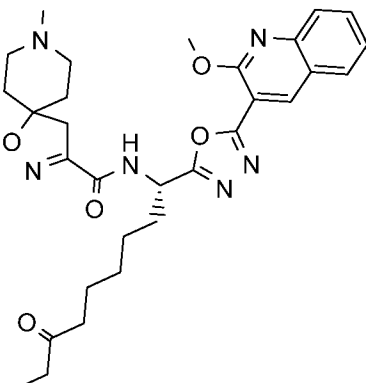
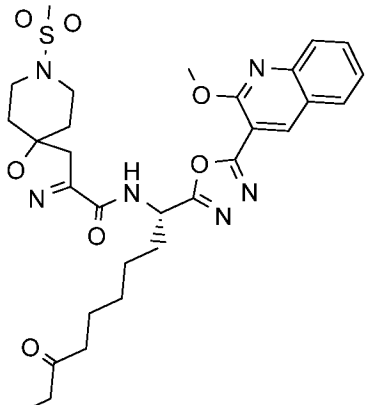
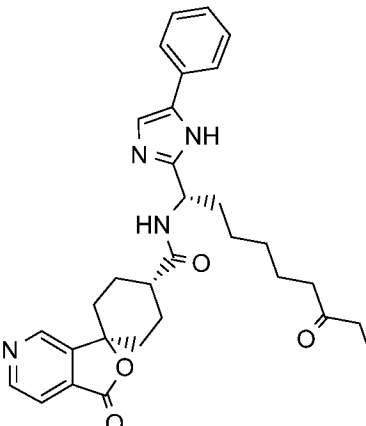
The amine monomer (0.1 mmol), the corresponding acid (0.100 mmol), and DIPEA (0.3 mmol) were mixed in DMF (1 ml), and treated with HATU (0.130 mmol). The reaction mixtures were stirred at rt for 20 minutes, 0.1 mL of water was added, and the mixture was stirred for 5 minutes, then filtered. The plate was sent to HTP for library purification.

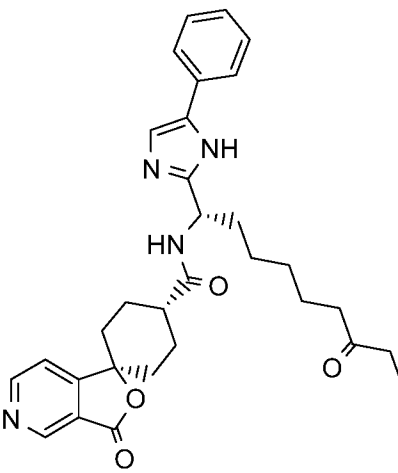
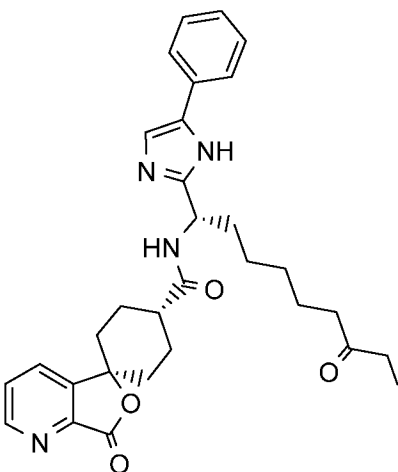
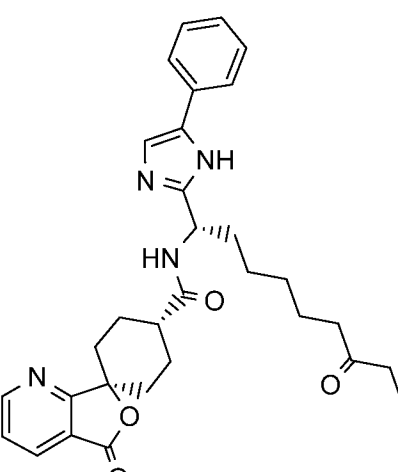
The following compounds were prepared by the above library synthesis:

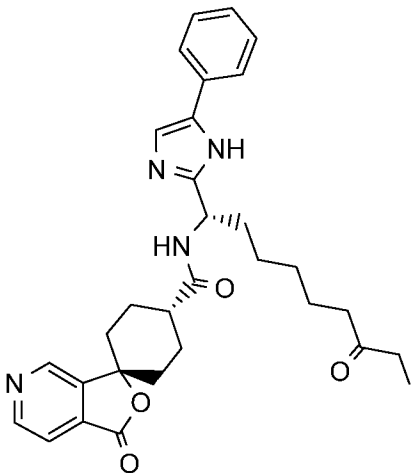
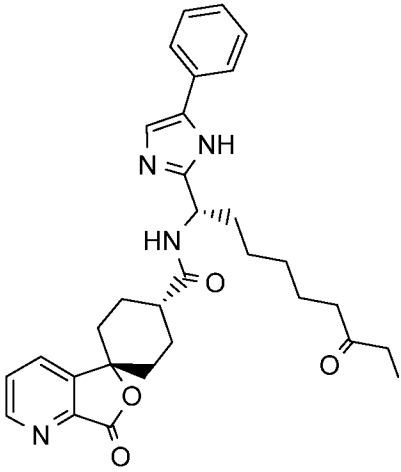
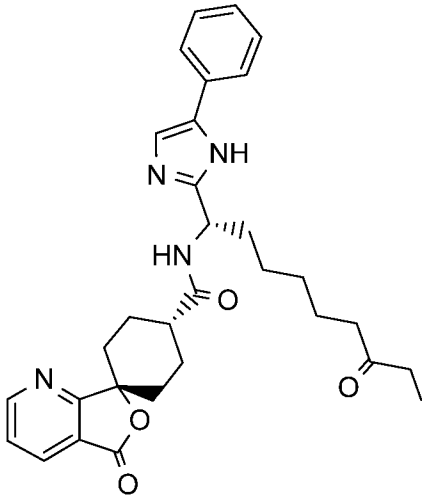
ID	Structure	Observed [M+H] ⁺
363		612.35

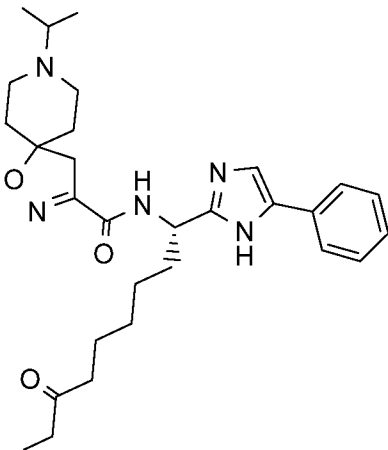
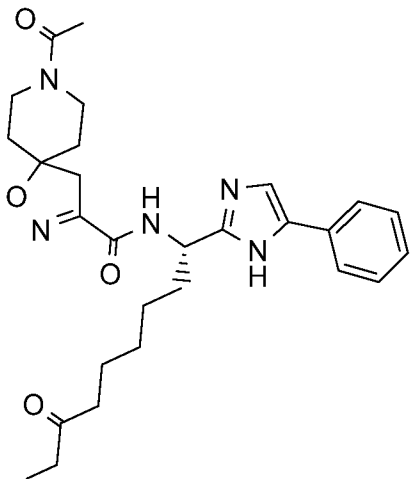
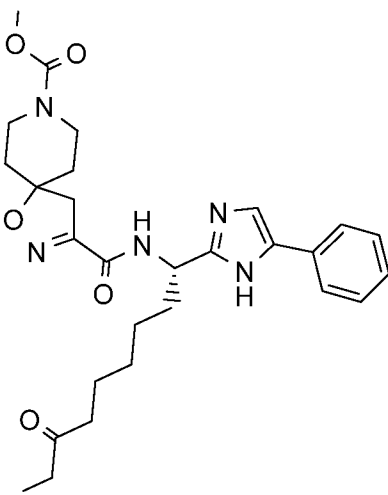
364		612.36
365		612.37
366		612.33

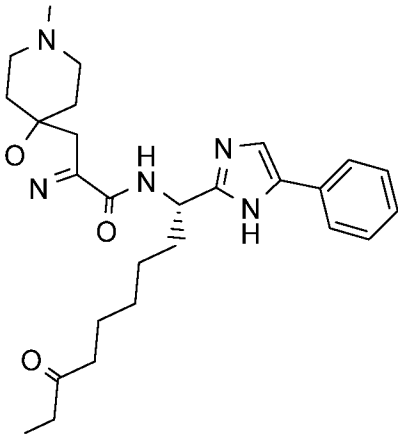
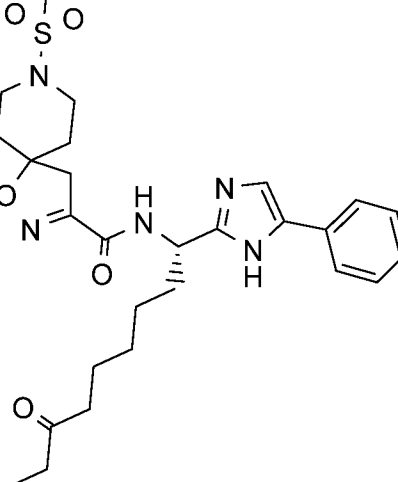
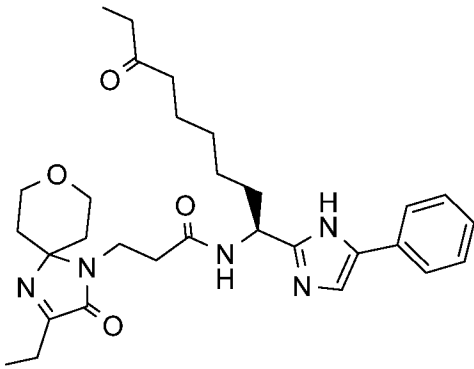
367		612.42
368		612.35
369		591.4

370		563.41
371		627.39
372		529.32

373		529.28
374		529.35
375		529.29

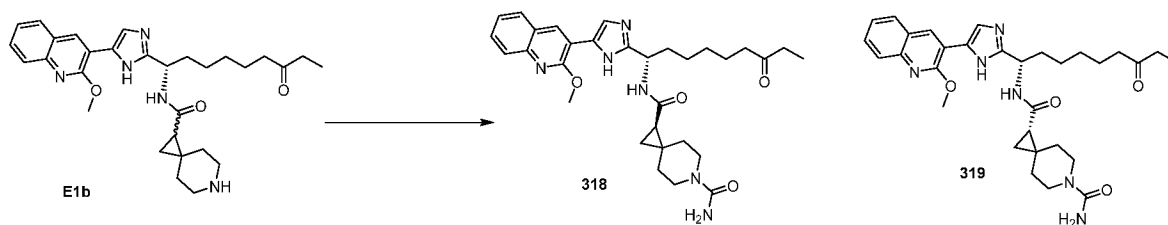
376		529.32
377		529.31
378		529.33

379		508.36
380		508.3
381		524.41

382		480.31
383		544.3
384		536.44

Example 87

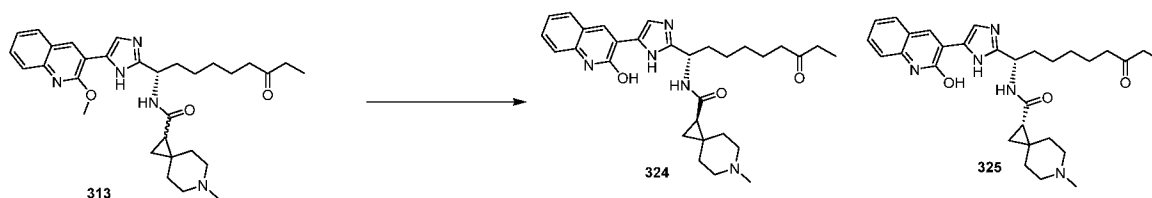
N1-((S)-1-(5-(2-methoxyquinolin-3-yl)-1H-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1,6-dicarboxamide (318 and 319)



To a 8 mL pressure vial with a pressure release cap was added N-((S)-1-(5-(2-methoxyquinolin-3-yl)-1H-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1-carboxamide, 2TFA (**E1b**, 66 mg, 0.089 mmol), urea (10.63 mg, 0.177 mmol), iron(III) nitrate nonahydrate (2.128 μ l, 8.85 μ mol), and toluene (885 μ l). The reaction was stirred at 110°C for 2 hours. The toluene was removed by blowing N₂ and the product was purified by C18 HPLC (Gilson, CH₃CN in water with 0.1% TFA: 0% to 50%) to give (R)-N1-((S)-1-(5-(2-methoxyquinolin-3-yl)-1H-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1,6-dicarboxamide, TFA (**318**, 1st peak), LCMS (ESI): 561.1 [M+H]⁺, and (S)-N1-((S)-1-(5-(2-methoxyquinolin-3-yl)-1H-imidazol-2-yl)-7-oxononyl)-6-azaspiro[2.5]octane-1,6-dicarboxamide, TFA (**319**, 2nd peak). LCMS (ESI): 561.1 [M+H]⁺.

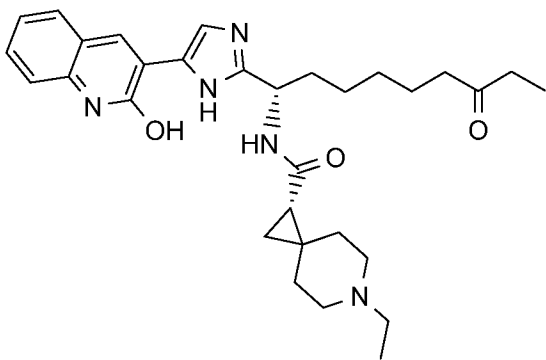
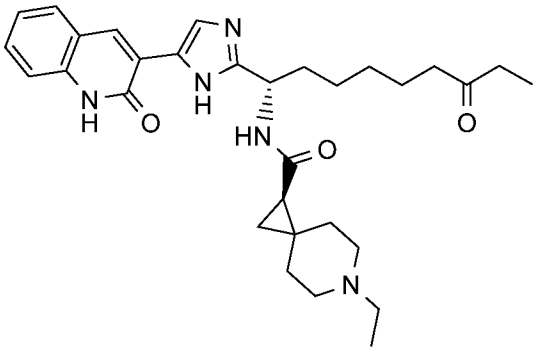
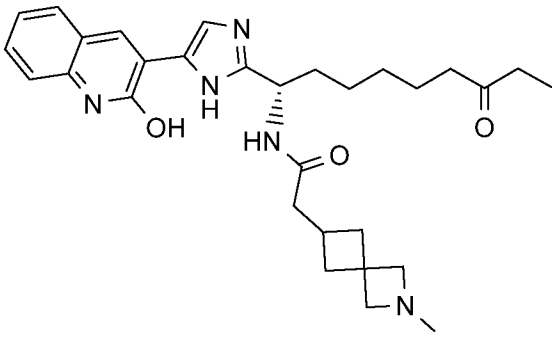
Example 88

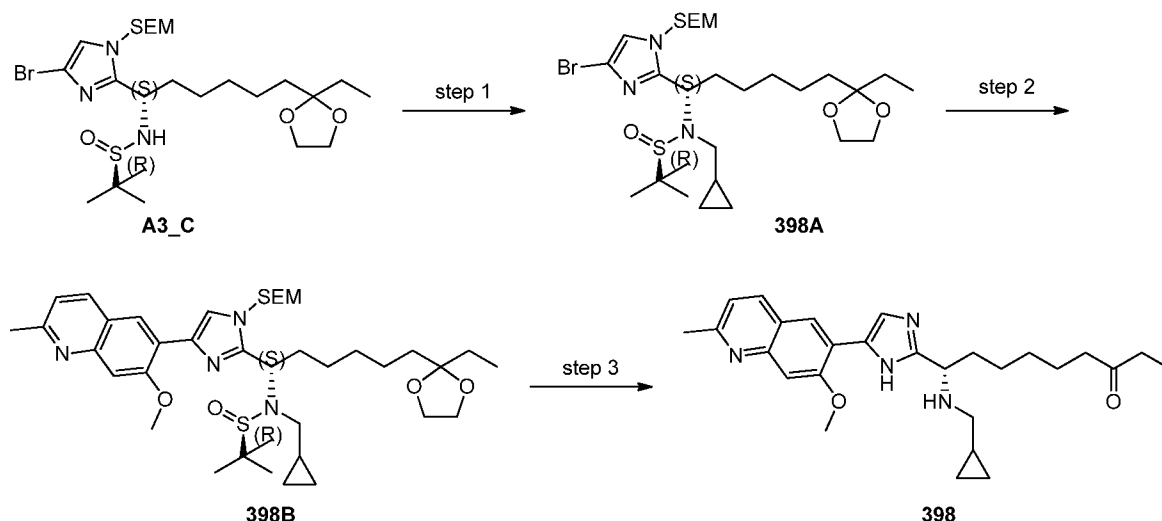
N-((S)-1-(5-(2-hydroxyquinolin-3-yl)-1H-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**324** and **325**)



To a 4 mL pressure vial with a pressure release cap was added N-((S)-1-(5-(2-methoxyquinolin-3-yl)-1H-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide (**313**, 150 mg, 0.282 mmol), HCl (23.17 μ l, 0.282 mmol), water (1411 μ l), and THF (1411 μ l). The reaction was stirred at 25°C for 16 hours. The crude reaction mixture was checked by LCMS. The product was purified by C18 chromatography (30g, CH₃CN in water with 0.1% TFA: 0% to 90%) to give (R)-N-((S)-1-(5-(2-hydroxyquinolin-3-yl)-1H-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide, 2TFA (**324**, first peak), LCMS (ESI): 518.4 [M+H]⁺; and (S)-N-((S)-1-(5-(2-hydroxyquinolin-3-yl)-1H-imidazol-2-yl)-7-oxononyl)-6-methyl-6-azaspiro[2.5]octane-1-carboxamide, 2TFA (**325**, 2nd peak), LCMS (ESI): 518.4 [M+H]⁺.

The following compounds were prepared using similar procedures as described for compounds **324** and **325**.

