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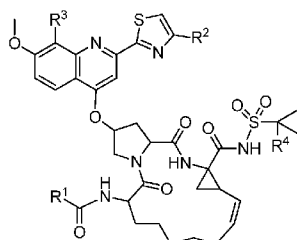
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(54) Title: COMPOUNDS AS HEPATITIS C INHIBITORS AND USES THEREOF IN MEDICINE



(I)

(57) Abstract: Provided herein are compounds as hepatitis C inhibitors and uses thereof in medicine. Specifically, provided herein is a compound of Formula (I) or a stereoisomer, a tautomer, an enantiomer, an N-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof, which can be used for treating HCV infection or hepatitis C diseases. Also provided herein are a pharmaceutically acceptable composition containing such compound and a method of treating HCV infection or hepatitis C diseases comprising administering the compound or pharmaceutical composition thereof disclosed herein.



COMPOUNDS AS HEPATITIS C INHIBITORS AND USES THEREOF IN MEDICINE**CROSS-REFERENCE TO RELATED APPLICATION**

[0001] This application claims priority to Chinese Patent Serial No. 201510080564.5, filed with the State Intellectual Property Office of China on February 13, 2015, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to a field of medicine, and compounds and compositions thereof for treating Hepatitis C virus (HCV) infection, and use of the compounds and the compositions thereof, and methods thereof. Particularly, the compounds disclosed herein can be used for inhibiting NS3/4A protease. More specifically, the present invention relates to compounds and pharmaceutical compositions thereof which can be used for inhibiting a function of NS3/4A protein coded by the hepatitis C virus (HCV), and a method of inhibiting NS3/4A protein function.

BACKGROUND OF THE INVENTION

[0003] HCV is a major human pathogen, infecting an estimated 170 million persons worldwide roughly five times the number infected by human immunodeficiency virus type 1. A substantial fraction of these HCV infected individuals develop serious progressive liver disease, including cirrhosis and hepatocellular carcinoma. Chronic HCV infection is thus a major worldwide cause of liver-related premature mortality.

[0004] Presently, the most effective HCV therapy employs a combination of alpha-interferon and ribavirin, leading to sustained efficacy in 40% of patients. Recent clinical results demonstrate that pegylated alpha-interferon is superior to unmodified alpha-interferon as monotherapy. However, even with experimental therapeutic regimens involving combinations of pegylated alpha-interferon and ribavirin, a substantial fraction of patients do not have a sustained reduction in viral load. The treatment has side effects in many patients, so they do not durably respond to treatment. Thus, new and effective methods of treating HCV infection are urgently needed.

[0005] HCV is a positive-stranded RNA virus. Based on a comparison of the deduced amino acid sequence and the extensive similarity in the 5' untranslated region, HCV has been classified as a separate genus in the Flaviviridae family. All members of the Flaviviridae family have

enveloped virions that contain a positive stranded RNA genome encoding all known virus-specific proteins via translation of a single, uninterrupted, open reading frame (ORF).

[0006] Considerable heterogeneity is found within nucleotide and encoded amino acid sequence throughout the HCV genome. At least seven major genotypes have been characterized, and more than 50 subtypes have been described. In HCV infected cells, viral RNA is translated into a polyprotein that is cleaved into ten individual proteins. At the amino terminus are structural proteins, follows E1 and E2. Additionally, there are six non-structural proteins, NS2, NS3, NS4A, NS4B, NS5A and NS5B, which play a function role in the HCV lifecycle (see, for example, Lindenbach *et al.*, *Nature*, **2005**, 436, 933-938).

[0007] The major genotypes of HCV differ in their distribution worldwide, and the clinical significance of the genetic heterogeneity of HCV remains elusive despite numerous studies of the possible effect of genotypes on pathogenesis and therapy.