ID	Structure	Observed $[M+H]^+$
291		532.4
292		532.4
326		518.1



Step 1: (R)-N-((S)-1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-N-(cyclopropylmethyl)-2-methylpropane-2-sulfinamide (398A):

NaH (22 mg, 0.550 mmol) was added to a stirred mixture of (R)-N-((S)-1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-2-methylpropane-2-sulfinamide (**A3_C**, 103 mg, 0.177 mmol) in DMF (2 mL) at 24°C and the mixture was stirred at 24°C for 30 mins, then (bromomethyl)cyclopropane (34 mg, 0.252 mmol) was added and the mixture was stirred at 24°C for 3 h. The mixture was diluted with water (5 mL), and extracted with ethyl acetate (3 x 10 mL). The combined organic fractions were washed with water (3 x 8 mL), brine (saturated, 8 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with EtOAc / petroleum ether = 0~50% to give (R)-N-((S)-1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-N-(cyclopropylmethyl)-2-methylpropane-2-sulfinamide (**398A**). LCMS (ESI) calc'd for

C₂₈H₅₂BrN₃O₄SSi [M+H]⁺: 634.3, found: 634.2

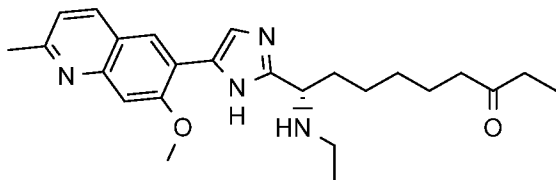
Step 2: (R)-N-(cyclopropylmethyl)-N-((S)-6-(2-ethyl-1,3-dioxolan-2-yl)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)hexyl)-2-methylpropane-2-sulfinamide (398B): PdCl₂(DTBPF) (10 mg, 0.015 mmol) was added to a mixture of (R)-N-((S)-1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-6-(2-ethyl-1,3-dioxolan-2-yl)hexyl)-N-(cyclopropylmethyl)-2-methylpropane-2-sulfinamide (**398A**, 90 mg, 0.142 mmol), 7-methoxy-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (**C1**, 54 mg, 0.180 mmol) and K₃PO₄ (121 mg, 0.570 mmol) in THF (2 mL) and water (0.2 mL) at 24°C and the mixture was stirred at 70°C for 3 h under N₂ protection. The mixture was diluted with water (15 mL) and extracted with DCM (3 x 10 mL). The combined

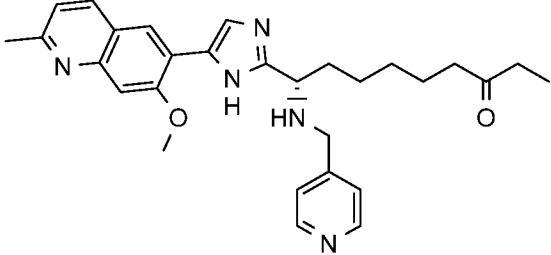
organic fractions were washed with brine (saturated, 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure to give (*R*)-*N*-(cyclopropylmethyl)-*N*-((*S*)-6-(2-ethyl-1,3-dioxolan-2-yl)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)hexyl)-2-methylpropane-2-sulfonamide (**398B**) which was used to the next step without further purification. LCMS (ESI) calc'd for C₃₉H₆₂N₄O₅SSi [M+H]⁺: 727.4, found: 727.4

Step 3: (*S*)-9-((cyclopropylmethyl)amino)-9-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)nonan-3-one (**398**): HCl (3 mL, 36.5 mmol) was added to a mixture of (*R*)-*N*-(cyclopropylmethyl)-*N*-((*S*)-6-(2-ethyl-1,3-dioxolan-2-yl)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)hexyl)-2-methylpropane-2-sulfonamide (**398B**, 100 mg, 0.138 mmol) in MeOH (5 mL) and water (1 mL) at 24°C and the mixture was stirred at 50°C for 15 h. The mixture was concentrated *in vacuo*. The residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.05% NH₃·H₂O, to give (*S*)-9-((cyclopropylmethyl)amino)-9-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)nonan-3-one (**398**).

L-(+)-tartaric acid (8 mg, 0.053 mmol) was added to (*S*)-9-((cyclopropylmethyl)amino)-9-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)nonan-3-one (**398**, 23 mg, 0.051 mmol) in acetonitrile (1 mL) and water (2 mL) at 24°C and the mixture was stirred at 24°C for 15 min. The mixture was lyophilized to give (*S*)-9-((cyclopropylmethyl)amino)-9-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)nonan-3-one (2*R*,3*R*)-2,3-dihydroxysuccinate. LCMS (ESI) calc'd for C₂₇H₃₆N₄O₂ [M+H]⁺: 449.3, found: 449.3. ¹H NMR (400 MHz, MeOD) δ 8.43 (s, 1H), 8.20 (d, *J* = 8.6 Hz, 1H), 7.75 (s, 1H), 7.41 (s, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 4.44-4.49 (m, 1H), 4.44 (s, 2H), 4.10 (s, 3H), 2.90 (brs, 1H), 2.61-2.74 (m, 1H), 2.61-2.73 (s, 3H), 2.32-2.42 (m, 4H), 2.24 (brs, 1H), 2.11 (brs, 1H), 1.46-1.57 (m, 2H), 1.25-1.40 (m, 3H), 1.03-1.23 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H), 0.66 (d, *J* = 7.4 Hz, 2H), 0.34 (brs, 2H).

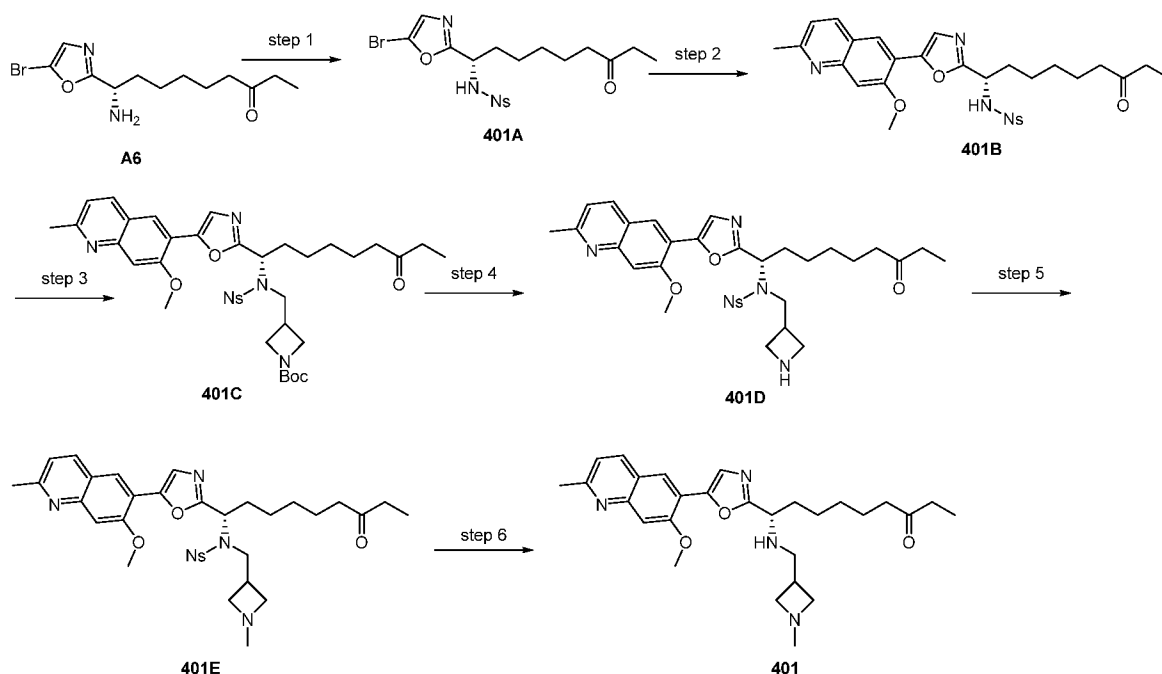
The following compounds were prepared using similar procedures as described for compound **398**.

ID	Structure	Observed [M+H] ⁺
403		423.3

404		486.1
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Example 90

(9S)-9-[5-(7-methoxy-2-methylquinolin-6-yl)-1,3-oxazol-2-yl]-9-[(1-methylazetidin-3-yl)methyl]amino}nonan-3-one (401)



Step 1: Preparation of (S)-N-(1-(5-bromooxazol-2-yl)-7-oxononyl)-2-nitrobenzenesulfonamide

(401A): 2-nitrobenzene-1-sulfonyl chloride (848 mg, 3.83 mmol) was added to a stirred mixture of (S)-9-amino-9-(5-bromooxazol-2-yl)nonan-3-one hydrochloride (**A6**, 1.0 g, 2.94 mmol) and TEA (2.0 mL, 14.35 mmol) in DCM (10 mL) at room temperature and the mixture was stirred at room temperature for 3 h. Water (5 mL) was added and the mixture was extracted with DCM (3 x 10 mL). The combined organic fractions were washed with brine (saturated, 1 x 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (ISCORF75; Sepa flash column), eluting with petroleum ether / EtOAc = 0~30% to give (S)-N-(1-(5-bromooxazol-2-yl)-7-oxononyl)-2-nitrobenzenesulfonamide (**401A**). LCMS (ESI) calc'd for C₁₈H₂₂BrN₃O₆S [M+H]⁺: 488.0, 490.0,

found: 488.1, 490.1. ¹H NMR (400 MHz, CDCl₃) δ 7.98 (dd, *J* = 1.6, 7.43 Hz, 1H), 7.88 (dd, *J* = 1.2, 7.8 Hz, 1H), 7.60-7.74 (m, 2H), 6.61 (s, 1H), 6.06 (d, *J* = 9.8 Hz, 1H), 4.64-4.76 (m, 1H), 2.35-2.46 (m, 4H), 1.86-1.96 (m, 2H), 1.56 (q, *J* = 7.3 Hz, 2H), 1.30-1.50 (m, 4H), 1.05 (t, *J* = 7.4 Hz, 3H).

- 5 Step 2: Preparation of (*S*)-*N*-(1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-2-nitrobenzenesulfonamide (**401B**): PdCl₂(DTBPF) (133 mg, 0.204 mmol) was added to a stirred mixture of 7-methoxy-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (**C1**, 643 mg, 2.149 mmol), (*S*)-*N*-(1-(5-bromooxazol-2-yl)-7-oxononyl)-2-nitrobenzenesulfonamide (**401A**, 1.0 g, 2.048 mmol) and potassium phosphate (1.3 g, 6.12 mmol) in THF (10 mL)/water (1 mL) at room temperature and the mixture was heated with stirring at 70°C for 8 h. The mixture was cooled to room temperature. Water (10 mL) was added and the mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic fractions were washed with brine (saturated, 1 x 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 1 / 2 to give (*S*)-*N*-(1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-2-nitrobenzenesulfonamide (**401B**). LCMS (ESI) calc'd for C₂₉H₃₂N₄O₇S [M+H]⁺: 581.2, found: 581.2

- 15 Step 3: Preparation of (*S*)-tert-butyl 3-((*N*-(1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-2-nitrophenylsulfonamido)methyl)azetidine-1-carboxylate (**401C**): DEAD (0.45 mL, 2.84 mmol) was added to a stirred mixture of (*S*)-*N*-(1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-2-nitrobenzenesulfonamide (**401B**, 500 mg, 0.861 mmol), tert-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (177 mg, 0.947 mmol) and PPh₃ (678 mg, 2.58 mmol) in THF (5 mL) at room temperature and the mixture was stirred at room temperature for 2 h. Water (10 mL) was added and the mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic fractions were washed with brine (saturated, 1 x 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 1 / 2 to give (*S*)-tert-butyl 3-((*N*-(1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-2-nitrophenylsulfonamido)methyl)azetidine-1-carboxylate (**401C**). LCMS (ESI) calc'd for C₃₈H₄₇N₅O₉S [M+H]⁺: 750.3, found: 750.3

20 Step 4: Preparation of (*S*)-*N*-(azetidin-3-ylmethyl)-*N*-(1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-2-nitrobenzenesulfonamide 2,2,2-trifluoroacetate (**401D**): TFA (1.2 mL, 15.58 mmol) was added to a stirred mixture of (*S*)-tert-butyl 3-((*N*-(1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-2-nitrophenylsulfonamido)methyl)azetidine-1-

carboxylate (**401C**, 600 mg, 0.800 mmol) in DCM (6 mL) at room temperature and the mixture was stirred at room temperature for 90 min. All the volatiles were removed off by evaporator to give (*S*)-*N*-(azetidin-3-ylmethyl)-*N*-(1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-2-nitrobenzenesulfonamide 2,2,2-trifluoroacetate (**401D**) which was directly used for next step. LCMS (ESI) calc'd for $C_{33}H_{39}N_5O_7S$ $[M+H]^+$: 650.3, found: 650.3

Step 5: Preparation of (*S*)-*N*-(1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-*N*-((1-methylazetidin-3-yl)methyl)-2-nitrobenzenesulfonamide (**401E**): Formaldehyde (0.5 mL, 6.72 mmol) was added to a stirred mixture of (*S*)-*N*-(azetidin-3-ylmethyl)-*N*-(1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-2-nitrobenzenesulfonamide 2,2,2-trifluoroacetate (**401D**, 611 mg, 0.800 mmol) in MeOH (12 mL) at room temperature and the mixture was stirred at room temperature for 30 min. Then $NaBH(OAc)_3$ (509 mg, 2.400 mmol) was added and it was stirred at 26°C for 30 min. Water (10 mL) was added then neutralized with $NaHCO_3$ (sat.) and the mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic fractions were washed with brine (saturated, 1 x 10 mL), dried (Na_2SO_4), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (ISCORF75; Sepa flash column), eluting with DCM / MeOH = 0~6% to give (*S*)-*N*-(1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-*N*-((1-methylazetidin-3-yl)methyl)-2-nitrobenzenesulfonamide (**401E**). LCMS (ESI) calc'd for $C_{34}H_{41}N_5O_7S$ $[M+H]^+$: 664.3, found: 664.3

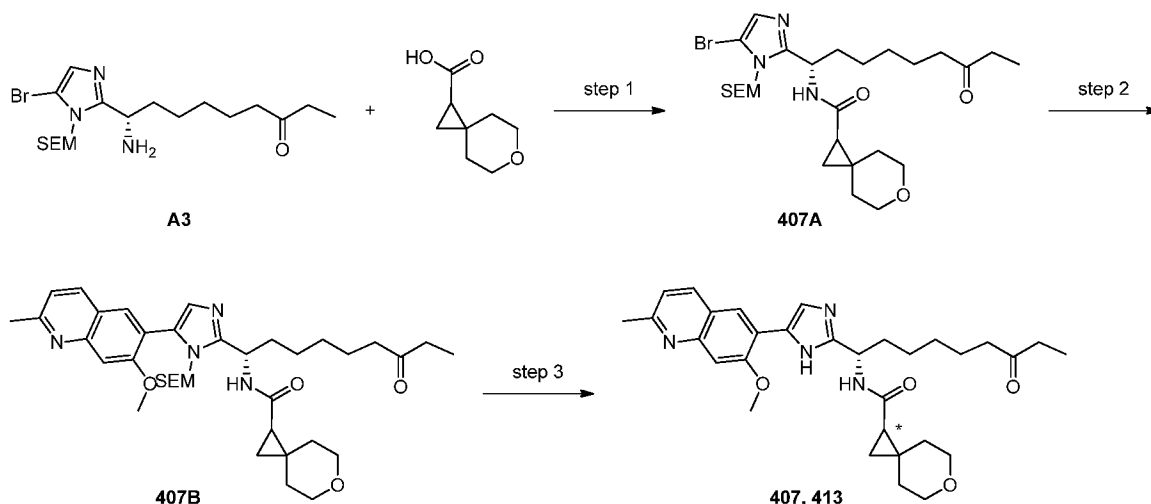
Step 6: Preparation of (*S*)-9-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-9-(((1-methylazetidin-3-yl)methyl)amino)nonan-3-one (**401**): Benzenethiol (0.2 mL, 1.948 mmol) was dissolved in 6 mL DMF, then 3.5 mL of the solution was added to a stirred mixture of (*S*)-*N*-(1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-*N*-((1-methylazetidin-3-yl)methyl)-2-nitrobenzenesulfonamide (**401E**, 350 mg, 0.527 mmol) and K_2CO_3 (729 mg, 5.27 mmol) in DMF (2 mL) at room temperature, and the mixture was stirred at room temperature for 2 h. The mixture was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.1% TFA, to give the TFA salt of the product. The salt was dissolved in MeOH, neutralized with $NaHCO_3$ (sat.), and the mixture was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.05% $NH_3 \cdot H_2O$, to give (*S*)-9-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-9-(((1-methylazetidin-3-yl)methyl)amino)nonan-3-one (**401**).

L-(+)-tartaric acid (35 mg, 0.233 mmol) was added to a stirred mixture of (*S*)-9-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-9-(((1-methylazetidin-3-yl)methyl)amino)nonan-3-one (**401**, 110 mg, 0.230 mmol) in acetonitrile (2 mL) and water (2 mL) at room temperature and the

mixture was made dry by lyophilization to give (*S*)-9-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-9-(((1-methylazetidin-3-yl)methyl)amino)nonan-3-one (2*R*,3*R*)-2,3-dihydroxysuccinate. LCMS (ESI) calc'd for C₂₈H₃₈N₄O₃ [M+H]⁺: 479.3, found: 479.2. ¹H NMR (400 MHz, MeOD) δ 8.22-8.28 (m, 2H), 7.63 (s, 1H), 7.42 (s, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 4.43 (s, 2H), 4.14-4.26 (m, 2H), 4.12 (s, 3H), 4.04 (t, *J* = 7.0 Hz, 1H), 3.93 (brs, 2H), 2.97-3.08 (m, 1H), 2.88 (brs, 2H), 2.86 (s, 3H), 2.70 (s, 3H), 2.39 (q, *J* = 7.7 Hz, 4H), 1.93-2.04 (m, 2H), 1.54 (q, *J* = 7.2 Hz, 2H), 1.24-1.46 (m, 4H), 0.94 (t, *J* = 7.4 Hz, 3H).

Example 90

N-{[(1*S*)-1-[5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl]-7-oxononyl}-6-oxaspiro[2.5]octane-1-carboxamide (407 and 413)



Step 1: Preparation of *N*-((*S*)-1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-oxaspiro[2.5]octane-1-carboxamide (407A): EDC (277 mg, 1.445 mmol) and 1*H*-benzo[*d*][1,2,3]triazol-1-ol (195 mg, 1.445 mmol) were added to a stirred mixture of 6-oxaspiro[2.5]octane-1-carboxylic acid (90 mg, 0.578 mmol) and DIPEA (0.303 mL, 1.734 mmol) in DMF (10 mL) at room temperature. Then (*S*)-9-amino-9-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)nonan-3-one (**A3**, 250 mg, 0.578 mmol) was added. The mixture was stirred at 25°C for 18 h. Water (10 mL) and brine (10 mL) was added to the reaction solution and it was extracted with EtOAc (50 mLX2). The organic phase was washed with brine (50 mL) and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with EtOAc: Petro.Ether = 5:1-1:1 to give *N*-((*S*)-1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-oxaspiro[2.5]octane-1-carboxamide (**407A**). LCMS (ESI) calc'd for C₂₆H₄₄BrN₃O₄Si [M+H]⁺: 570.2, found: 572.2

Step 2: Preparation of *N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-oxaspiro[2.5]octane-1-carboxamide (**407B**): 7-methoxy-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (**C1**, 182 mg, 0.610 mmol) and K₃PO₄ (325 mg, 1.525 mmol) were added to a stirred mixture of *N*-((*S*)-1-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-oxaspiro[2.5]octane-1-carboxamide (**407A**, 290 mg, 0.508 mmol) in 1,4-dioxane (6 mL) and water (1 mL). The mixture was replaced with N₂. Then PdCl₂(DTBPF) (33 mg, 0.051 mmol) was added at room temperature and the mixture was heated with stirring at 70°C for 2 h. The mixture was cooled to room temperature. Water (10 mL) was added and the mixture was extracted with ethyl acetate (2 x 10 mL). The combined organic fractions were washed with brine (2 x 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 2:1-1:2 to give *N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-oxaspiro[2.5]octane-1-carboxamide (**407B**). LCMS (ESI) calc'd for C₃₇H₅₄N₄O₅Si [M+H]⁺: 663.4, found: 663.4

Step 3: Preparation of *N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-oxaspiro[2.5]octane-1-carboxamide (**407** and **413**): TFA (4 mL, 51.9 mmol) was added to a stirred mixture of *N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-oxaspiro[2.5]octane-1-carboxamide (**407B**, 300 mg, 0.453 mmol) in DCM (2 mL) at room temperature and the mixture was stirred at room temperature for 1 h. The reaction solution was concentrated to afford racemic of *N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-7-oxononyl)-6-oxaspiro[2.5]octane-1-carboxamide] which was separated by chira SFC by Chiralcel AD column, gradient: 40% of ethanol (0.1% NH₄OH), and then made into a tartarate by the method described previously.

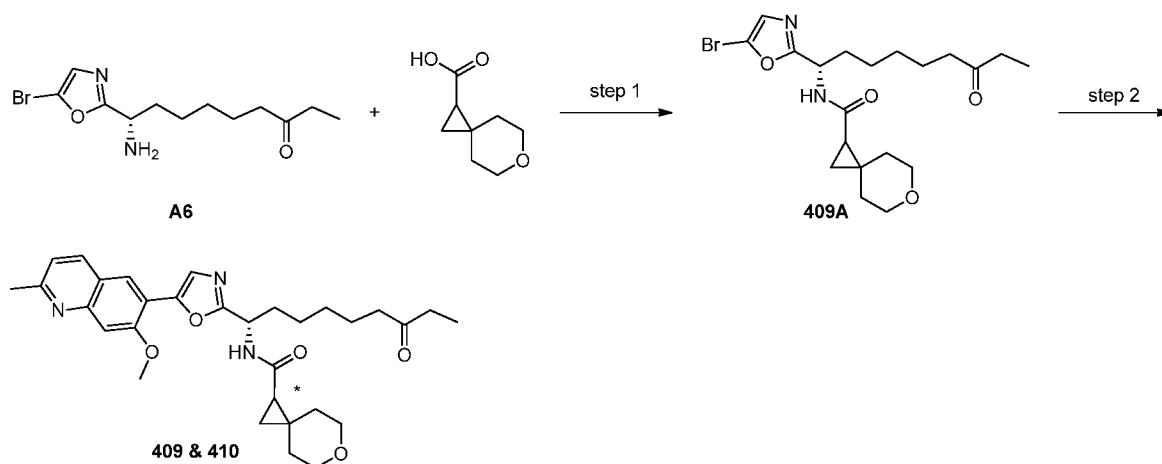
407, peak 2. LCMS (ESI) calc'd for C₃₁H₄₀N₄O₄ [M+H]⁺: 533.3, found: 533.1. ¹H NMR (400 MHz, MeOD) δ 8.36 (s, 1H), 8.29 (d, *J* = 8.2 Hz, 1H), 7.65 (s, 1H), 7.43 (s, 1H), 7.37 (d, *J* = 8.22 Hz, 1H), 5.10 (t, *J* = 7.24 Hz, 1H), 4.50 (s, 2H), 4.11 (s, 3H), 3.59-3.80 (m, 4H), 2.73 (s, 3H), 2.41-2.48 (m, 4H), 1.90-2.09 (m, 2H), 1.66-1.78 (m, 3H), 1.53-1.62 (m, 3H), 1.43-1.52 (m, 2H), 1.32-1.43 (m, 3H), 1.29 (s, 1H), 1.15 (t, *J* = 4.7 Hz, 1H), 0.99 (t, *J* = 7.4 Hz, 3H), 0.88 (dd, *J* = 4.3, 8.2 Hz, 1H).

413, peak 2. LCMS (ESI) calc'd for C₃₁H₄₀N₄O₄ [M+H]⁺: 533.3, found: 533.1. ¹H NMR (400 MHz, MeOD) δ 8.39 (s, 1H), 8.31 (d, *J* = 8.4 Hz, 1H), 7.66 (s, 1H), 7.46 (s, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 4.93-5.13 (m, 1H), 4.51 (s, 2H), 4.14 (s, 3H), 3.71-3.82 (m, 2H), 3.44-3.58 (m, 2H),

2.76 (s, 3H), 2.43-2.50 (m, 4H), 1.95-2.07 (m, 2H), 1.54-1.70 (m, 6H), 1.30-1.51 (m, 6H), 1.17 (t, $J = 4.9$ Hz, 1H), 1.01 (t, $J = 7.4$ Hz, 3H), 0.90 (dd, $J = 4.5, 8.0$ Hz, 1H).

Example 91

N-{[(1*S*)-1-[5-(7-methoxy-2-methylquinolin-6-yl)-1,3-oxazol-2-yl]-7-oxononyl]-6-oxaspiro[2.5]octane-1-carboxamide (409 and 410)



Step 1: Preparation of *N*-((*S*)-1-(5-bromooxazol-2-yl)-7-oxononyl)-6-oxaspiro[2.5]octane-1-carboxamide (409A): To a solution of 6-oxaspiro[2.5]octane-1-carboxylic acid (92 mg, 0.589

mmol) in DMF (10 mL) was added HOBT (198 mg, 1.295 mmol), EDC (248 mg, 1.295 mmol)

and DIPEA (0.411 mL, 2.355 mmol). The mixture was stirred at rt for 15 min. (*S*)-9-amino-9-(5-bromooxazol-2-yl)nonan-3-one hydrochloride (A6, 200 mg, 0.589 mmol) was added. The mixture was stirred at rt for 21 h. Ethyl acetate (40 mL) was added, the solution was washed sequentially with saturated NaCl solution (40 mL). The aqueous layer was extracted with ethyl acetate (40 mL*2). The combined organic layers were washed with saturated NaCl solution (40

mL*2). The organic layer was dried over anhydrous Na₂SO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica, Petro. ether: ethyl acetate = 2:1 to 1:1) to yield *N*-((*S*)-1-(5-bromooxazol-2-yl)-7-oxononyl)-6-oxaspiro[2.5]octane-1-carboxamide (409A). LCMS (ESI) calc'd for C₂₀H₃₀BrN₂O₄ [M+H]⁺: 441.1, found: 443.1. ¹H NMR (400 MHz, CDCl₃) δ 6.89 (d, $J = 2.6$ Hz, 1H), 6.18-6.18 (m, 1H), 6.17-6.36 (m, 1H), 5.10-5.24 (m, 1H), 3.71 (t, $J = 5.1$ Hz, 2H), 3.54-3.67 (m, 2H), 2.31-2.46 (m, 4H), 1.85-1.96 (m, 1H), 1.76-1.82 (m, 1H), 1.70-1.76 (m, 3H), 1.51-1.58 (m, 2H), 1.41-1.48 (m, 1H), 1.35-1.38 (m, 1H), 1.27-1.34 (m, 3H), 1.18-1.24 (m, 1H), 1.02 (t, $J = 7.3$ Hz, 3H), 0.84 (m, 1H).

Step 2: Preparation of *N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-

6-oxaspiro[2.5]octane-1-carboxamide (409 and 410): *N*-((*S*)-1-(5-bromooxazol-2-yl)-7-

oxononyl)-6-oxaspiro[2.5]octane-1-carboxamide (409A, 220 mg, 0.498 mmol), 7-methoxy-2-

methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (**C1**, 179 mg, 0.598 mmol), K_3PO_4 (317 mg, 1.495 mmol) and $PdCl_2(DTBPF)$ (33 mg, 0.051 mmol) were dissolved in a mixture of dioxane (10 mL) and water (2 mL). The reaction mixture was stirred under nitrogen at 70°C for 2 h. After it cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (silica, Pet. ether: EtOAc = 1:2 to 1:5) to give racemic of *N*-((*S*)-1-(5-(7-methoxy-2-methylquinolin-6-yl)oxazol-2-yl)-7-oxononyl)-6-oxaspiro[2.5]octane-1-carboxamide.

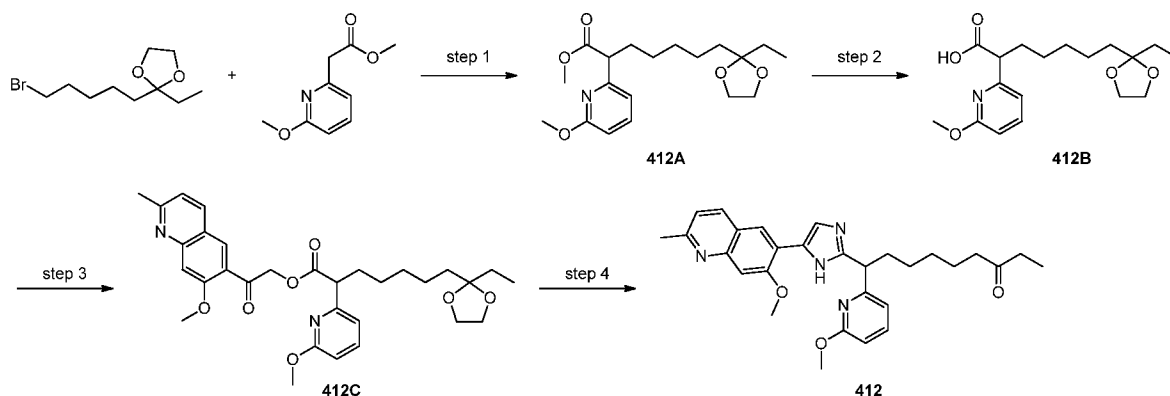
The diastereoisomers were separated by chiral SFC and then made into a tartarate by previously described methods.

409, from peak 1, 79 mg, yellow solid. ^1H NMR (400 MHz, MeOD) δ 8.21-8.34 (m, 2H), 7.59 (s, 1H), 7.44 (s, 1H), 7.35 (d, J = 8.6 Hz, 1H), 5.10-5.25 (m, 1H), 4.49 (s, 2H), 4.12 (s, 3H), 3.74-3.75 (m, 2H), 3.69 (m, 1H), 3.55-3.62 (m, 1H), 2.71 (s, 3H), 2.35-2.50 (m, 4H), 2.00-2.10 (m, 1H), 1.80-1.94 (m, 1H), 1.70-1.80 (m, 1H), 1.60-1.70 (m, 2H), 1.62-1.69 (m, 1H), 1.55-1.58 (m, 3H), 1.44-1.48 (m, 2H), 1.38-1.40 (m, 2H), 1.14-1.15 (m, 1H), 0.97 (t, J = 7.3 Hz, 3H), 0.88-0.89 (m, 1H). LCMS (ESI) calc'd for $C_{31}H_{40}N_3O_5$ $[M+H]^+$: 534.3, found: 534.3

410, peak 2, 78 mg, yellow solid. ^1H NMR (400 MHz, MeOD) δ 8.27 (d, J = 8.2 Hz, 1H), 8.23 (s, 1H), 7.60 (s, 1H), 7.44 (s, 1H), 7.36 (d, J = 8.2 Hz, 1H), 5.17 (d, J = 8.2 Hz, 1H), 4.50 (s, 2H), 4.12 (s, 3H), 3.74 (t, J = 5.0 Hz, 2H), 3.52 (s, 2H), 2.71 (s, 3H), 2.43 (q, J = 7.8 Hz, 4H), 2.00-2.16 (m, 1H), 1.90-2.00 (m, 1H), 1.60-1.70 (m, 3H), 1.54-1.60 (m, 3H), 1.43-1.50 (m, 1H), 1.30-1.40 (m, 3H), 1.20-1.30 (m, 1H), 1.16 (t, J = 4.6 Hz, 1H), 0.97 (t, J = 7.1 Hz, 3H), 0.87 (dd, J = 4.6, 7.7 Hz, 1H). LCMS (ESI) calc'd for $C_{31}H_{40}N_3O_5$ $[M+H]^+$: 534.3, found: 534.4

Example 92

9-[5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl]-9-(6-methoxypyridin-2-yl)nonan-3-one (412)



Step 1: Preparation of methyl 7-(2-ethyl-: LiHMDS (12 mL, 12.00 mmol) was added to a stirred mixture of methyl 2-(6-methoxypyridin-2-yl)acetate (described in WO2014/79136 A1,

1000 mg, 5.52 mmol) in THF (20 mL) at -78°C and the mixture was stirred -78°C for 1 h. Then 2-(5-bromopentyl)-2-ethyl-1,3-dioxolane (described in Synthesis, 2003, 14, 2194 - 2198, 1386 mg, 5.52 mmol) in THF (5 mL) was added portionwise and the reaction mixture was allowed to warm up to room temperature and left stirring overnight. The reaction mixture was quenched
5 with H₂O (50 mL) and extracted with EtOAc (50 mLX2). The organic phases were collected, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 100:1-50:1 to give methyl 7-(2-ethyl-1,3-dioxolan-2-yl)-2-(6-methoxypyridin-2-yl)heptanoate (**412A**). LCMS (ESI) calc'd for C₁₉H₂₉NO₅ [M+H]⁺: 352.2, found: 352.2.

10 Step 2: Preparation of 7-(2-ethyl-1,3-dioxolan-2-yl)-2-(6-methoxypyridin-2-yl)heptanoic acid (**412B**): LiOH (61 mg, 2.55 mmol) in water (2 mL) was added to a stirred mixture of methyl 7-(2-ethyl-1,3-dioxolan-2-yl)-2-(6-methoxypyridin-2-yl)heptanoate (**412A**, 300 mg, 0.854 mmol) in MeOH (2 mL) at room temperature and the mixture was stirred at 65°C for 2 h. The solution was concentrated to afford 7-(2-ethyl-1,3-dioxolan-2-yl)-2-(6-methoxypyridin-2-yl)heptanoic
15 acid (**412B**) was used in the next step without further purification. LCMS (ESI) calc'd for C₁₈H₂₇NO₅ [M+H]⁺: 338.2, found: 337.9

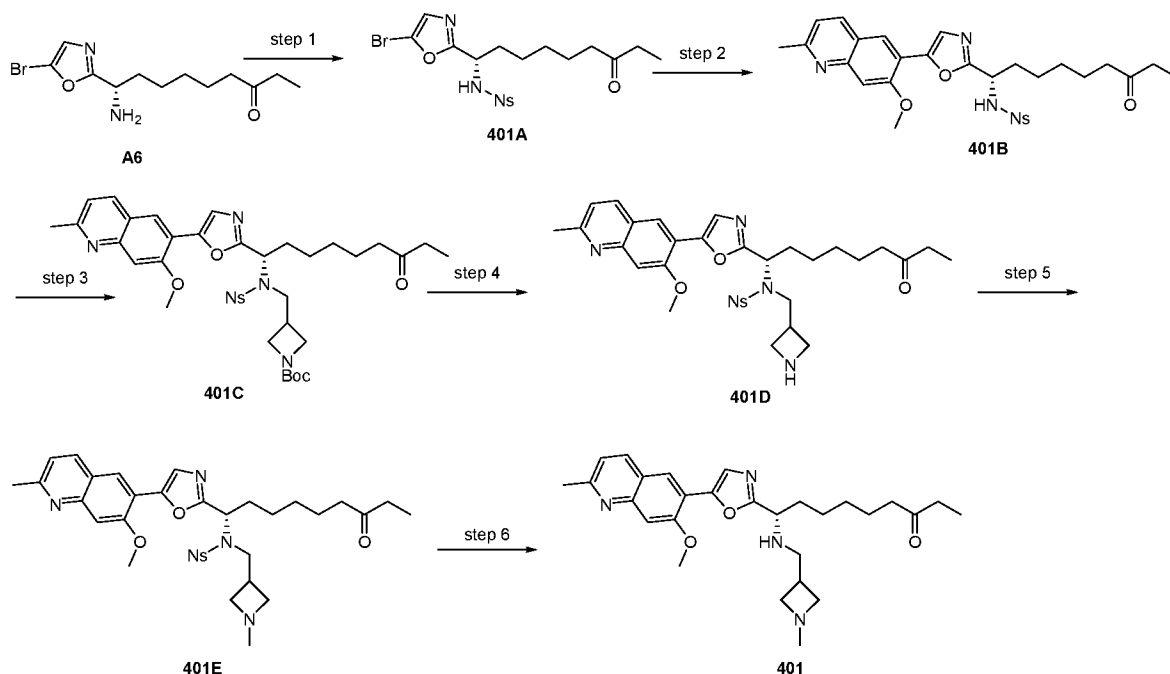
Step 3: Preparation of 2-(7-methoxy-2-methylquinolin-6-yl)-2-oxoethyl 7-(2-ethyl-1,3-dioxolan-2-yl)-2-(6-methoxypyridin-2-yl)heptanoate (**412C**): 2-chloro-1-(7-methoxy-2-methylquinolin-6-yl)ethanone (256 mg, 1.024 mmol) was added to a stirred mixture of 7-(2-ethyl-1,3-dioxolan-2-yl)-2-(6-methoxypyridin-2-yl)heptanoic acid (**412B**, 288 mg, 0.854 mmol) and K₂CO₃ (59 mg, 0.427 mmol) in DMF (2 mL) at 25°C and the mixture was stirred at room temperature for 24 h. The mixture was diluted with ethyl acetate (10 mL), washed with brine (saturated, 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 5:1-
20 1:2 to give 2-(7-methoxy-2-methylquinolin-6-yl)-2-oxoethyl 7-(2-ethyl-1,3-dioxolan-2-yl)-2-(6-methoxypyridin-2-yl)heptanoate (**412C**). LCMS (ESI) calc'd for C₃₁H₃₈N₂O₇ [M+H]⁺: 551.3, found: 551.3

Step 4: Preparation of 9-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-9-(6-methoxypyridin-2-yl)nonan-3-one (**412**): NH₄OAc (574 mg, 7.45 mmol) was added to a stirred
30 mixture of 2-(7-methoxy-2-methylquinolin-6-yl)-2-oxoethyl 7-(2-ethyl-1,3-dioxolan-2-yl)-2-(6-methoxypyridin-2-yl)heptanoate (**412C**, 410 mg, 0.745 mmol) in toluene (20 mL) at room temperature and the mixture was heated with stirring at 110°C for 18 h. The mixture was cooled to rt, water (10 mL) was added and the mixture was extracted with ethyl acetate (2 x 10 mL). The combined organic fractions were washed with water (10 mL), dried (Na₂SO₄), filtered and

the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether/EtOAc = 2:1-1:2, and then further purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.1% TFA to give 9-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-9-(6-methoxypyridin-2-yl)nonan-3-one (**412**). LCMS (ESI) calc'd for C₂₉H₃₄N₄O₃ [M+H]⁺: 487.3, found: 487.0. ¹H NMR (400 MHz, CDCl₃) δ 8.86 (brs, 1H), 8.64-8.72 (m, 1H), 8.35-8.42 (m, 1H), 7.86 (brs, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.44-7.50 (m, 1H), 7.09 (d, *J* = 7.1 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 4.84-4.95 (m, 1H), 4.20 (s, 3H), 3.97-4.05 (m, 3H), 3.02 (s, 3H), 2.32-2.43 (m, 4H), 1.98-2.24 (m, 2H), 1.45-1.55 (m, 2H), 1.21-1.34 (m, 4H), 1.03 (t, *J* = 7.3 Hz, 3H).