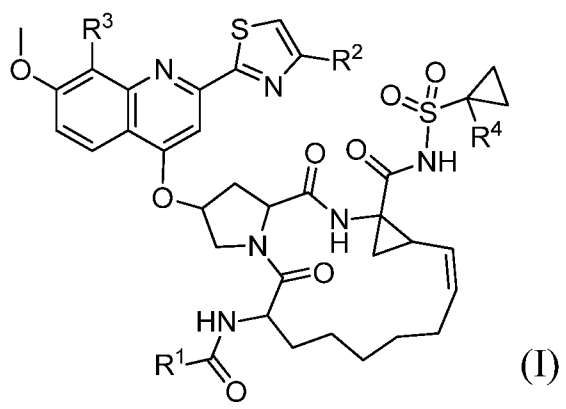
[0008] The single strand HCV RNA genome is approximately 9500 nucleotides in length and has a single open reading frame (ORF) encoding a single large polyprotein of about 3000 amino acids. In infected cells, this polyprotein is cleaved at multiple sites by cellular and viral proteases to produce the structural and non-structural (NS) proteins. In the case of HCV, the generation of mature non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A and NS5B) is effected by two viral proteases. The first one is believed to be a metalloprotease and cleaves at the NS2-NS3 junction; the second one is a serine protease within the N-terminal region of NS3 (also referred herein as NS3 protease) and mediates all the subsequent cleavages downstream of NS3, both in cis, at the NS3-NS4A cleavage site, and in trans, for the remaining NS4A-NS4B, NS4B-NS5A, NS5A-NS5B sites. The NS4A protein appears to serve multiple functions, acting as a cofactor for the NS3 protease and possibly assisting in the membrane localization of NS3 and other viral replicase components. The complex formation of the NS3 protein with NS4A seems necessary to the processing events, enhancing the proteolytic efficiency at all of the sites. The NS3 protein also exhibits nucleoside triphosphatase and RNA helicase activities. NS5B (also referred to herein as HCV polymerase) is a RNA-dependent RNA polymerase that is involved in the replication of HCV.

SUMMARY OF THE INVENTION

[0009] The compounds disclosed herein are used for treating HCV-infection in a patient, and which inhibit HCV viral replication selectively.

[0010] The present invention relates to a macrocyclic compound, which has an obvious advantage on inhibitory activity against HCV replicons compared with TMC-435 (Simeprevir) already on the market, the compound of the invention has a better inhibitory effect on various HCV genotype (such as GT1a, GT1b, CT2a, GT3a, GT4a, GT5a), especially on GT2a. The compounds or pharmaceutical composition thereof disclosed herein have a good inhibitory effect on HCV infection, especially on HCV NS3/4A protein.

[0011] In one aspect, provided herein is a compound having Formula (I) or a stereoisomer, a tautomer, an enantiomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



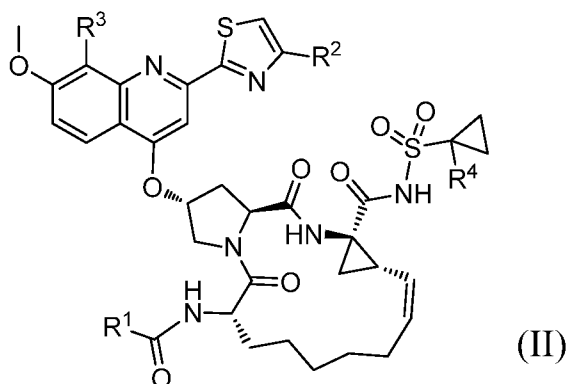
wherein R^1 is C_{6-10} aryl or C_{1-9} heteroaryl;

each of R^2 and R^3 is independently H, F, Cl, Br, I, amino, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{2-10} heterocyclyl, C_{6-10} aryl or C_{1-9} heteroaryl; and

R^4 is H, deuterium or C_{1-6} alkyl, and

wherein each the C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{2-10} heterocyclyl, C_{6-10} aryl, C_{1-9} heteroaryl and amino is independently and optionally substituted with 1, 2, 3 or 4 substituents independently selected from deuterium, hydroxy, amino, F, Cl, Br, I, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylamino, C_{3-10} cycloalkyl, C_{2-10} heterocyclyl, C_{6-10} aryl and C_{1-9} heteroaryl.

[0012] In some embodiments, provided herein is a compound having Formula (II) or a stereoisomer, a tautomer, an enantiomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof



[0013] In some embodiments, wherein R^1 of Formula (I) or (II) is phenyl or 5-6 membered heteroaryl; each of the phenyl and 5-6 membered heteroaryl is independently and optionally substituted with 1, 2, 3 or 4 substituents independently selected from deuterium, hydroxy, amino, F, Cl, Br, I, cyano, nitro, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{1-3} alkylamino, C_{3-10} cycloalkyl, C_{2-10} heterocyclyl and C_{6-10} aryl.

[0014] In some embodiments, wherein R^1 of Formula (I) or (II) is phenyl, furyl, thienyl, thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, oxadiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyridyl, quinolyl, indolyl or acridinyl, and wherein each R^1 is independently and optionally substituted with 1, 2, 3 or 4 substituents independently selected from deuterium, hydroxy, amino, F, Cl, Br, I, cyano, nitro, trifluoromethyl, difluoroethyl, trifluoromethoxy, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *i*-butyl, *t*-butyl, vinyl, ethynyl, methoxy, ethoxy, cyclopropyl, cyclobutyl, cyclopentyl and phenyl.

[0015] In some embodiments, each of R^2 and R^3 of Formula (I) or (II) is independently H, F, Cl, Br, I, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *i*-butyl, trifluoromethyl, trifluoromethoxy, *t*-butyl, vinyl, propenyl, ethynyl, propinyl, methoxy, ethoxy, cyclopropyl, cyclobutyl, cyclopentyl, phenyl, methylamino and ethylamino.

[0016] In some embodiments, wherein R^4 of Formula (I) or (II) is H, deuterium, methyl, deuterated methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl or *t*-butyl.

[0017] In some embodiments, wherein R^1 of Formula (I) or (II) is 5-6 membered heteroaryl; and wherein the 5-6 membered heteroaryl is independently and optionally substituted with 1, 2, 3 or 4 substituents independently selected from deuterium, hydroxy, amino, F, Cl, Br, I, cyano, nitro, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy and C_{1-3} alkylamino; R^2 of Formula (I) or (II) is C_{1-6} alkyl; R^3 of Formula (I) or (II) is C_{1-3} alkyl; and R^4 of Formula (I) or (II) is H or C_{1-3} alkyl.

[0018] In other aspect, provided herein is a pharmaceutical composition comprising the compound disclosed herein.

[0019] In some embodiments, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof.

[0020] In some embodiments, the pharmaceutical composition further comprises an anti-HCV agent, wherein the anti-HCV agent is interferon, ribavirin, IL-2, IL-6, IL-12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, imiquimod, an inosine5'-monophosphate dehydrogenase inhibitor, amantadine, rimantadine, bavituximab, CIVACIRTM, boceprevir, telaprevir, erlotinib, daclatasvir, simeprevir, asunaprevir, vaniprevir, faldaprevir, paritaprevir, danoprevir, sovalprevir, grazoprevir, vedoprevir, BZF-961, GS-9256, narlaprevir, ANA975, ombitasvir, EDP239, PPI-668, velpatasvir, samatasvir, elbasvir, MK-8325, GSK-2336805, PPI-461, BI-2013335, ciluprevir, ACH-1095, VX-985, IDX-375, VX-500, VX-813, PHX-1766, PHX-2054, IDX-136, IDX-316, modithromycin, VBY-376, TMC-649128, mericitabine, sofosbuvir, INX-189, IDX-184, IDX102, R-1479, UNX-08189, PSI-6130, PSI-938, PSI-879, nesbuvir, HCV-371, VCH-916, lomibuvir, MK-3281, dasabuvir, ABT-072, filibuvir, deleobuvir, tegobuvir, A-837093, JKT-109, GI-59728, GL-60667, AZD-2795, TMC647055, MK-3682, GS-9669, odalasvir, furaprevir, setrobuvir, alisporivir, BIT-225, AV-4025, ACH-3422, MK-2748, MK-8325, JNJ-47910382, ABP-560, TD-6450, TVB-2640, ID-12, PPI-383, A-848837, RG-7795, BC-2125 or a combination thereof; wherein the interferon is interferon α -2b, pegylated interferon α , interferon α -2a, pegylated interferon α -2a, consensus interferon- α , interferon γ or a combination thereof.