Example 93

9-amino-10-methoxy-9-[5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl]decan-3-one
(**414**)



Step 1: (S)-methyl 2-amino-3-methoxypropanoate (414B**):** SOCl₂ (7 mL, 96 mmol) was added to a stirred mixture of (S)-2-amino-3-methoxypropanoic acid (**414A**, 10 g, 84 mmol) in MeOH (20 mL) at 25°C and the mixture was heated with stirring at 80°C for 2 h. The mixture was cooled, diluted with MeOH (20 mL) and the solvent was evaporated under reduced pressure. The residue was washed with aqueous Na₂CO₃ (saturated, 20 mL), extracted with EtOAc (20 mL x 2), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure to give (S)-methyl 2-amino-3-methoxypropanoate (**414B**). LCMS (ESI) calc'd for C₅H₁₁NO₃ [M+H]⁺: 134.0, found: 134.1

Step 2: (*S,E*)-methyl 2-(benzylideneamino)-3-methoxypropanoate (414C): Sodium sulfate (107 g, 751 mmol) was added to a stirred mixture of (*S*)-methyl 2-amino-3-methoxypropanoate (414B, 10 g, 75 mmol) and benzaldehyde (10 g, 94 mmol) in DCM (2 mL) at 25°C and the mixture was stirred at room temperature for 8 h. The reaction was concentrated to give (*S,E*)-methyl 2-(benzylideneamino)-3-methoxypropanoate (414C) which was used to the next step without further purification.

Step 3: (*E*)-methyl 2-(benzylideneamino)-2-(methoxymethyl)pent-4-enoate (414D): 3-bromoprop-1-ene (20 g, 165 mmol) in 20 mL of acetonitrile was added to a stirred mixture of (*S,E*)-methyl 2-(benzylideneamino)-3-methoxypropanoate (414C, 20 g, 90 mmol), KOH (5.07 g, 90 mmol), K₂CO₃ (24.99 g, 181 mmol) and benzyltriethylammonium chloride (2.059 g, 9.04 mmol) in acetonitrile (300 mL) at room temperature and the mixture was stirred at room temperature for 18 h. The mixture was filtered and the filter cake was washed with CH₃CN (200 mL). The filtrate was concentrated to dryness. The mixture was diluted with 500 mL of EtOAc, washed with brine (2 x 200 mL), dried over Na₂SO₄, filtered and concentrated to afford (*E*)-methyl 2-(benzylideneamino)-2-(methoxymethyl)pent-4-enoate (414D) which was used to the next step without purification.

Step 4: methyl 2-((tert-butoxycarbonyl)amino)-2-(methoxymethyl)pent-4-enoate (414E): HCl (10 mL, 122 mmol) was added to water (300 mL) and then it was added to a stirred mixture of (*E*)-methyl 2-(benzylideneamino)-2-(methoxymethyl)pent-4-enoate (414D, 20 g, 77 mmol) in toluene (300 mL) at room temperature and the mixture was stirred at room temperature for 18 h. The aqueous layer was separated and used to next step without purification.

15 mL aqueous above (~4 g of methyl 2-amino-2-(methoxymethyl)pent-4-enoate) was basified with solid NaHCO₃ to pH = 8 and then DCM (50 mL) was added. Boc₂O (6 mL, 25.8 mmol) was added. The mixture was stirred at room temperature for 18 h. The mixture was added 20 mL of EtOAc, the aqueous layer was separated and extracted with 10 mL of EtOAc. The combined organic fractions were washed with water (10 mL), brine (saturated, 1 x 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 0 to 5% to give methyl 2-((tert-butoxycarbonyl)amino)-2-(methoxymethyl)pent-4-enoate (414E). ¹H NMR (400 MHz, CDCl₃) δ 5.55-5.71 (m, 1H), 5.03-5.12 (m, 2H), 3.78-3.81 (m, 1H), 3.74 (s, 3H), 3.60-3.64 (m, 1H), 3.31-3.32 (m, 3H), 2.79-2.90 (m, 1H), 2.48-2.58 (m, 1H), 1.41 (s, 9H).

Step 5: 2-((tert-butoxycarbonyl)amino)-2-(methoxymethyl)pent-4-enoic acid (414F): Lithium hydroxide (0.526 g, 21.95 mmol) in water (2 mL) was added to a stirred solution of methyl 2-((tert-butoxycarbonyl)amino)-2-(methoxymethyl)pent-4-enoate (414E, 3 g, 10.98 mmol) in

MeOH (10 mL) at room temperature and the mixture was stirred at 26°C for 2 h. The mixture was cooled and HCl (4 M, 10 mL) was added to adjust pH=5-6 and the mixture was extracted with ethyl acetate (20 mLx3). The organic phase was concentrated to give the title compound which was used to the next step directly.

- 5 Step 6: 2-(7-methoxy-2-methylquinolin-6-yl)-2-oxoethyl 2-((tert-butoxycarbonyl)amino)-2-(methoxymethyl)pent-4-enoate (414G): 2-chloro-1-(7-methoxy-2-methylquinolin-6-yl)ethanone (289 mg, 1.157 mmol) was added to a stirred mixture DIPEA (1 mL, 5.73 mmol) and 2-((tert-butoxycarbonyl)amino)-2-(methoxymethyl)pent-4-enoic acid (**414F**, 300 mg, 1.157 mmol) in DMF (2 mL) at rt and the mixture was stirred at rt for 18 h. Water (20 mL) was added and the
10 mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic fractions were washed with brine (20 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 100:1 - 1:1 to give 2-(7-methoxy-2-methylquinolin-6-yl)-2-oxoethyl 2-((tert-butoxycarbonyl)amino)-2-(methoxymethyl)pent-4-enoate (**414G**,). LCMS (ESI)
15 calc'd for C₂₅H₃₂N₂O₇ [M+H]⁺: 473.2, found: 473.1

- Step 7: tert-butyl (1-methoxy-2-(4-(7-methoxy-2-methylquinolin-6-yl)-1H-imidazol-2-yl)pent-4-en-2-yl)carbamate (414H): NH₄OAc (2.94 g, 38.1 mmol) was added to a stirred mixture of 2-(7-methoxy-2-methylquinolin-6-yl)-2-oxoethyl 2-((tert-butoxycarbonyl)amino)-2-(methoxymethyl)pent-4-enoate (**414G**, 1.8 g, 3.81 mmol) in toluene (10 mL) at 130°C and the
20 mixture was stirred at 130°C for 2 h. Water (20 mL) was added and the mixture was extracted with ethyl acetate (2 x 10 mL). The combined organic fractions were washed with brine (saturated, 10 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (ISCORF75; Sepa flash column), eluting with petroleum ether / EtOAc = 100:1 - 1:1 to give tert-butyl (1-methoxy-2-(4-(7-methoxy-2-methylquinolin-6-yl)-1H-imidazol-2-yl)pent-4-en-2-yl)carbamate (**414H**). LCMS
25 (ESI) calc'd for C₂₅H₃₂N₄O₄ [M+H]⁺: 453.2, found: 453.1

- Step 8: tert-butyl 2-(2-((tert-butoxycarbonyl)amino)-1-methoxypent-4-en-2-yl)-4-(7-methoxy-2-methylquinolin-6-yl)-1H-imidazole-1-carboxylate (414I): A mixture of tert-butyl (1-methoxy-2-(4-(7-methoxy-2-methylquinolin-6-yl)-1H-imidazol-2-yl)pent-4-en-2-yl)carbamate (**414H**, 500
30 mg, 1.105 mmol), DMAP (135 mg, 1.105 mmol) and Boc₂O (0.3 mL, 1.292 mmol) in DCM (10 mL) was stirred at 25°C for 12 h. The mixture was concentrated to dryness and purified by silica gel flash chromatography (ISCORF75; Sepa flash column), eluting with petroleum ether / EtOAc = 100 : 1 - 1:1 to give tert-butyl 2-(2-((tert-butoxycarbonyl)amino)-1-methoxypent-4-en-2-yl)-4-

(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazole-1-carboxylate (**414I**). LCMS (ESI) calc'd for $C_{30}H_{40}N_4O_6$ $[M+H]^+$: 553.2, found: 553.1

Step 9: (*E*)-tert-butyl 2-(2-((tert-butoxycarbonyl)amino)-1-methoxy-8-oxodec-4-en-2-yl)-4-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazole-1-carboxylate (**414J**): Zhan's catalyst (50 mg,

5 0.068 mmol) was added to the solution of tert-butyl 2-(2-((tert-butoxycarbonyl)amino)-1-methoxypent-4-en-2-yl)-4-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazole-1-carboxylate (**414I**, 350 mg, 0.633 mmol) and hept-6-en-3-one (200 mg, 1.783 mmol) in degassed toluene (3 mL), the resultant mixture was stirred at 100°C for 12 h under N_2 atmosphere. The residue was purified by preparative TLC on silica gel, eluting with petroleum ether / EtOAc = 1:1 to give
10 (*E*)-tert-butyl 2-(2-((tert-butoxycarbonyl)amino)-1-methoxy-8-oxodec-4-en-2-yl)-4-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazole-1-carboxylate (**414J**). LCMS (ESI) calc'd for $C_{35}H_{48}N_4O_7$ $[M+H]^+$: 637.3, found: 637.5

Step 10: tert-butyl 2-(2-((tert-butoxycarbonyl)amino)-1-methoxy-8-oxodecan-2-yl)-4-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazole-1-carboxylate (**414K**): 10% Pd-C (50 mg, 0.047

15 mmol) was added to a stirred mixture of (*E*)-tert-butyl 2-(2-((tert-butoxycarbonyl)amino)-1-methoxy-8-oxodec-4-en-2-yl)-4-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazole-1-carboxylate (**414J**, 100 mg, 0.157 mmol) in MeOH (3 mL) at 25 °C and The mixture was degassed and backfilled with H_2 (three times). The resulting mixture was stirred under 15 psi of H_2 at room temperature for 2 h. The mixture was filtered and the filter cake was washed with
20 MeOH (10 mL). The filtrate was concentrated to give tert-butyl 2-(2-((tert-butoxycarbonyl)amino)-1-methoxy-8-oxodecan-2-yl)-4-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazole-1-carboxylate (**414K**). LCMS (ESI) calc'd for $C_{35}H_{50}N_4O_7$ $[M+H]^+$: 639.3, found: 639.4

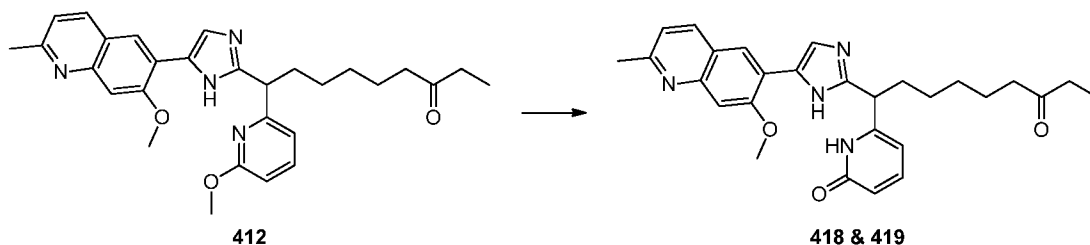
Step 11: 9-amino-10-methoxy-9-(4-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-

25 yl)decan-3-one (**414**): TFA (0.2 mL, 0.055 mmol) was added to a stirred mixture of tert-butyl 2-(2-((tert-butoxycarbonyl)amino)-1-methoxy-8-oxodecan-2-yl)-4-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazole-1-carboxylate (**414K**, 35 mg, 0.055 mmol) in DCM (1 mL) at 25°C. The resulting mixture was stirred at room temperature for 2 h. Aqueous $NaHCO_3$ (saturated, 3 mL) was added and the mixture was extracted with DCM (2 x 4 mL). The combined organic
30 fractions were washed with brine (saturated, 2 mL), dried (Na_2SO_4), filtered and the solvent was evaporated under reduced pressure. The residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.1% TFA, to give 9-amino-10-methoxy-9-(4-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)decan-3-one (**414**). LCMS (ESI) calc'd for $C_{25}H_{34}N_4O_3$ $[M+H]^+$: 439.2, found: 439.1. ^1H NMR (400 MHz, MeOD) δ 8.89-8.98

(m, 1H), 8.77-8.87 (m, 1H), 7.84-7.91 (m, 1H), 7.66-7.75 (m, 1H), 7.52-7.60 (m, 1H), 4.20-4.28 (m, 3H), 3.86-3.95 (m, 1H), 3.76-3.84 (m, 1H), 3.41-3.51 (m, 1H), 2.86-2.98 (m, 3H), 2.35-2.45 (m, 4H), 1.96-2.20 (m, 2H), 1.45-1.59 (m, 2H), 1.11-1.35 (m, 4H), 0.90-1.02 (m, 3H).

Example 94

5 6-{1-[5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl]-7-oxononyl}pyridin-2(1*H*)-one (418&419)



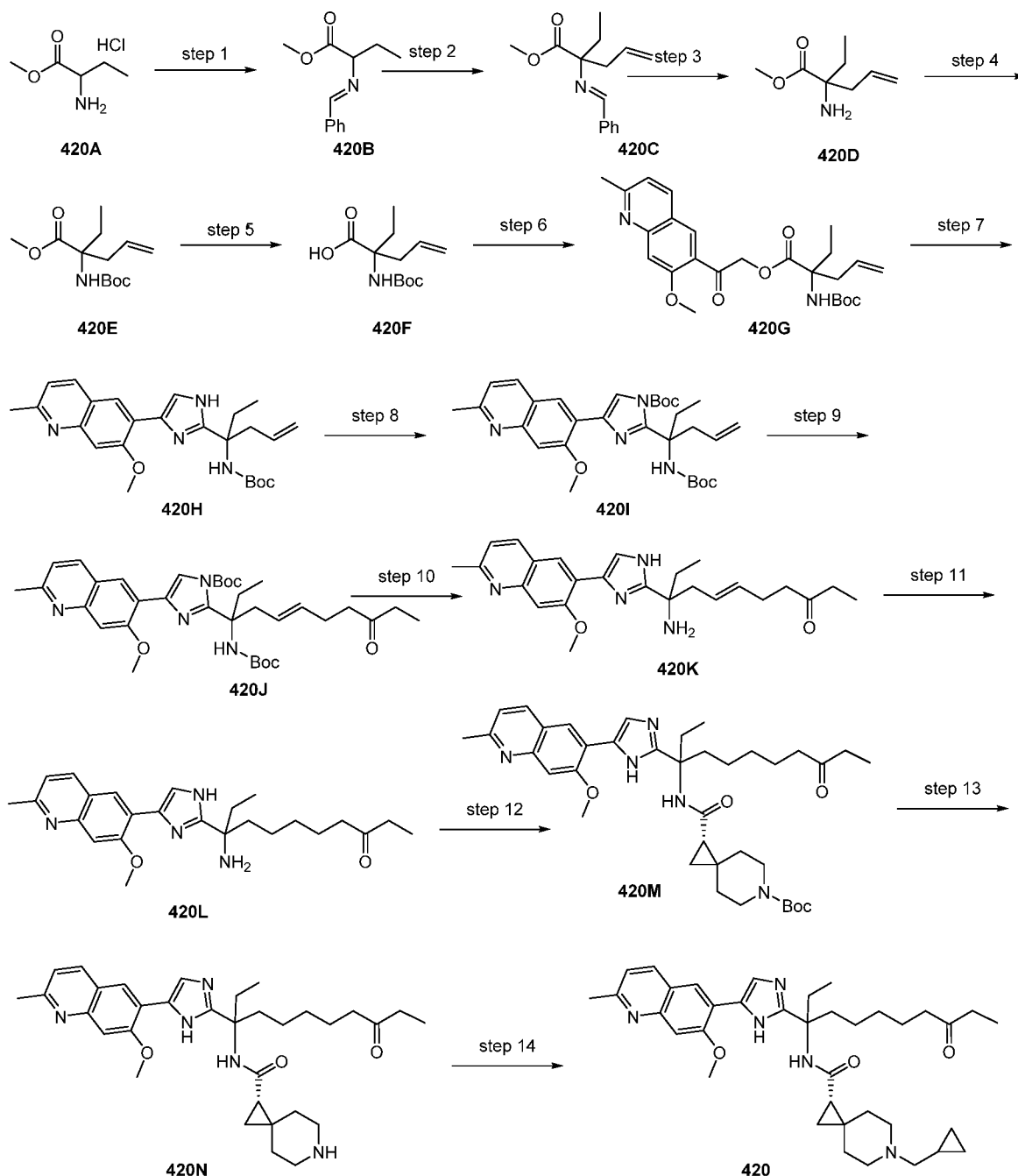
HCl (1 mL, 12.18 mmol) was added to a stirred mixture of 9-(5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)-9-(6-methoxypyridin-2-yl)nonan-3-one (**412**, 94 mg, 0.193 mmol) in dioxane (1 mL) at room temperature and the mixture was stirred at 100 °C for 7 h. The reaction solution was concentrated and the residue was dissolved in DCM (10 mL) and adjusted to pH=9 with NaHCO₃ saturated (aqueous). The organic phase was dried over Na₂SO₄, filtered and concentrated to give racemic of 6-(1-[5-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl]-7-oxononyl)pyridin-2(1*H*)-one which was further separated by chiral SFC on AD
15 column, gradient with 35% EtOH (0.1% NH₄OH). It was then made into a tartarate by previously described methods.

418, from peak 1, 38 mg as a yellow solid. LCMS (ESI) calc'd for C₂₈H₃₂N₄O₃ [M+H]⁺: 473.2, found: 473.1. ¹H NMR (400 MHz, MeOD) δ 8.52 (s, 1H), 8.42 (d, *J* = 8.2 Hz, 1H), 7.70 (s, 1H), 7.56 (dd, *J* = 7.2, 9.1 Hz, 1H), 7.39-7.49 (m, 2H), 6.44 (d, *J* = 9.0 Hz, 1H), 6.35 (d, *J* = 6.8 Hz, 1H), 4.52 (s, 2H), 4.10-4.19 (m, 4H), 2.77 (s, 3H), 2.42 (m, 4H), 2.15-2.29 (m, 1H), 2.02-2.14 (m, 1H), 1.55 (t, *J* = 7.0 Hz, 2H), 1.27-1.43 (m, 4H), 0.97 (t, *J* = 7.4 Hz, 3H).
20

419, from peak 2, 34 mg as a yellow solid. LCMS (ESI) calc'd for C₂₈H₃₂N₄O₃ [M+H]⁺: 473.2, found: 473.0. ¹H NMR (400 MHz, MeOD) δ 8.50 (s, 1H), 8.39 (d, *J* = 8.6 Hz, 1H), 7.69 (s, 1H), 7.56 (dd, *J* = 7.1, 9.0 Hz, 1H), 7.38-7.46 (m, 2H), 6.44 (d, *J* = 9.0 Hz, 1H), 6.34 (d, *J* = 6.6 Hz, 1H), 4.51 (s, 2H), 4.11-4.17 (m, 4H), 2.76 (s, 3H), 2.42 (m, 4H), 2.21 (dd, *J* = 4.6, 8.6 Hz, 1H), 2.04-2.12 (m, 1H), 1.51-1.59 (m, 2H), 1.29-1.40 (m, 4H), 0.97 (t, *J* = 7.3 Hz, 3H).
25

Example 95

(1*S*)-6-(cyclopropylmethyl)-*N*-{3-[4-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl]-9-oxoundecan-3-yl}-6-azaspiro[2.5]octane-1-carboxamide (**420**):



Step 1: Preparation of compound (E)-methyl 2-(benzylideneamino)butanoate (420B): To a solution of methyl 2-aminobutanoate hydrochloride (**420A**, 12.00 g, 78 mmol), benzaldehyde (9.12 g, 86 mmol) in toluene (100 mL) was added triethylamine (9.09 g, 90 mmol) drop wise over 5 min at ambient temperature (< 30°C). The reaction mixture was heated to 70°C and stirred for 4 h. Another portion of methyl 2-aminobutanoate hydrochloride (4.75 g, 31 mmol) was added, followed by additions of benzaldehyde (1.9 g, 18 mmol) and TEA (5 mL) to the reaction. The reaction was completed detected by ¹H NMR. The mixture was cooled and concentrated *in*

vacuo to give (*E*)-methyl 2-(benzylideneamino)butanoate (**420B**) which was used immediately in next step without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.36 (s, 1H), 7.77 (dd, *J* = 1.6, 7.4 Hz, 2H), 7.37-7.50 (m, 3H), 3.96 (dd, *J* = 5.7, 7.6 Hz, 1H), 3.63 (s, 3H), 1.89-1.93 (m, 1H), 1.68-1.82 (m, 1H), 0.83 (t, *J* = 7.4 Hz, 3H).

- 5 Step 2: Preparation of compound (*E*)-methyl 2-(benzylideneamino)-2-ethylpent-4-enoate (**420C**): 3-bromoprop-1-ene (21.36 g, 177 mmol) was added to a stirred mixture of (*E*)-methyl 2-(benzylideneamino)butanoate (**420B**, 30.20 g, 147 mmol), potassium hydroxide (8.26 g, 147 mmol) and potassium carbonate (61.0 g, 441 mmol) in MeCN (200 mL) at 26°C and the mixture was stirred at room temperature for 24 h. ¹H NMR showed almost complete consumption of the
- 10 starting compound. The mixture was filtered and the cake was washed with MeCN (10 mL), the filtrate was concentrated to dryness to give (*E*)-methyl 2-(benzylideneamino)-2-ethylpent-4-enoate (**420C**) which was used to the next step without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.30 (s, 1H), 7.70-7.80 (m, 2H), 7.37-7.47 (m, 3H), 5.61-5.70 (m, 1H), 4.96-5.10 (m, 2H), 3.63 (s, 3H), 2.50-2.66 (m, 2H), 1.72-1.94 (m, 2H), 0.71-0.86 (m, 3H).

- 15 Step 3: Preparation of compound methyl 2-amino-2-ethylpent-4-enoate (**420D**): 2 M HCl (100 mL) was added to a stirred mixture of (*E*)-methyl 2-(benzylideneamino)-2-ethylpent-4-enoate (**420C**, 37.14 g, 0.151 mol) in toluene (100 mL) at room temperature and the mixture was stirred at room temperature for 24 h. The aqueous layer was separated and basified by sat. NaOH solution. The solution was extracted with EtOAc (100 mL*2), dried over Na₂SO₄,
- 20 filtered and concentrated to methyl 2-amino-2-ethylpent-4-enoate (**420D**) which was used in next step without purification.

- Step 4: Preparation of compound methyl 2-((tert-butoxycarbonyl)amino)-2-ethylpent-4-enoate (**420E**): Boc₂O (19.64 g, 90 mmol) and triethylamine (16.72 mL, 120 mmol) were added to a stirred mixture of methyl 2-amino-2-ethylpent-4-enoate (**420D**, 9.43 g, 60.0 mmol) in DCM (40
- 25 mL) at room temperature and the mixture was stirred at room temperature for 24 h. The mixture was diluted with H₂O (40 mL), and extracted with DCM (40 mL*2). The combined organic fractions were washed with sat. NaCl (40 mL) solution, dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 0 to 5% to afford the title compound
- 30 (**420E**). LCMS (ESI) calc'd for C₁₃H₂₄NO₄ [M+H]⁺: 258.2, found: 258.2. ¹H NMR (400 MHz, CDCl₃) δ 5.55-5.78 (m, 1H), 5.03-5.10 (m, 2H), 3.74 (s, 3H), 3.00-3.02 (m, 1H), 2.44-2.56 (m, 1H), 2.16-2.34 (m, 1H), 1.69-1.88 (m, 1H), 1.42 (s, 9H), 0.77 (t, *J* = 7.4 Hz, 3H).

Step 5: Preparation of compound 2-((tert-butoxycarbonyl)amino)-2-ethylpent-4-enoic acid (**420F**): Lithium hydroxide monohydrate (2.218 g, 52.9 mmol) was added to a stirred mixture of

methyl 2-((tert-butoxycarbonyl)amino)-2-ethylpent-4-enoate (**420E**, 6.80 g, 26.4 mmol) in MeOH (60 mL) and water (20 mL) at room temperature and the mixture was stirred at 50 °C for 19 h. The mixture was cooled, the aqueous layer was separated and adjusted pH to 5 with citric acid, extracted with ethyl acetate (40 mL*3), dried (Na₂SO₄), filtered and evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with DCM: MeOH = 10:1 to give 2-((tert-butoxycarbonyl)amino)-2-ethylpent-4-enoic acid (**420F**). LCMS (ESI) calc'd for C₁₂H₂₂NO₄ [M+H]⁺: 244.2, found: 244.2.

Step 6: Preparation of compound 2-(7-methoxy-2-methylquinolin-6-yl)-2-oxoethyl 2-((tert-butoxycarbonyl)amino)-2-ethylpent-4-enoate (**420G**): 2-chloro-1-(7-methoxy-2-methylquinolin-6-yl)ethanone (1.129 g, 4.52 mmol) was added to a stirred mixture of 2-((tert-butoxycarbonyl)amino)-2-ethylpent-4-enoic acid (**420F**, 1.00 g, 4.11 mmol) and DIPEA (0.531 g, 4.11 mmol) in DMF (3 mL) at room temperature and the mixture was stirred at room temperature for 20 h. The temperature was raised to 50°C and 0.1 eq. of NaI and another portion of 2-chloro-1-(7-methoxy-2-methylquinolin-6-yl)ethanone (280 mg) were added, and the mixture was stirred for 10 h. Another portion of 2-chloro-1-(7-methoxy-2-methylquinolin-6-yl)ethanone (600 mg) was added and the mixture was stirred for 16 h. The mixture was diluted with H₂O (20 mL), extracted with EtOAc (30 mL*2), washed with sat. NaCl solution (40 mL), dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with petroleum ether / EtOAc = 3:1 to give 2-(7-methoxy-2-methylquinolin-6-yl)-2-oxoethyl 2-((tert-butoxycarbonyl)amino)-2-ethylpent-4-enoate (**420G**). LCMS (ESI) calc'd for C₂₅H₃₃N₂O₆ [M+H]⁺: 457.2, found: 457.2

Step 7: Preparation of compound tert-butyl (3-(4-(7-methoxy-2-methylquinolin-6-yl)-1H-imidazol-2-yl)hex-5-en-3-yl)carbamate (**420H**): A solution of the 2-(7-methoxy-2-methylquinolin-6-yl)-2-oxoethyl 2-((tert-butoxycarbonyl)amino)-2-ethylpent-4-enoate (**420G**, 900 mg, 1.971 mmol) and NH₄OAc (1520 mg, 19.71 mmol) in toluene (25 mL) was maintained at 110°C for approximately 10 h. Another NH₄OAc (1.0 g) was added, and the reaction was held at 110°C for another 10 h. The mixture was cooled and washed with water, saturated aq. NaHCO₃ until a basic pH was obtained, then it was washed with brine. The organic phase was then dried over Na₂SO₄ and concentrated under reduced pressure. Purification of the resulting residue by flash chromatography on silica gel (Pet. ether/EtOAc = 2:1 to 1:1) yielded tert-butyl (3-(4-(7-methoxy-2-methylquinolin-6-yl)-1H-imidazol-2-yl)hex-5-en-3-yl)carbamate (**420H**). LCMS (ESI) calc'd for C₂₅H₃₃N₄O₃ [M+H]⁺: 437.3, found: 437.3

Step 8: Preparation of tert-butyl 2-(3-((tert-butoxycarbonyl)amino)hex-5-en-3-yl)-4-(7-methoxy-2-methylquinolin-6-yl)-1H-imidazole-1-carboxylate (**420I**): Boc-anhydride (0.287 mL,

1.237 mmol) was added to tert-butyl (3-(4-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)hex-5-en-3-yl)carbamate (**420H**, 270 mg, 0.618 mmol) and Et₃N (0.345 mL, 2.474 mmol) in DCM (6 mL) at 24°C and the mixture was stirred at rt for 18 h. The mixture was evaporated under reduced pressure. The residue was purified by silica gel column flash chromatography, eluting with EtOAc / petroleum ether = 0~25% to give tert-butyl 2-(3-((tert-butoxycarbonyl)amino)hex-5-en-3-yl)-4-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazole-1-carboxylate (**420I**). LCMS (ESI) calc'd for C₃₀H₄₀N₄O₅ [M+H]⁺: 537.3, found: 537.4

Step 9: Preparation of (*E*)-tert-butyl 2-(3-((tert-butoxycarbonyl)amino)-9-oxoundec-5-en-3-yl)-4-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazole-1-carboxylate (**420J**): UMICORE M71

SIPR (18 mg, 0.022 mmol) and hept-6-en-3-one (100 mg, 0.894 mmol) were added to the degassed solution of tert-butyl 2-(3-((tert-butoxycarbonyl)amino)hex-5-en-3-yl)-4-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazole-1-carboxylate (**420I**, 240 mg, 0.447 mmol) in toluene (3 mL), and the resultant mixture was stirred at 60°C for 17 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (ISCORF75; Sepa flash column), eluting with petroleum ether / EtOAc = 10:1-3:1 to give (*E*)-tert-butyl 2-(3-((tert-butoxycarbonyl)amino)-9-oxoundec-5-en-3-yl)-4-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazole-1-carboxylate (**420J**) and recovered tert-butyl 2-(3-((tert-butoxycarbonyl)amino)hex-5-en-3-yl)-4-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazole-1-carboxylate. LCMS (ESI) calc'd for C₃₅H₄₈N₄O₆ [M+H]⁺: 621.4, found: 621.4

Step 10: Preparation of (*E*)-9-amino-9-(4-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)undec-6-en-3-one (**420K**): TFA (1 mL, 12.98 mmol) was added to the solution of (*E*)-tert-butyl 2-(3-((tert-butoxycarbonyl)amino)-9-oxoundec-5-en-3-yl)-4-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazole-1-carboxylate (**420J**, 180 mg, 0.290 mmol) in DCM (10 mL), and the resultant mixture was stirred at 24°C for 4 h. The mixture was concentrated *in vacuo* to give (*E*)-9-amino-9-(4-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)undec-6-en-3-one (**420K**) which was used to the next step without purification. LCMS (ESI) calc'd for C₂₅H₃₂N₄O₂ [M+H]⁺: 421.3, found: 421.3

Step 11: Preparation of 9-amino-9-(4-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)undecan-3-one (**420L**): Pd/C (40 mg, 0.376 mmol) was added to the degassed solution of (*E*)-9-amino-9-(4-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)undec-6-en-3-one (**420K**, 122 mg, 0.290 mmol) in MeOH (5 mL), and the resultant mixture was stirred under a H₂ balloon at rt for 24 h. The reaction mixture was concentrated *in vacuo* to give 9-amino-9-(4-(7-methoxy-2-methylquinolin-6-yl)-1*H*-imidazol-2-yl)undecan-3-one (**420L**) and used directly in next step. LCMS (ESI) calc'd for C₂₅H₃₄N₄O₂ [M+H]⁺: 423.4, found: 423.3

Step 12: Preparation of (1S)-tert-butyl 1-((3-(5-(7-methoxy-2-methylquinolin-6-yl)-1H-imidazol-2-yl)-9-oxoundecan-3-yl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (420M):

DIPEA (0.3 mL, 1.718 mmol), HOBT (91 mg, 0.592 mmol) and EDC (181 mg, 0.947 mmol) were added to the solution of (S)-6-(tert-butoxycarbonyl)-6-azaspiro[2.5]octane-1-carboxylic acid (121 mg, 0.473 mmol) and 9-amino-9-(4-(7-methoxy-2-methylquinolin-6-yl)-1H-imidazol-2-yl)undecan-3-one (**420L**, 100 mg, 0.237 mmol) in DMF (0.5 mL), the resultant mixture was stirred at rt for 16 h. DMF was removed *in vacuo*. The residue was purified by silica gel column flash chromatography, eluting with DCM / MeOH = 50:1~20:1 to give (1S)-tert-butyl 1-((3-(5-(7-methoxy-2-methylquinolin-6-yl)-1H-imidazol-2-yl)-9-oxoundecan-3-yl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**420M**). LCMS (ESI) calc'd for C₃₈H₅₃N₅O₅ [M+H]⁺: 660.4, found: 660.5

Step 13: Preparation of (1S)-N-(3-(5-(7-methoxy-2-methylquinolin-6-yl)-1H-imidazol-2-yl)-9-oxoundecan-3-yl)-6-azaspiro[2.5]octane-1-carboxamide (420N):

TFA (1.0 mL, 12.98 mmol) was added to the solution of (1S)-tert-butyl 1-((3-(5-(7-methoxy-2-methylquinolin-6-yl)-1H-imidazol-2-yl)-9-oxoundecan-3-yl)carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**420M**, 150 mg, 0.227 mmol) in DCM (10 mL), and the resultant mixture was stirred at 24°C for 3 h. The mixture was concentrated *in vacuo* to give (1S)-N-(3-(5-(7-methoxy-2-methylquinolin-6-yl)-1H-imidazol-2-yl)-9-oxoundecan-3-yl)-6-azaspiro[2.5]octane-1-carboxamide (**420N**) which was used to the next step without purification. LCMS (ESI) calc'd for C₃₃H₄₅N₅O₃ [M+H]⁺: 560.4, found: 560.4

Step 14: Preparation of (1S)-6-(cyclopropylmethyl)-N-(3-(5-(7-methoxy-2-methylquinolin-6-yl)-1H-imidazol-2-yl)-9-oxoundecan-3-yl)-6-azaspiro[2.5]octane-1-carboxamide (420):

Cyclopropanecarbaldehyde (239 mg, 3.40 mmol) was added to the solution of (1S)-N-(3-(5-(7-methoxy-2-methylquinolin-6-yl)-1H-imidazol-2-yl)-9-oxoundecan-3-yl)-6-azaspiro[2.5]octane-1-carboxamide (**420N**, 127 mg, 0.227 mmol) in MeOH (6 mL), and the resultant mixture was stirred at rt for 16 h. Sodium triacetoxyborohydride (90 mg, 0.425 mmol) was added to the reaction mixture, and it was stirred for 3 h. The residue was purified by preparative HPLC (reverse phase C-18 column), eluting with acetonitrile/water + 0.1% TFA, to give (1S)-6-(cyclopropylmethyl)-N-(3-(5-(7-methoxy-2-methylquinolin-6-yl)-1H-imidazol-2-yl)-9-oxoundecan-3-yl)-6-azaspiro[2.5]octane-1-carboxamide (**420**). LCMS (ESI) calc'd for C₃₇H₅₁N₅O₃ [M+H]⁺: 614.4, found: 614.4.

Solid NaHCO₃ (200 mg) was added to the solution of (1S)-6-(cyclopropylmethyl)-N-(3-(5-(7-methoxy-2-methylquinolin-6-yl)-1H-imidazol-2-yl)-9-oxoundecan-3-yl)-6-azaspiro[2.5]octane-1-carboxamide (30 mg, 0.049 mmol) (TFA salt) in MeOH (5 mL), and the bottle was shaken for

a few minutes, salt was filtered off and the filtrate was concentrated to give the free base of **420**. LCMS (ESI) calc'd for $C_{37}H_{51}N_5O_3$ $[M+H]^+$: 614.4, found: 614.2. ^1H NMR (400 MHz, MeOD) δ 8.40 (brs, 1H), 8.18 (d, $J = 8.4$ Hz, 1H), 7.45-7.61 (m, 1H), 7.39 (s, 1H), 7.27-7.35 (m, 1H), 4.08 (s, 3H), 3.34-3.50 (m, 1H), 3.16 (brs, 1H), 2.89 (brs, 2H), 2.69 (s, 3H), 2.23-2.48 (m, 6H), 1.80-2.22 (m, 4H), 1.45-1.58 (m, 2H), 1.05-1.37 (m, 6H), 0.72-1.02 (m, 8H), 0.64 (brs, 2H), 0.27 (brs, 2H).

HUMAN HDAC ENZYME INHIBITOR FLUOR-DE-LYS ASSAY

Materials

Recombinant human HDAC8 (BML-SE145-0100) and HDAC10 (BML-SE559-0050) enzymes, HDAC substrates BML-KI104 and BML-KI178, and HDAC developer solutions BML-KI105 and BML-KI176 were purchased from Enzo Life Sciences. Recombinant human HDAC5 and HDAC11 were purchased from BPS Bioscience (catalog numbers 50045 and 50021). Substrate Boc-Lys(TFA)-AMC was obtained from Bachem (catalog number I-1985). HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) was obtained from Indofine and trichostatin A (TSA) was obtained from Sigma-Aldrich. D-myoinositol-1,4,5,6-tetrakisphosphate potassium salt (IP₄) was obtained from Carbosynth (catalog MI 16761). HEPES pH 8.0 was obtained from Boston BioProducts, Tween-20 from Fisher Scientific (BP337), TCEP from Calbiochem and 7.5% bovine serum albumin (BSA) from Life Technologies (15260037). 384-well, black assay plates were obtained from Corning (3575).

Recombinant human HDAC1, HDAC2, and HDAC3/SMRT heterodimer were prepared by Merck Research Laboratories. Full length human HDAC1-FLAG was stably expressed in HEK-293F cells and purified using an anti-FLAG affinity chromatography with FLAG peptide (100 μ g/ml) elution. The final concentration of HDAC1 was 1.98 μ M by Western Blot analysis and 1.39 μ M by active site titration. Full length human HDAC2-FLAG was expressed in baculovirus infected Sf9 cells and purified using an anti-FLAG affinity chromatography with FLAG peptide (100 μ g/ml) elution. The eluted protein was then passed over an anti-HDAC1 immunoaffinity column to remove any complexes containing HDAC1. The final concentration of HDAC2 was 16.8 μ M by Western Blot analysis and 7.6 μ M by active site titration. Full length human HDAC3-FLAG was expressed in HEK-293F cells along with SMRT (amino acids 1-899)-6xHis; plasmid APP-0024) and purified using an anti-FLAG affinity chromatography with FLAG peptide (100 μ g/ml) elution. The eluted protein was then passed over an anti-HDAC1 immunoaffinity

column to remove any complexes containing HDAC1. The final concentration of the HDAC3/SMRT complex was 2.03 μ M by Western Blot analysis and 1.37 μ M by active site titration.