[0021] In some embodiments, the pharmaceutical composition further comprises at least one HCV inhibitor.

[0022] In other embodiments, the HCV inhibitor inhibits HCV replication process and/or a function of an HCV viral protein, and wherein the HCV replication process is a whole viral cycle consisting of HCV entry, uncoating, translation, replication, assembly and egress; and wherein the HCV viral proteins comprise a metalloproteinase, non-structural protein NS2, NS3, NS4A, NS4B, NS5A or NS5B, an internal ribosome entry site (IRES) or inosine-5'-monophosphate dehydrogenase (IMPDH) required in HCV viral replication.

[0023] In other aspect, provide herein is use of the compound or the pharmaceutical

composition disclosed herein in the manufacture of a medicament for inhibiting HCV replication process and/or a function of an HCV viral protein, and wherein the HCV replication process is a whole viral cycle consisting of HCV entry, uncoating, translation, replication, assembly and egress; and wherein the HCV viral proteins comprise metalloproteinase, non-structural protein NS2, NS3, NS4A, NS4B, NS5A or NS5B, an internal ribosome entry site (IRES) and inosine-5'-monophosphate dehydrogenase (IMPDH) required in HCV viral replication.

[0024] In other aspect, provided herein is use of the compound or the pharmaceutical composition disclosed herein in the manufacture of a medicament for preventing, managing, treating or lessening the severity of HCV infection or a HCV disorder.

[0025] In other aspect, provided herein is the compound or the pharmaceutical composition thereof disclosed herein for use in inhibiting HCV replication process and/or a function of an HCV viral protein, wherein the HCV replication process is a whole viral cycle consisting of HCV entry, uncoating, translation, replication, assembly and egress; and wherein the HCV viral protein comprises a metalloproteinase, non-structural protein NS2, NS3, NS4A, NS4B, NS5A or NS5B, an internal ribosome entry site (IRES), or inosine-5'-monophosphate dehydrogenase (IMPDH) required in HCV viral replication.

[0026] In other aspect, provided herein is the compound or the pharmaceutical composition thereof for use in preventing, managing, treating or lessening the severity of HCV infection or a HCV disorder.

[0027] In other aspect, provided herein is a method of inhibiting HCV replication process and/or a function of an HCV viral protein in a subject comprising administering to the subject the compound or the pharmaceutical composition, wherein the HCV replication process is a whole viral cycle consisting of HCV entry, uncoating, translation, replication, assembly and egress; and wherein the HCV viral protein comprises a metalloproteinase, non-structural protein NS2, NS3, NS4A, NS4B, NS5A or NS5B, an internal ribosome entry site (IRES), or inosine-5'-monophosphate dehydrogenase (IMPDH) required in HCV viral replication.

[0028] In other aspect, provided herein is a method of preventing, managing, treating or lessening the severity of HCV infection or a HCV disorder in a patient comprising administering the patient a therapeutically effective amount of the compound or the pharmaceutical composition thereof disclosed herein.

[0029] In other aspect, provided herein is a method of preparing, separating or purifying the

compound of Formula (I) or (II).