HDAC inhibition assays

5 The histone deacetylase activities of HDAC1, HDAC2, HDAC3, HDAC6, and HDAC8 were measured in modified FLUOR DE LYS assays in 384-well format. In this assay, HDAC enzymes are initially incubated with an ϵ -acetyl (or –trifluoroacetyl)-L-lysine-containing substrate with a C-terminal amide having aminomethylcoumarin as the amine component. HDACs cleave the ϵ -acetyl group, rendering the resulting product susceptible to
10 AMC cleavage by trypsin. The released AMC is then detected by its fluorescence. The HDAC 1, 2 assays employed buffer A, which contained 20 mM HEPES, pH 8.0, 1 mM $MgCl_2$, 137 mM NaCl, 2.7 mM KCl, 0.05% BSA. The HDAC3/SMRT assay employed buffer B, consisting of 20 mM HEPES, pH 8.0, 1 mM $MgCl_2$, 50 mM NaCl, 2.7 mM KCl, 0.05% BSA, 0.005% Tween 20, and 10 μ M IP₄. The HDAC6 assay employed buffer C,
15 consisting of 20 mM HEPES, pH 8.0, 1 mM $MgCl_2$, 137 mM NaCl, 2.7 mM KCl, 0.5 mM TCEP (Calbiochem) and 0.05% BSA. The HDAC8 assay employed buffer D, consisting of 20 mM HEPES, pH 8.0, 1 mM $MgCl_2$, 100 mM NaCl, 20 mM KCl, 0.1% n-octyl- β -D-glucoside (Anatrace) and 0.05% BSA. All steps were performed at room temperature (23°C). The assay was performed by pre-incubating serial dilutions of test compounds with the target
20 HDAC prior to initiation with substrate. Each compound was titrated in a 10-point dose response, using a 1:3 fold dilution scheme, with 0.15 μ l of solution added by ECHO555 to the plate, followed by the addition of 20 μ l of the appropriate HDAC isoform diluted in appropriate assay buffer. The incubation was allowed to proceed for 3 hours, then the appropriate substrate diluted in assay buffer (final substrate concentration $\sim K_m$) was added
25 and the reaction allowed to proceed for 60 min. Final conditions used for each assay were: 1. HDAC 1, 0.3 nM total enzyme, 20 μ M substrate BML-KI104; 2. HDAC 2, 1.5 nM total enzyme, 40 μ M substrate BML-KI104; 3. HDAC 3/SMRT, 0.3 nM total enzyme, 20 μ M substrate BML-KI104; 4. HDAC 6, 1.3 nM total enzyme, 2.5 μ M substrate BML-KI104; 5. HDAC 8, 1.3 nM total enzyme, 200 μ M substrate BML-KI178; The final high dose of test
30 compound was 30 μ M. For potent compounds, 900 nM was used as the final high dose. The reactions were stopped and developed by addition of 30 μ l of HDAC developer solution containing a saturating level of HDAC inhibitor as follows: 1. HDACs 1, 2, 3 and 6, developer BML-KI105 (stock diluted 1:125, containing 20 μ M SAHA, 2. HDAC 8, developer BML-KI176 (1:100 plus 40 μ M SAHA, and the plates were shaken to assure good

mixing, briefly centrifuged, incubated for 30 minutes at room temperature and then the fluorescence intensity (excitation 380nm, emission 460nm) measured using a PHERAstar plate reader. For each assay plate, both minimal inhibition (100% DMSO; 0% inhibition) and maximal inhibition (either 10 μ M SAHA or 100 μ M TSA; 100% inhibition) controls were added. For data analysis, background subtracted product (fluorescence) vs. time data for each inhibitor concentration was fitted using a 4-parameter fit.

All compounds prepared were tested in the binding assays with HDAC1, 2, 3, 6 and 8.

KARN ASSAY

Cell Maintenance

KARN cells (Jurkat 2C4) were licensed from the laboratory of Dr. John Karn, Case Western Reserve University, School of Medicine. The details regarding this cell line are published (Pearson, R., Kin, Y.K., Hokello, J., Lassen, K., Friedman, J., Tyagi, M., Karn, J., 2008, *J. Virol.* 82:12291-12303). The cells were grown in a T175 flask (Thermo Fisher, catalog number 159910) in RPMI 1640 containing L-glutamine and phenol red (Life Technologies, catalog number 11875-085), 5% heat inactivated fetal bovine serum (FBS; Life Technologies, catalog number 10100-147) and 100 μ g/ml Penicillin-Streptomycin (Life Technologies, catalog number 15140-122) at 37°C. An atmosphere of 5% CO₂ and 90% humidity was used for all culture work. Cells were split and reseeded into T175 flasks at a density of 0.2 x 10⁶ cells/ml, in 40 ml of media, every 3-4 days.

KARN Assay

Day 1: After the 3-4 day growth period, the cells were transferred from the T175 flask to a 50 ml conical tube and gently pelleted at 1000 rpm for 5 minutes. The supernatant was removed and the cells gently resuspended in assay media RPMI 1640 medium containing L-glutamine but without Phenol Red (Life Technologies, catalog number 11835-030), 5% FBS and 100 μ g/ml Penicillin-Streptomycin, and then reseeded such that the original flask is now divided into two T175 flasks. These flasks were returned to the incubator.

Day 2: Cell Preparation: The next day, the cells were transferred from each T175 flask to an individual 50 ml conical tube and gently pelleted at 1000 rpm for 5 minutes. The cells were gently resuspended in assay media (30 ml) and pelleted again. The cell pellets were each resuspended in 30 ml of RPMI 1640 medium containing L-glutamine but without Phenol Red, 100 μ g/ml Penicillin-Streptomycin and containing either 0.1% or 5% normal human serum (NHS; Biospecialty, catalog number 115-00 Anticoagulant free). The cells were counted using the ViCell (Beckman Coulter) and diluted as necessary. A Multidrop (Combi, Thermo

Scientific) with a sterile head was used to seed the cells into the wells of a 384-well solid black plate with lid (Perkin Elmer, catalog number 6007660) at 4000 cells/30 μ l/well for the 5% NHS assay media and 6000 cells/30 μ l/well for 0.1% NHS assay. The plates were covered and returned to the incubator prior to compound addition.

- 5 Compound Preparation: Solutions of control inhibitor suberoylanilide hydroxamic acid (SAHA; Sigma, catalog number SML0061) and test compounds in 100% DMSO were titrated into 384-well polypropylene plates (Labcyte, catalog number P-05525) using a 20-point dose response and 2-fold dilutions. The reference compounds, DMSO and SAHA were then added to the compound plate. Using the Access system (Labcyte), 120 nl of these inhibitor and control
- 10 solutions were added to the individual wells of the plates containing the cells, and the plates were then returned to the incubator for ~20 hr (range from 18-24 hr). The final high concentration for SAHA and the test compounds in the assays was 40 μ M. The final DMSO concentration in all wells was 0.4%. The minimal induction reference compound used was DMSO and the maximal induction reference compound used was SAHA (2 μ M final concentration in the assay).
- 15 Day 3: The luciferase detection reagent was prepared by transferring the contents of one bottle of Steady-Glo buffer to one bottle of Steady-Glo substrate (Steady-Glo Luciferase Assay System, Promega, catalog number E2520), followed by gently mixing until the substrate was thoroughly dissolved and the solution was equilibrated to room temperature. The cell culture assay plates were removed from the incubator and brought to room temperature (15 min). The
- 20 Steady-Glo Reagent was added to the plates (30 μ l/well), which were then covered with a black lid and incubated for 10 minutes at room temperature. The plates were then read for luminescence on an Envision (Perkin Elmer) using the ultrasensitive mode (US LUM), 0.1 counts per second and 384-well aperture. Luminescence counts in the DMSO reference wells were considered as 0% induction, while those in the 2 μ M SAHA reference wells were
- 25 considered as 100% induction. Dose response curves were plotted as test compound concentration (X-axis) vs. percent activation (Y-axis) using a 4-parameter fit based on the Levenberg-Marquardt algorithm.

All HDAC inhibitors were tested

- All compounds prepared were tested in the binding assays with HDAC1, 2, 3, 6 and 8
- 30 and in the KARN assays for their cell functional activity. This data is provided below:

ID	HDAC1 IC ₅₀ (nM)	HDAC2 IC ₅₀ (nM)	HDAC3 IC ₅₀ (nM)	HDAC6 IC ₅₀ (nM)	HDAC8 IC ₅₀ (nM)	Karn EC ₅₀ (nM) 0.1% NHS	Karn EC ₅₀ (nM) 5% NHS
2	70.40	423.3	11.48	7,202	11,970	5,537	10,530
3	29.12	111.0	17.87	18,360	8,281	8,435	10,800

4	28.44	121.3	12.26	5,619	2,992	1,386	1,824
5	14.23	42.6	5.74	6,554	2,638	786	1,181
6	12.70	40.7	5.77	1,394	420	506	1,245
7	1.78	5.9	< 1.50	3,947	1,557	235	521
8	< 1.50	3.2	< 1.50	107	199	181	246
9	3.00	12.0	2.90	1,456	6,523	1,599	2,212
10	2.21	6.2	< 1.50	1,147	1,208	130	166
11	4.20	10.1	2.78	2,275	4,237	416	484
12	3.31	11.6	< 1.50	11,460	15,120	216	186
13	0.35	4.0	0.57	11,770	15,390	522	504
14	2.22	9.1	< 1.50	20,870	17,910	151	121
15	20.40	74.9	20.33	1,687	8,923	2,688	3,525
16	27.58	91.4	4.70	29,180	7,471	570	1,804
17	7.19	26.7	< 1.50	16,400	4,701	154	537
18	13.51	53.1	4.46	> 45,000	5,335	1,142	853
19	43.60	159.4	19.13	18,960	16,780	2,729	3,771
20	1.91	18.1	2.54	9,829	5,422	294	269
21	6.75	24.2	1.82	3,537	2,022	151	911
22	1.66	7.6	< 1.50	12,510	7,927	154	201
23	< 1.50	2.4	< 1.50	25,510	6,639	83	104
24	6.34	44.3	1.75	14,420	11,070	540	575
25	3.47	34.4	3.57	15,940	5,383	775	643
26	12.25	73.8	3.36	27,850	7,566	1,834	1,504
27	44.17	228.3	11.54	> 45,000	14,820	2,628	3,612
28	129.20	388.3	38.84	> 45,000	13,390	543	2,505
29	24.26	132.6	4.43	22,460	4,204	818	1,313
30	29.30	197.8	5.61	> 45,000	14,050	2,453	3,230
31	48.89	287.4	9.89	43,300	8,791	2,045	3,426
32	114.10	619.0	22.98	> 45,000	17,620	3,341	8,058
33	15.84	78.4	26.52	> 45,000	30,240	2,867	2,766
34	65.58	254.1	45.18	18,660	> 45,000	1,590	1,791
35	1.68	12.4	1.39	875	26,540	575	559
36	2.33	12.8	< 1.50	4,441	11,270	773	851
37	60.83	206.4	7.52	> 1,500	> 45,000	712	4,839
38	75.80	363.9	10.81	> 450	> 45,000	845	6,759
39	2.80	11.7	1.78	23,610	9,370	161	259
40	0.56	6.3	0.91	17,650	6,802	166	276
41	0.41	5.0	0.67	17,460	6,364	193	165
42	97.85	177.1	100.70	8,972	> 45,000	548	1,351
43	16.98	96.1	10.69	22,540	39,610	566	1,162
44	3.70	15.6	1.93	8,249	19,190	107	175
45	35.20	154.8	18.89	14,820	20,730	1,233	1,260
46	58.92	229.2	34.81	17,060	38,080	2,112	1,669
47	0.31	< 1.5	0.21	6,301	9,835	105	97
48	0.22	1.7	0.26	9,466	12,620	77	55
49	27.98	94.9	22.20	> 15,000	> 15,000	1,060	1,284
50	0.36	2.1	0.29	9,044	12,420	247	322
51	25.85	116.9	13.81	36,930	19,650	1,564	2,071
52	6.18	26.9	3.36	> 45,000	6,929	1,731	2,207
53	47.86	219.3	26.80	43,320	29,490	1,605	3,532
54	10.67	51.3	3.12	> 45,000	12,260	254	1,111
55	35.55	164.2	12.11	> 45,000	16,190	558	2,726
56	5.73	30.5	2.23	12,590	12,500	284	452

57	4.55	26.6	2.95	14,910	7,500	226	360
61	5.67	38.5	6.22	> 900	> 900	830	763
62	49.99	330.8	111.00	> 900	> 900	2,871	3,617
63	7.91	31.3	2.20	619	3,089	234	1,786
64	21.47	83.2	5.53	3,580	6,351	647	5,036
65	44.91	306.3	20.55	> 45,000	40,050	2,186	4,388
66	147.10	> 900.0	166.60	> 450	> 1,500	27	14
67	19.64	100.8	14.21	1,283	2,594	6,483	6,347
68	8.74	126.2	8.59	6,805	4,413	> 40,000	
69	0.47	2.2	0.95	9,491	6,481	76	88
70	0.32	2.3	0.34	2,891	1,589	60	51
71	0.18	1.4	0.16	> 900	> 900	32	40
72	1.29	5.4	1.20	> 1,500	> 15,000	257	305
73	31.00	137.8	9.57	6,514	3,071	740	1,454
74	8.21	36.2	3.74	7,847	4,527	351	376
75	29.30	101.4	2.59	> 45,000	27,250	275	801
76	3.85	19.7	2.88	26,610	16,750	233	409
77	1.53	4.8	< 1.50	198	21,690	194	311
78	18.29	62.3	13.82	33,490	> 45,000	911	1,445
79	3.31	13.4	1.58	3,136	9,743	193	219
80	2.89	14.8	2.96	1,684	> 45,000	435	501
81	88.15	337.5	69.02	3,866	5,354	6,433	10,730
82	7.87	34.6	6.17	84	3,592	761	640
83	< 1.50	< 1.5	< 1.50	2,624	15,180	64	60
84	9.95	63.8	16.31	3,781	14,270	632	1,184
85	8.35	40.8	10.12	> 450	> 4,500	9,315	11,840
86	15.86	64.8	12.12	3,329	3,169	1,065	1,507
87	2.42	12.9	3.27	5,362	7,664	400	369
88	3.29	11.0	2.21	1,227	3,136	220	175
89	3.63	19.3	2.27	7,590	9,702	219	237
90	0.28	1.6	0.38	1,013	2,639	52	33
91	4.38	14.2	3.26	27,490	31,880	207	274
92	< 1.50	< 1.5	< 1.50	2,977	6,261	52	56
93	7.15	25.6	5.76	955	31,780	688	736
94	9.13	34.0	4.01	2,301	44,190	502	549
95	5.26	31.5	3.95	1,249	20,490	522	747
96	6.90	44.5	9.90	7,300	> 45,000	1,372	1,511
97	6.52	23.0	4.38	7,090	> 45,000	563	660
98	3.59	9.9	3.77	1,769	3,416	10,970	12,790
99	3.55	17.8	2.59	110	32,920	162	310
100	< 1.50	< 1.5	< 1.50	11,920	8,252	68	64
101	< 1.50	< 1.5	< 1.50	7,372	6,647	41	36
102	7.27	26.7	2.66	1,947	3,259	290	301
103	12.31	33.7	4.64	10,470	13,470	3,161	2,734
104	< 1.50	< 1.5	< 1.50	5,298	5,016	33	28
105	0.92	5.3	1.18	1,506	2,885	126	942
106	1.73	7.9	< 1.50	1,462	2,783	143	1,066
107	0.15	1.4	0.36	208	3,738	37	81
108	0.11	0.6	0.13	4,279	3,763	26	19
109	3.52	9.4	2.98	13,400	> 15,000	706	579
110	102.50	343.0	55.83	1,355	> 45,000	2,028	2,419
111	1.83	5.9	1.95	4,241	23,680	213	236
112	0.24	1.1	0.24	7,760	5,381	61	55

113	1.37	6.6	1.42	> 4,500	2,178	58	107
114	1.12	4.7	1.04	4,087	26,980	207	220
115	< 1.50	2.0	< 1.50	4,287	15,400	239	209
116	4.37	15.7	3.88	4,729	> 15,000	630	617
117	26.08	110.2	31.91	93	1,931	1,622	2,583
118	26.50	103.9	20.40	95	2,988	1,232	1,877
119	0.50	2.1	0.51	> 150	> 1,500	98	103
120	27.39	73.1	15.44	22,250	28,680	2,879	3,756
121	1.39	4.4	1.16	4,815	15,310	232	242
122	56.68	156.9	20.50	> 45,000	29,270	1,132	2,844
123	34.82	94.6	7.59	> 15,000	> 15,000	868	3,900
124	0.92	4.6	0.63	137	16,000	111	151
125	< 1.50	5.6	< 1.50	254	23,440	154	256
126	0.19	1.3	0.19	18,120	6,478	53	33
127	0.24	1.8	0.34	364	76	37	60
128	7.09	22.7	3.71	759	5,577	442	1,144
129	27.04	89.0	14.22	> 15,000	7,721	828	1,241
130	5.60	15.3	2.27	2,123	6,002	503	598
131	0.48	2.5	0.57	2,275	2,775	126	128
132	2.33	6.5	< 1.50	3,681	8,058	169	281
133	< 1.50	2.1	< 1.50	879	2,057	89	81
134	10.46	51.6	4.00	1,762	574	2,414	2,192
135	14.63	43.5	10.98	> 15,000	18,270	1,119	1,376
136	10.25	31.2	6.41	> 4,500	4,805	2,500	
137	7.78	17.2	4.72	2,758	33,540	434	443
138	1.32	7.9	1.62	1,474	10,090	210	223
139	5.28	26.1	2.39	4,447	12,040	532	552
140	0.97	4.5	0.95	611	4,113	113	155
141	12.18	38.4	1.98	1,490	2,113	146	1,452
142	18.70	84.1	10.01	3,668	5,123	311	544
143	65.13	206.6	32.01	3,665	13,120	1,245	1,333
144	< 1.50	3.0	< 1.50	> 4,500	4,487	361	317
145	5.85	12.6	2.61	5,762	4,271	641	746
146	1.06	3.3	0.64	7,729	7,705	122	112
147	2.29	10.3	< 1.50	3,662	2,768	3,584	2,852
148	0.23	2.3	0.37	749	3,561	93	110
149	0.50	3.9	0.62	3,662	2,720	92	73
150	0.19	1.4	0.25	7,055	4,375	114	135
151	5.74	21.8	3.94	5,815	3,176	583	864
152	0.94	4.0	0.85	19,180	5,062	128	96
153	5.44	13.5	6.14	10,380	> 15,000	452	447
154	6.03	19.5	2.76	18,080	12,080	518	476
155	6.91	18.4	2.05	8,937	8,135	354	398
156	5.03	15.1	1.98	7,527	5,831	1,356	1,357
157	5.39	11.9	4.01	8,527	4,178	451	557
158	0.90	4.2	1.02	> 150	> 1,500	125	200
159	0.44	2.4	0.49	2,948	4,625	73	57
160	1.89	12.1	2.75	10,420	16,830	200	234
161	54.47	162.6	32.99	11,710	26,810	1,366	1,465
162	3.24	9.5	2.84	6,531	> 45,000	257	305
163	0.76	2.3	0.60	456	> 900	57	57
164	1.52	3.2	< 1.50	74	16,650	123	170
165	1.18	8.0	2.14	11,900	14,660	140	385