[0030] The foregoing merely summarizes certain aspects disclosed herein and is not intended to be limiting in nature. These aspects and other aspects and embodiments are described more fully below.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS AND GENERAL TERMINOLOGY

[0031] Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. The invention is intended to cover all alternatives, modifications, and equivalents which may be included within the scope of the present invention as defined by the claims. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. The present invention is in no way limited to the methods and materials described herein. In the event that one or more of the incorporated literature, patents, and similar materials differs from or contradicts this application, including but not limited to defined terms, term usage, described techniques, or the like, this application controls.

[0032] It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable sub-combination.

[0033] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one skilled in the art to which this invention belongs. All patents and publications referred to herein are incorporated by reference in their entirety.

[0034] As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, and the Handbook of Chemistry and Physics, 75th Ed. 1994. Additionally, general principles of organic chemistry are described in “Organic Chemistry”, Thomas Sorrell, University Science Books, Sausalito: **1999**, and Smith *et al.*, “March’s Advanced Organic Chemistry”, John Wiley & Sons, New York: **2007**, the entire contents of which are hereby incorporated by reference.

[0035] The grammatical articles “a”, “an” and “the”, as used herein, are intended to include “at

least one” or “one or more” unless otherwise indicated herein or clearly contradicted by the context. Thus, the articles are used herein to refer to one or more than one (*i.e.* at least one) of the grammatical objects of the article. By way of example, “a component” means one or more components, and thus, possibly, more than one component is contemplated and may be employed or used in an implementation of the described embodiments.

[0036] As used herein, the term “subject” refers to an animal. Typically the animal is a mammal. A subject also refers to for example, primates (*e.g.*, humans, male or female), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a primate. In yet other embodiments, the subject is a human.

[0037] As used herein, “patient” refers to a human (including adults and children) or other animal. In one embodiment, “patient” refers to a human.

[0038] The term “comprise” is an open expression, it means comprising the contents disclosed herein, but don’t exclude other contents.

[0039] “Stereoisomers” refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space. Stereoisomers include enantiomer, diastereomers, conformer (rotamer), geometric (cis/trans) isomer, atropisomer, *etc.*

[0040] “Chiral” refers to molecules which have the property of non-superimposability of the mirror image partner, while the term “achiral” refers to molecules which are superimposable on their mirror image partner.

[0041] “Enantiomers” refers to two stereoisomers of a compound which are non-superimposable mirror images of one another.

[0042] “Diastereomer” refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, *e.g.* melting points, boiling points, spectral properties or biological activities. Mixture of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography such as HPLC.

[0043] Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., “Stereochemistry of Organic Compounds”, John Wiley & Sons, Inc., New York, 1994.

[0044] Many organic compounds exist in optically active forms, *i.e.*, they have the ability to

rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes *D* and *L*, or *R* and *S*, are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes *d* and *l* or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or *l* meaning that the compound is levorotatory. A compound prefixed with (+) or *d* is dextrorotatory. A specific stereoisomer may be referred to as an enantiomer, and a mixture of such stereoisomers is called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process.

[0045] Any asymmetric atom (*e.g.*, carbon or the like) of the compound(s) disclosed herein can be present in racemic or enantiomerically enriched, for example the (*R*)-, (*S*)- or (*R,S*)-configuration. In certain embodiments, each asymmetric atom has at least 50 % enantiomeric excess, at least 60 % enantiomeric excess, at least 70 % enantiomeric excess, at least 80 % enantiomeric excess, at least 90 % enantiomeric excess, at least 95 % enantiomeric excess, or at least 99 % enantiomeric excess in the (*R*)- or (*S*)- configuration.

[0046] Depending on the choice of the starting materials and procedures, the compounds can be present in the form of one of the possible stereoisomers or as mixtures thereof, such as racemates and diastereoisomer mixtures, depending on the number of asymmetric carbon atoms. Optically active (*R*)- and (*S*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be *E* or *Z* configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a *cis*- or *trans*-configuration.

[0047] Any resulting mixtures of stereoisomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric isomers, enantiomers, diastereomers, for example, by chromatography and/or fractional crystallization. *Cis* and *trans* isomers are diastereomer.