166	0.37	2.2	0.32	229	5,664	469	591
167	0.97	8.0	1.12	3,320	8,272	122	253
168	0.45	3.2	0.49	300	23,590	62	80
169	< 1.50	2.2	< 1.50	83	7,579	91	78
170	5.79	16.9	4.84	923	835	436	1,155
171	0.49	2.4	0.40	309	> 15,000	134	143
172	< 1.50	< 1.5	< 1.50	326	3,873	17	21
173	< 1.50	2.0	< 1.50	972	> 15,000	85	51
174	0.55	2.1	0.43	951	1,215	67	82
175	0.18	1.1	0.25	> 150	> 150	48	84
176	0.26	1.2	0.25	> 1,500	> 4,500	45	76
177	0.24	2.0	0.28	341	2,560	22	41
178 (A10)	106.60	385.9	54.87	> 45,000	3,261	6,790	10,390
179	58.27	379.5	17.50	9,526	8,660	2,414	2,392
180	5.40	29.6	2.55	2,121	270	371	666
181	< 1.50	< 1.5	< 1.50	144	5,251	52	63
182	0.06	0.6	0.09	460	4,483	24	13
183	< 1.50	2.4	< 1.50	898	10,440	58	93
184	9.51	38.8	18.40	9,281	> 45,000	1,634	2,764
185	15.14	38.0	25.99	36,410	> 45,000	1,329	2,965
186	0.11	0.2	0.04	305	> 900	7	14
187	0.07	0.1	0.13	269	> 900	8	10
188	0.64	1.2	0.20	> 900	> 900	41	66
189	7.33	30.0	2.34	159	27,470	282	300
190	11.82	43.5	5.03	562	3,106	967	1,447
191	2.16	5.3	1.68	2,051	43,150	366	343
192	2.11	3.9	0.69	> 900	> 900	178	138
193	3.01	10.9	1.81	> 900	> 900	284	297
195	0.86	9.7	1.71	21,460	7,864	163	216
196	1.42	6.0	0.73	759	> 900	154	162
197	5.13	23.6	2.59	3,384	7,542	369	538
198	0.87	3.8	0.65	426	> 900	147	176
199	0.35	1.3	0.26	216	300	62	83
200	1.46	14.2	1.48	> 900	> 900	35	52
201	7.18	32.6	8.06	35,760	14,240	359	403
202	1.21	4.9	0.98	34,930	8,775	210	501
204	0.34	3.9	0.70	592	> 900	165	152
205	4.52	16.3	2.65	306	> 900	478	646
206	0.26	0.7	0.10	> 900	> 900	66	83
207	0.24	2.1	0.36	1,346	1,593	55	58
208	< 1.50	3.2	< 1.50	756	1,449	53	63
209 (A8)	52.94	150.8	21.60	> 900	144	1,442	4,946
210	0.26	2.2	0.54	> 900	> 900	30	39
211	< 1.50	< 1.5	< 1.50	328	6,131	17	15
215	0.89	4.0	1.15	> 900	> 900	93	93
216	7.11	34.8	13.51	786	> 900	194	278
217	4.56	50.3	10.94	> 900	> 900	576	518
218	0.05	0.7	0.12	> 900	> 900	34	34
219	0.10	1.8	0.34	> 900	> 900	78	101
220	29.87	250.8	33.46	> 900	> 900	3,809	3,931
221	8.62	54.5	13.65	> 900	> 900	344	581

222	1.61	24.5	4.67	> 900	> 900	298	364
223	1.54	9.7	2.06	237	> 900	272	559
224 (A13)	38.74	444.5	92.08	> 900	> 900	5,001	6,966
225	0.60	6.2	1.14	759	> 900	217	247
226	1.32	5.1	1.25	> 900	> 900	160	199
228	0.12	0.6	0.19	> 900	> 900	22	22
229	0.09	0.7	0.21	451	> 900	31	29
230	0.40	2.7	0.72	396	> 900	88	83
231	1.26	19.2	3.26	220	> 900	589	535
232	1.33	21.4	4.47	> 900	> 900	144	248
233	3.59	25.2	8.80	> 900	> 900	166	230
234	0.56	14.1	2.99	> 900	> 900	160	262
235	0.70	12.4	2.19	> 900	> 900	249	411
236	0.36	9.9	1.07	> 900	> 900	442	476
237	2.41	27.2	6.06	> 900	> 900	235	274
238	0.22	1.9	0.27	7,780	6,504	66	45
239	13.86	77.4	15.28	> 45,000	20,610	324	581
240	5.73	38.1	2.95	38,410	26,690	247	346
241	0.32	2.0	0.42	45	> 1,500	65	32
242	3.94	16.1	< 1.50	133	5,102	1,686	2,768
243	0.04	0.4	0.04	347	6,262	6	10
243	< 1.50	< 1.5	< 1.50	990	2,842	24	32
244	0.08	0.7	0.10	> 1,500	> 4,500	117	137
245	0.05	0.5	0.07	694	9,012	18	22
246	176.80	769.0	155.00			1,944	3,772
247	38.95	214.4	35.92	> 45,000	21,830	9,635	10,810
248	5.84	24.1	3.62	> 45,000	22,330	183	429
249	17.40	88.3	20.05	19,340	31,470	> 40,000	
250	80.70	191.7	122.40	21,920	38,290	3,731	4,103
251	2.73	12.6	1.82	41,660	29,360	143	216
252	56.56	185.3	66.08	33,930	29,640	1,597	2,883
253	30.42	111.3	16.66	> 45,000	26,770	1,866	2,335
254	29.41	131.2	29.62	> 45,000	38,670	5,343	6,040
255	168.30	490.6	81.91	12,130	5,793	13,320	14,800
256	74.64	280.2	57.95	3,934	1,095	23,660	> 40,000
257	64.84	185.0	49.69	36,600	10,420	8,085	10,560
258	7.82	23.8	3.35	38,680	16,360	7,439	7,835
259	23.85	95.0	18.29	3,144	6,144	7,929	8,177
260	13.05	52.5	5.31	28,430	> 15,000	717	913
261	25.24	102.2	16.45	2,467	4,594	1,384	1,499
262	4.42	18.8	3.36	33,490	12,580	773	851
263	< 1.50	< 1.5	< 1.50	873	4,522	140	181
264	1.79	5.9	< 1.50	1,712	1,144	78	143
265	5.14	12.4	3.86	630	4,602	142	370
266	155.20	371.6	74.14	42,490	19,280	9,898	13,850
267	46.68	169.7	34.27	6,374	11,600		
268	3.89	17.2	3.07	1,778	6,082	205	330
269	5.18	36.7	8.30	> 900	> 900	746	1,214
271	1.90	7.7	< 1.50	464	1,754	154	634
272	2.08	8.2	< 1.50	449	1,246	163	721
273	< 1.50	3.4	< 1.50	400	1,965	111	438
274	4.25	14.8	2.68	357	6,890	228	634

275	0.23	< 1.5	0.35	158	3,978	26	57
276	1.56	9.1	1.57	1,285	5,003	1,560	4,781
277	1.75	6.1	< 1.50	405	1,921	140	708
278	2.06	7.9	< 1.50	479	980	166	1,001
279	1.94	6.7	< 1.50	362	5,116	160	860
280	29.98	122.3	10.63	11,140	10,800	1,020	919
281	22.49	93.1	10.11	3,725	20,890	2,138	2,173
282	1.80	8.1	< 1.50	2,195	10,710	294	247
283	0.98	5.8	1.08	1,458	8,576	251	283
284	18.65	82.1	6.09	13,450	14,950	606	598
285	5.47	24.6	2.10	260	9,186	257	1,008
286	1.00	6.1	1.08	342	3,870	116	406
287	3.66	18.6	11.86	351	2,778	81	325
288	7.10	26.5	2.32	285	5,280	295	1,317
289	63.14	258.7	21.72	10,430	3,748	1,064	1,090
290	15.38	73.5	4.08	5,988	5,232	415	519
291	0.23	2.0	0.31	741	> 15,000	192	295
292	5.85	23.6	< 1.50	> 1,500	> 4,500	992	1,379
293	2.03	8.2	2.14	727	8,197	75	175
294	0.46	3.9	0.78	415	4,924	63	277
295	6.44	17.4	1.73	973	3,231	113	180
296	3.68	13.8	11.99	41,600	3,606	232	6,839
297	27.88	120.3	9.69	8,172	8,460	5,842	15,790
298	36.46	143.7	10.45	5,066	1,693	7,009	11,750
299	12.19	35.8	6.56	2,364	27,810	7,001	9,267
300	199.00	801.6	38.74	23,180	11,090	9,206	10,250
301	24.63	77.6	15.79	3,479	29,520	24,250	
302	49.36	121.3	37.56	821	> 45,000	4,462	7,431
303	17.23	40.5	10.49	982	29,230	2,429	4,255
304	3.59	8.0	3.23	447	20,820	17,290	
305	47.28	160.0	21.71	636	> 45,000	2,204	3,089
306	12.86	58.2	9.93	1,169	> 45,000	690	691
307	62.93	617.4	16.95	12,140	13,490	3,700	2,571
308	27.31	97.7	27.35	1,277	> 45,000	2,690	3,699
309	6.91	19.3	7.19	529	23,980	1,353	1,917
310	33.02	167.2	10.41	6,048	6,496	1,493	1,922
311	0.99	5.4	1.28	385	2,657	131	841
312	1.62	7.1	< 1.50	299	2,024	155	633
313	< 1.50	2.3	< 1.50	246	3,018	57	272
314	1.03	5.1	0.86	405	2,573	131	811
315	< 1.50	3.7	< 1.50	459	1,947	86	688
316	< 1.50	5.4	< 1.50	387	1,684	151	660
317	0.87	5.0	0.84	186	4,890	591	1,718
318	6.22	27.3	2.02	551	1,195	861	4,595
319	20.88	41.4	2.59	1,169	2,271	1,560	9,848
320	6.07	31.4	1.68	709	14,650	339	1,366
321	0.19	1.4	0.19	158	3,379	27	83
322	0.72	3.6	0.80	219	2,491	74	287
323	4.74	12.4	< 1.50	376	2,295	284	1,292
324	4.91	13.5	< 1.50	1,444	> 4,500	1,172	1,210
325	0.24	1.7	0.31	423	> 4,500	154	216
326	3.27	9.0	1.58	> 1,500	> 4,500	2,395	3,816
327	0.76	5.3	0.93	187	3,872	73	232

328	1.24	6.5	1.23	395	3,309	73	322
329	4.76	18.8	1.87	> 150	7,035	262	1,142
330	8.28	31.4	2.87	632	13,690	309	1,149
331	2.24	10.3	1.69	490	2,033	154	896
332	2.73	13.1	3.10	745	14,090	78	343
333	3.46	9.9	< 1.50	1,107	6,093	113	719
334	< 1.50	< 1.5	< 1.50	552	> 4,500	145	236
335	0.29	2.3	0.36	329	3,279	31	63
336	0.09	0.7	0.09	189	3,129	16	30
337	0.11	< 1.5	0.18	160	5,664	32	57
338	0.27	2.0	0.28	405	2,934	44	111
339	1.95	9.3	< 1.50	518	2,328	162	720
340	< 1.50	2.2	< 1.50	184	3,721	19	83
341	0.42	2.5	0.43	8,970	11,920	44	70
342	0.48	5.0	0.67	> 45,000	> 45,000	211	159
344	< 1.50	1.6	< 1.50	862	3,416	37	54
345	4.14	22.5	5.24	260	2,865	305	835
346	< 1.50	< 1.5	< 1.50	545	3,161	46	57
347	0.40	2.2	0.41	4,218	8,301	42	59
348	0.24	< 1.5	0.33	1,528	7,183	27	29
349	0.28	3.1	0.46	7,689	10,060	51	46
350	0.31	2.5	0.45	4,440	5,548	19	29
351	1.57	7.1	1.32	1,473	5,829		
352	0.53	3.1	0.63	693	4,359	115	97
353	0.38	3.3	0.54	5,559	8,867	142	166
354	1.82	11.3	2.18	354	798	264	295
355	3.30	9.5	< 1.50	382	3,159	356	1,353
356	< 1.50	2.5	< 1.50	664	> 4,500		
357	0.55	4.1	0.75	7,838	9,219	50	58
358	0.20	1.6	0.29	2,019	5,568	101	134
359	< 1.50	< 1.5	< 1.50	2,277	6,274	54	44
360	< 1.50	5.0	< 1.50	4,403	9,315	231	162
361	0.19	1.1	0.15	221	38,700	26	24
362	1.89	6.9	< 1.50	765	3,478	298	1,276
363	85.48	234.4	33.45	2,037	25,520	2,080	4,810
364	62.97	247.7	21.79	1,990	32,150	1,768	4,311
365	61.25	208.1	23.20	1,943	28,370	1,554	3,826
366	89.42	321.5	37.26	2,760	> 45,000	1,496	5,361
367	25.86	67.6	10.69	2,111	21,420	1,326	4,492
368	50.54	149.3	20.61	2,377	21,700	1,572	5,241
369	18.55	68.2	11.81	2,498	19,860	804	1,684
370	10.76	41.8	8.87	1,744	8,646	752	1,434
371	86.67	286.6	30.23	4,655	> 45,000	5,000	6,040
372	92.55	416.1	14.10	10,210	7,734	2,652	5,246
373	95.64	422.6	18.77	10,100	6,672	1,647	5,340
374	92.74	422.9	15.77	11,220	8,176	2,581	5,397
375	116.60	478.7	19.88	10,200	8,880	1,448	9,329
376	49.95	239.1	9.02	10,850	4,842	1,862	3,676
377	47.10	232.5	6.90	8,289	3,015		
378	46.05	219.8	7.08	10,760	2,956	1,309	2,992
379	21.87	100.1	4.77	8,588	3,288	472	771
380	69.82	326.3	8.92	16,200	6,332	1,917	2,407
381	178.70	637.3	26.06	32,310	7,472	2,735	6,414

382	32.91	145.5	8.02	12,110	6,637	665	1,074
383	96.53	427.1	16.68	16,050	8,956	2,624	3,260
384	37.31	153.8	12.58	10,290	8,933	2,215	2,408
386	7.82	54.7	12.42	> 900	> 900	934	1,063
387	25.80	207.1	48.14	> 900	> 900	1,545	1,699
389	21.40	98.3	30.15	> 900	> 900	1,120	1,553
390	18.02	158.7	39.42	309	> 900	674	1,676
391	9.57	74.5	18.60	> 900	> 900	460	541
393	0.05	0.1	0.05	325	> 900	21	22
394	0.05	0.3	0.10	76	> 900	18	24
395	2.42	36.3	6.78	> 900	> 900	618	725
397	1.36	6.6	2.66	> 900	> 900	279	327
398	185.70	809.6	240.70	> 900	> 900	5,504	10,190
400	6.41	39.7	8.61	> 900	> 900	577	557
401	32.08	179.0	51.33	> 900	> 900	1,845	2,210
403	248.30	> 900.0	283.20	> 900	> 900	5,344	5,598
404	367.40	> 900.0	501.40	> 900	> 900	> 40,000	> 40,000
405	0.30	2.0	0.70	163	> 900	65	57
406	0.83	2.5	1.05	> 900	300	280	279
407	0.90	20.2	3.68	> 900	> 900	336	977
408	3.82	36.1	7.37	647	> 900	250	593
409	10.46	100.2	32.18	> 900	> 900	811	1,862
410	17.55	143.4	43.93	> 900	> 900	663	1,391
A30 (411)	60.59	304.3	95.60	> 900	542	1,487	5,610
413	16.21	155.5	61.85	> 900	> 900	348	1,266
414	> 900.00	> 900.0	> 900.00	> 900	> 900	> 40,000	> 40,000
415	3.31	33.1	7.82	> 900	> 900	105	118
416	< 1.58	4.5	1.11	> 900	> 900	11	15
420	484.30	329.9	327.70	> 900	> 900	11,850	> 40,000
422	0.17	0.7	0.08	113	> 900	15	10

Treatment or Prevention of HIV Infection

The Compounds of Formula I may be useful in the activation of HIV latency, the treatment of HIV infection and/or reduction of the likelihood or severity of symptoms of HIV infection and the inhibition of HIV viral replication and/or HIV viral production in a cell-based system. For example, the Compounds of Formula I may be useful in treating infection by HIV after suspected past exposure to HIV by such means as blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to subject blood during surgery or other medical procedures.

Accordingly, in one embodiment, the invention provides methods for treating HIV infection in a subject, the methods comprising administering to the subject an effective amount of at least one Compound of Formula I or a pharmaceutically acceptable salt or prodrug thereof. In a specific embodiment, the amount administered is effective to treat or prevent infection by HIV in the subject. In another specific embodiment, the amount administered is

effective to inhibit HIV viral replication and/or viral production in the subject. In one embodiment, the HIV infection has progressed to AIDS.

The Compounds of Formula I are also useful in the preparation and execution of screening assays for antiviral compounds. For example the Compounds of Formula I may be useful for identifying resistant HIV cell lines harboring mutations, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the Compounds of Formula I may be useful in establishing or determining the binding site of other antivirals to the HIV Integrase.

The compositions and combinations of the present invention may be useful for treating a subject suffering from infection related to any HIV genotype.

Combination Therapy

In another embodiment, the present methods for treating or preventing HIV infection can further comprise the administration of one or more additional therapeutic agents which are not Compounds of Formula I.

In one embodiment, the additional therapeutic agent is an antiviral agent.

In another embodiment, the additional therapeutic agent is an immunomodulatory agent, such as an immunosuppressive agent.

Accordingly, in one embodiment, the present invention provides methods for treating a viral infection in a subject, the method comprising administering to the subject: (i) at least one Compound of Formula I (which may include two or more different Compounds of Formula I), or a pharmaceutically acceptable salt or prodrug thereof, and (ii) at least one additional therapeutic agent that is other than a Compound of Formula I, wherein the amounts administered are together effective to treat or prevent a viral infection.

When administering a combination therapy of the invention to a subject, therapeutic agents in the combination, or a pharmaceutical composition or compositions comprising therapeutic agents, may be administered in any order such as, for example, sequentially, concurrently, together, simultaneously and the like. The amounts of the various actives in such combination therapy may be different amounts (different dosage amounts) or same amounts (same dosage amounts). Thus, for non-limiting illustration purposes, a Tricyclic Heterocycle Compound and an additional therapeutic agent may be present in fixed amounts (dosage amounts) in a single dosage unit (*e.g.*, a capsule, a tablet and the like).

In one embodiment, at least one Compound of Formula I is administered during a time when the additional therapeutic agent(s) exert their prophylactic or therapeutic effect, or *vice versa*.

In another embodiment, at least one Compound of Formula I and the additional therapeutic agent(s) are administered in doses commonly employed when such agents are used as monotherapy for treating a viral infection.

5 In another embodiment, at least one Compound of Formula I and the additional therapeutic agent(s) are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating a viral infection.

10 In still another embodiment, at least one Compound of Formula I and the additional therapeutic agent(s) act synergistically and are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating a viral infection.

In one embodiment, at least one Compound of Formula I and the additional therapeutic agent(s) are present in the same composition. In one embodiment, this composition is suitable for oral administration. In another embodiment, this composition is suitable for intravenous administration. In another embodiment, this composition is suitable for subcutaneous administration. In still another embodiment, this composition is suitable for parenteral administration.

20 Viral infections and virus-related disorders that may be treated or prevented using the combination therapy methods of the present invention include, but are not limited to, those listed above.

In one embodiment, the viral infection is HIV infection.

In another embodiment, the viral infection is AIDS.

25 The at least one Compound of Formula I and the additional therapeutic agent(s) can act additively or synergistically. A synergistic combination may allow the use of lower dosages of one or more agents and/or less frequent administration of one or more agents of a combination therapy. A lower dosage or less frequent administration of one or more agents may lower toxicity of therapy without reducing the efficacy of therapy.

In one embodiment, the administration of at least one Compound of Formula I and the additional therapeutic agent(s) may inhibit the resistance of a viral infection to these agents.

30 As noted above, the present invention is also directed to use of a compound of Formula I with one or more anti-HIV agents. An "anti-HIV agent" is any agent which is directly or indirectly effective in the inhibition of HIV reverse transcriptase or another enzyme required for HIV replication or infection, the treatment or prophylaxis of HIV infection, and/or the treatment, prophylaxis or delay in the onset or progression of AIDS. It is understood that an

anti-HIV agent is effective in treating, preventing, or delaying the onset or progression of HIV infection or AIDS and/or diseases or conditions arising therefrom or associated therewith. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of one or more anti-HIV agents selected from HIV antiviral agents, immunomodulators, anti-infectives, or vaccines useful for treating HIV infection or AIDS. Suitable HIV antivirals for use in combination with the compounds of the present invention include, for example, those listed in Table A as follows:

Table A

Name	Trade Name
abacavir, ABC	Ziagen®
abacavir + lamivudine	Epzicom®
abacavir + lamivudine + zidovudine	Trizivir®
amprenavir	Agenerase®
atazanavir	Reyataz®
AZT, zidovudine, azidothymidine	Retrovir®
darunavir	Prezista®
ddC, zalcitabine, dideoxycytidine	Hivid®
ddI, didanosine, dideoxyinosine	Videx®
ddI (enteric coated)	Videx EC®
delavirdine, DLV	Rescriptor®
dolutegravir	Tivicay®
doravirine	
efavirenz, EFV	Sustiva®, Stocrin®
efavirenz + emtricitabine + tenofovir DF	Atripla®
EFdA (4'-ethynyl-2'-fluoro-2'-deoxyadenosine)	
emtricitabine, FTC	Emtriva®
emtricitabine + tenofovir DF	Truvada®
emvirine	Coactinon®
enfuvirtide	Fuzeon®
enteric coated didanosine	Videx EC®
etravirine, TMC-125	Intelence®
fosamprenavir calcium	Lexiva®
indinavir	Crixivan®
lamivudine, 3TC	Epivir®
lamivudine + zidovudine	Combivir®
lopinavir	
lopinavir + ritonavir	Kaletra®
maraviroc	Selzentry®
nelfinavir	Viracept®
nevirapine, NVP	Viramune®
raltegravir	Isentress®
rilpivirine, TMC-278	Edurant®
ritonavir	Norvir®
saquinavir	Invirase®, Fortovase®
stavudine, d4T, didehydrodeoxythymidine	Zerit®

tenofovir DF (DF = disoproxil fumarate), TDF	Viread®
tipranavir	Aptivus®

Some of the drugs listed in the table are used in a salt form; e.g., abacavir sulfate, indinavir sulfate, atazanavir sulfate, nelfinavir mesylate.

In one embodiment, one or more anti-HIV drugs are selected from, raltegravir, lamivudine, abacavir, ritonavir, darunavir, atazanavir, emtricitabine, tenofovir, rilpivirine, doravirine, EFdA and lopinavir.

In another embodiment, the compound of formula I is used in combination with raltegravir.

In another embodiment, the compound of formula I is used in combination with lamivudine.

In still another embodiment, the compound of formula I is used in combination with atazanavir.

In another embodiment, the compound of formula I is used in combination with darunavir.

In another embodiment, the compound of formula I is used in combination with rilpivirine.

In one embodiment, the compound of formula I is used in combination with lamivudine and abacavir.

In another embodiment, the compound of formula I is used in combination with EFdA.

In another embodiment, the compound of formula I is used in combination with emtricitabine and tenofovir.

In still another embodiment, the compound of formula I is used in combination with doravirine.

In another embodiment, the compound of formula I is used in combination with ritonavir and lopinavir.

In one embodiment, the compound of formula I is used in combination with abacavir and lamivudine.

In another embodiment, the compound of formula I is used in combination with lopinavir and ritonavir.

In one embodiment, the present invention provides pharmaceutical compositions comprising (i) a compound of formula I or a pharmaceutically acceptable salt or prodrug thereof; (ii) a pharmaceutically acceptable carrier; and (iii) one or more additional anti-HIV agents

selected from lamivudine, abacavir, ritonavir and lopinavir, or a pharmaceutically acceptable salt or prodrug thereof, wherein the amounts present of components (i) and (iii) are together effective for the treatment or prophylaxis of infection by HIV or for the treatment, prophylaxis, or delay in the onset or progression of AIDS in the subject in need thereof.

5 In another embodiment, the present invention provides a method for the treatment or prophylaxis of infection by HIV or for the treatment, prophylaxis, or delay in the onset or progression of AIDS in a subject in need thereof, which comprises administering to the subject (i) a compound of formula I or a pharmaceutically acceptable salt or prodrug thereof and (ii) one or more additional anti-HIV agents selected from lamivudine, abacavir, ritonavir and lopinavir,
10 or a pharmaceutically acceptable salt or prodrug thereof, wherein the amounts administered of components (i) and (ii) are together effective for the treatment or prophylaxis of infection by HIV or for the treatment, prophylaxis, or delay in the onset or progression of AIDS in the subject in need thereof.

 It is understood that the scope of combinations of the compounds of this invention
15 with anti-HIV agents is not limited to the HIV antivirals listed in Table A, but includes in principle any combination with any pharmaceutical composition useful for the treatment or prophylaxis of AIDS. The HIV antiviral agents and other agents will typically be employed in these combinations in their conventional dosage ranges and regimens as reported in the art, including, for example, the dosages described in the Physicians' Desk Reference, Thomson PDR,
20 Thomson PDR, 57th edition (2003), the 58th edition (2004), the 59th edition (2005), and the like. The dosage ranges for a compound of the invention in these combinations are the same as those set forth above.

 The doses and dosage regimen of the other agents used in the combination therapies of the present invention for the treatment or prevention of HIV infection may be
25 determined by the attending clinician, taking into consideration the approved doses and dosage regimen in the package insert; the age, sex and general health of the subject; and the type and severity of the viral infection or related disease or disorder. When administered in combination, the Tricyclic Heterocycle Compound(s) and the other agent(s) may be administered simultaneously (*i.e.*, in the same composition or in separate compositions one right after the
30 other) or sequentially. This is particularly useful when the components of the combination are given on different dosing schedules, *e.g.*, one component is administered once daily and another component is administered every six hours, or when the pharmaceutical compositions are different, *e.g.*, one is a tablet and one is a capsule. A kit comprising the separate dosage forms is therefore advantageous.

Compositions and Administration

When administered to a subject, the Compounds of Formula I may be administered as a component of a composition that comprises a pharmaceutically acceptable carrier or vehicle. The present invention provides pharmaceutical compositions comprising an effective amount of at least one Compound of Formula I and a pharmaceutically acceptable carrier. In the pharmaceutical compositions and methods of the present invention, the active ingredients will typically be administered in admixture with suitable carrier materials suitably selected with respect to the intended form of administration, *i.e.*, oral tablets, capsules (either solid-filled, semi-solid filled or liquid filled), powders for constitution, oral gels, elixirs, dispersible granules, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier, such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid forms) and the like. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. Powders and tablets may be comprised of from about 0.5 to about 95 percent inventive composition. Tablets, powders, cachets and capsules may be used as solid dosage forms suitable for oral administration.

Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrants include starch, methylcellulose, guar gum, and the like. Sweetening and flavoring agents and preservatives may also be included where appropriate.

Liquid form preparations include solutions, suspensions and emulsions and may include water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously

therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimize therapeutic effects, *i.e.*, antiviral activity and the like. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

In one embodiment, the one or more Compounds of Formula I are administered orally.

In another embodiment, the one or more Compounds of Formula I are administered intravenously.

In one embodiment, a pharmaceutical preparation comprising at least one Compound of Formula I is in unit dosage form. In such form, the preparation is subdivided into unit doses containing effective amounts of the active components.

Compositions may be prepared according to conventional mixing, granulating or coating methods, respectively, and the present compositions can contain, in one embodiment, from about 0.1% to about 99% of the Compound(s) of Formula I by weight or volume. In various embodiments, the present compositions can contain, in one embodiment, from about 1% to about 70% or from about 5% to about 60% of the Compound(s) of Formula I by weight or volume.

The compounds of Formula I may be administered orally in a dosage range of 0.001 to 1000 mg/kg of mammal (e.g., human) body weight per day in a single dose or in divided doses. One dosage range is 0.01 to 500 mg/kg body weight per day orally in a single dose or in divided doses. Another dosage range is 0.1 to 100 mg/kg body weight per day orally in single or divided doses. For oral administration, the compositions may be provided in the form of tablets or capsules containing 1.0 to 500 milligrams of the active ingredient, particularly 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the subject to be treated. The specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health,

sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

For convenience, the total daily dosage may be divided and administered in portions during the day if desired. In one embodiment, the daily dosage is administered in one portion. In another embodiment, the total daily dosage is administered in two divided doses over a 24 hour period. In another embodiment, the total daily dosage is administered in three divided doses over a 24 hour period. In still another embodiment, the total daily dosage is administered in four divided doses over a 24 hour period.

The unit dosages of the Compounds of Formula I may be administered at varying frequencies. In one embodiment, a unit dosage of a Compound of Formula I may be administered once daily. In another embodiment, a unit dosage of a Compound of Formula I may be administered twice weekly. In another embodiment, a unit dosage of a Compound of Formula I may be administered once weekly. In still another embodiment, a unit dosage of a Compound of Formula I may be administered once biweekly. In another embodiment, a unit dosage of a Compound of Formula I may be administered once monthly. In yet another embodiment, a unit dosage of a Compound of Formula I may be administered once bimonthly. In another embodiment, a unit dosage of a Compound of Formula I may be administered once every 3 months. In a further embodiment, a unit dosage of a Compound of Formula I may be administered once every 6 months. In another embodiment, a unit dosage of a Compound of Formula I may be administered once yearly.

The amount and frequency of administration of the Compounds of Formula I will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the subject as well as severity of the symptoms being treated. The compositions of the invention can further comprise one or more additional therapeutic agents, selected from those listed above herein.

Kits

In one aspect, the present invention provides a kit comprising a therapeutically effective amount of at least one Compound of Formula I, or a pharmaceutically acceptable salt or prodrug of said compound and a pharmaceutically acceptable carrier, vehicle or diluent.

In another aspect the present invention provides a kit comprising an amount of at least one Compound of Formula I, or a pharmaceutically acceptable salt or prodrug of said compound and an amount of at least one additional therapeutic agent listed above, wherein the amounts of the two or more active ingredients result in a desired therapeutic effect. In one embodiment, the one or more Compounds of Formula I and the one or more additional

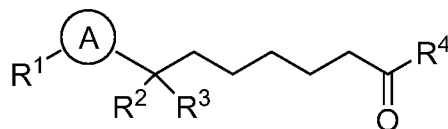
therapeutic agents are provided in the same container. In one embodiment, the one or more Compounds of Formula I and the one or more additional therapeutic agents are provided in separate containers.

The present invention is not to be limited by the specific embodiments disclosed in the examples that are intended as illustrations of a few aspects of the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the scope of the appended claims.

A number of references have been cited herein, the entire disclosures of which are incorporated herein by reference.

WHAT IS CLAIMED IS:

1. A compound of the formula:



wherein $\textcircled{\text{A}}$ is a five-membered heteroaryl ring which is optionally substituted with halo,
 5 cyano, R^5 , R^6 , $(\text{C}=\text{O})\text{N}(\text{R}^5)_2$, $\text{NR}^5(\text{C}=\text{O})\text{N}(\text{R}^5)_2$, $(\text{C}=\text{O})\text{R}^6$ or $(\text{C}_{1-3} \text{ alkyl})\text{O}(\text{C}=\text{O})\text{R}^4$;

R^1 is phenyl, bicyclic aryl, tricyclic aryl or heteroaryl, which may be monocyclic, bicyclic or
 tricyclic, wherein said phenyl and heteroaryl groups are optionally substituted with one to four
 groups independently selected from the group consisting of halo, oxo, cyano, C_{2-3} alkenyl, R^5 ,
 R^6 , OR^5 , $\text{N}(\text{R}^5)_2$, $(\text{C}=\text{O})\text{NHR}^6$, $\text{NR}^5(\text{C}=\text{O})\text{N}(\text{R}^5)_2$, $\text{NR}^5(\text{C}=\text{NR}^5)\text{N}(\text{R}^5)_2$, SO_2R^5 , $\text{SO}_2\text{N}(\text{R}^5)_2$,
 10 $\text{NR}^5\text{SO}_2\text{R}^5$, and $\text{NR}^5\text{SO}_2\text{N}(\text{R}^5)_2$;

R^2 is selected from the group consisting of hydrogen, $\text{N}(\text{R}^5)_2$, $\text{NR}^5(\text{C}=\text{O})\text{R}^5$, $\text{NR}^5(\text{C}=\text{O})\text{N}(\text{R}^5)_2$,
 $\text{NR}^5(\text{C}=\text{NR}^5)\text{N}(\text{R}^5)_2$, $\text{NR}^5(\text{C}=\text{O})\text{R}^6$, $\text{NR}^5(\text{C}_{1-3}\text{alkyl})\text{R}^6$ and $\text{NR}^5(\text{C}=\text{O})(\text{C}_{1-3}\text{alkyl})\text{R}^6$;

R^3 is selected from hydrogen, C_{1-6} alkyl or CH_2OR^5 ;

R^4 is C_{1-6} alkyl, or C_{3-6} cycloalkyl, which is optionally substituted with one to three substituents
 15 independently selected from the group consisting of halo and hydroxyl, or C_{3-6} cycloalkyl;
 each R^5 is independently hydrogen, cyano, or C_{1-6} alkyl, which is optionally substituted with
 NH_2 , $\text{N}(\text{CH}_3)_2$, $\text{NH}(\text{CH}_3)_2$, $\text{N}(\text{CH}_2\text{CH}_3)_2$, or one to three halo;

R^6 is

(a) heterocyclyl, which may be monocyclic, bicyclic or tricyclic,

20 (b) C_{3-6} cycloalkyl,

(c) phenyl, or

(d) heteroaryl, which may be monocyclic, bicyclic or tricyclic,

wherein said heterocyclyl, cycloalkyl, phenyl and heteroaryl groups are optionally substituted
 with one to four groups independently selected from the group consisting of halo, cyano, oxo,

25 R^5 , OR^5 , $(\text{C}=\text{O})\text{R}^5$, $(\text{C}=\text{O})\text{OR}^5$, $\text{N}(\text{R}^5)_2$, $(\text{C}=\text{O})\text{N}(\text{R}^5)_2$, $\text{NR}^5(\text{C}=\text{O})\text{R}^5$, $\text{NR}^5(\text{C}=\text{O})\text{N}(\text{R}^5)_2$,

$\text{NR}^5(\text{C}=\text{NR}^5)\text{N}(\text{R}^5)_2$, SO_2R^5 , $\text{SO}_2\text{N}(\text{R}^5)_2$, $\text{NR}^5\text{SO}_2\text{R}^5$, $\text{NR}^5\text{SO}_2\text{N}(\text{R}^5)_2$, C_{2-3} alkenyl, benzyl,

benzyl- OR^5 , $\text{CH}_2(\text{C}_{3-6} \text{ cycloalkyl})$, $\text{CH}_2(\text{heteroaryl})$, heteroaryl, heterocyclyl and C_{3-6} cycloalkyl;
 or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1 wherein $\textcircled{\text{A}}$ is selected from imidazolyl, oxazolyl,
 30 oxadiazolyl or triazolyl, wherein said groups are optionally substituted with halo, cyano or C_{1-3}
 alkyl; or a pharmaceutically acceptable salt thereof.

3. The compound of Claim 1 or 2 wherein R^4 is ethyl; or a pharmaceutically acceptable salt thereof.

4. The compound of any one of Claims 1 to 3 wherein R^1 is azaindazolyl, benzoxazolyl, benzothiazolyl, carbazolyl, chromenyl, cinnoliny, dihydroisoquinoliny, imidazolyl, imidazopyridiny, indazolyl, isoquinoliny, naphthaleny, naphthyridiny, phenyl, pyridiny, pyrimidiny, quinoliny, quinoxaliny, or tetrahydroepaminonaphthaleny, tetrahydromethanonaphthaleny, wherein said groups are optionally substituted with one to three groups optionally selected from the group consisting of halo, oxo, cyano, C_{2-3} alkenyl, R^5 , R^6 , OR^5 , $N(R^5)_2$, $(C=O)NHR^6$ and SO_2R^5 ; or a pharmaceutically acceptable salt thereof.

5. The compound of any one of Claims 1 to 4 wherein R^2 is $NH(C=O)R^6$ or $NH(C=O)(C_{1-3}alkyl)R^6$ and R^6 is selected from the group consisting of azaspirobicyclooctanecyclopropanyl, azetidiny, azaspirohepatnyl, azaspirohexanyl, azaspirononanyl, azaspirooctanyl, cyclopropyl, diazaspirooctanyl, dihydropyrroloindoly, dihydroethanoquinoliny, isoxazolyl, oxadiazaspirodeceny, oxaspirooctanyl, pyridiny, quinuclidine, spirooctanyl, spirocyclohexanefuopyridiny, tetrahydrocyclopentaindoly, tetrahydropyranyl and thiazolyl, wherein said groups are optionally substituted with one or two groups independently selected from the group consisting of halo, oxo, R^5 , OR^5 , $(C=O)N(R^5)_2$, C_{2-3} alkenyl, benzyl, benzyl- OR^5 , $CH_2(C_{3-6} cycloalkyl)$, $CH_2(heteroaryl)$, heteroaryl and C_{3-6} cycloalkyl; or a pharmaceutically acceptable salt thereof.

6. The compound of any one of Claims 1 to 5 wherein R^3 is hydrogen, or a pharmaceutically acceptable salt thereof.

7. A compound being one of the compounds numbered 1-422 in the above specification, or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition comprising an effective amount of a compound of Claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

9. A method for the inhibition of HDAC in a subject in need thereof which comprises administering to the subject an effective amount of a compound of any of Claims 1 to 7, or a pharmaceutically acceptable salt thereof.

10. A method for the treatment of infection by HIV or for the treatment, prophylaxis, or delay in the onset or progression of AIDS in a subject in need thereof, which comprises administering to the subject an effective amount of a compound of any of Claims 1 to 7, or a pharmaceutically acceptable salt thereof.

11. A compound of any of Claims 1 to 7, or a pharmaceutically acceptable salt thereof, for use in the preparation of a medicament for the inhibition of HDAC, for the treatment

or prophylaxis of infection by HIV, or for the treatment, prophylaxis, or delay in the onset or progression of AIDS in a subject in need thereof.

12. The pharmaceutical composition of claim 8, further comprising one or more additional therapeutic agents selected from lamivudine, abacavir, ritonavir, darunavir, atazanavir, emtricitabine, tenofovir, rilpivirine and lopinavir.

13. The method of claim 10, further comprising administering to the subject one or more additional therapeutic agents selected from lamivudine, abacavir, ritonavir, darunavir, atazanavir, emtricitabine, tenofovir, rilpivirine and lopinavir, wherein the amounts administered of the compound of any of Claims 1 to 7 and the one or more additional therapeutic agents, are together effective to treat infection by HIV or to treat, prevent or delay the onset or progression of AIDS.