[0048] Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by methods known to those skilled in the art, *e.g.*, by separation of the diastereomeric salts thereof. Racemic products can also be resolved by chiral chromatography, *e.g.*, high performance liquid chromatography (HPLC) using a chiral adsorbent. Preferred enantiomers can also be prepared by asymmetric syntheses. See, for example, Jacques, *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, **1981**); *Principles of*

Asymmetric Synthesis (2nd Ed. Robert E. Gawley, Jeffrey Aubé, Elsevier, Oxford, UK, **2012**); Eliel, E.L. Stereochemistry of Carbon Compounds (McGraw-Hill, NY, **1962**); Wilen, S.H. Tables of Resolving Agents and Optical Resolutions p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN **1972**); Chiral Separation Techniques: A Practical Approach (Subramanian, G. Ed., Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2007**).

[0049] The term “tautomer” or “tautomeric form” refers to structural isomers of different energies which are interconvertible via a low energy barrier. Where tautomerization is possible (*e.g.* in solution), a chemical equilibrium of tautomers can be reached. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons. A specific example of keto-enol tautomerization is the interconversion of pentane-2,4-dione and 4-hydroxypent-3-en-2-one tautomers. Another example of tautomerization is phenol-keto tautomerization. The specific example of phenol-keto tautomerisms is pyridin-4-ol and pyridin-4(3*H*)-one tautomerism. Unless otherwise stated, all tautomeric forms of the compounds disclosed herein are within the scope of the invention.

[0050] As described herein, compounds disclosed herein may optionally be substituted with one or more substituents, such as are illustrated generally below, or as exemplified by particular classes, subclasses, and species of the invention. It will be appreciated that the phrase “optionally substituted” is used interchangeably with the phrase “substituted or unsubstituted”. In general, the term “substituted” refers to the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group. When more than one position in a given structure can be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at each position. When a substituent is defined by using “independently selected from...” means that the substituent is independent from each other, each selection of substituent can be identical or different.

[0051] Furthermore, what need to be explained is that the phrase “each...is independently” and “each of...and...is independently”, unless otherwise stated, should be broadly understood. The specific options expressed by the same symbol are independent of each other in different groups;

or the specific options expressed by the same symbol are independent of each other in same groups.

[0052] At various places in the present specification, substituents of compounds disclosed herein are disclosed in groups or in ranges. It is specifically intended that the invention include each and every individual subcombination of the members of such groups and ranges. For example, the term “C₁₋₆ alkyl” is specifically intended to individually disclose methyl, ethyl, C₃ alkyl, C₄ alkyl, C₅ alkyl, and C₆ alkyl.

[0053] At various places in the present specification, linking substituents are described. Where the structure clearly requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable lists “alkyl” or “aryl” then it is understood that the “alkyl” or “aryl” represents a linking alkylene group or arylene group, respectively.

[0054] The term “alkyl” or “alkyl group” refers to a saturated linear or branched-chain monovalent hydrocarbon group of 1-20 carbon atoms, wherein the alkyl group is optionally substituted with one or more substituents described herein. Unless otherwise stated, the alkyl group contains 1-20 carbon atoms. In some embodiments, the alkyl group contains 1-12 carbon atoms. In other embodiments, the alkyl group contains 1-6 carbon atoms. In still other embodiments, the alkyl group contains 1-4 carbon atoms. In yet other embodiments, the alkyl group contains 1-3 carbon atoms.

[0055] Some non-limiting examples of the alkyl group include, methyl (Me, -CH₃), ethyl (Et, -CH₂CH₃), *n*-propyl (*n*-Pr, -CH₂CH₂CH₃), isopropyl (*i*-Pr, -CH(CH₃)₂), *n*-butyl (*n*-Bu, -CH₂CH₂CH₂CH₃), isobutyl (*i*-Bu, -CH₂CH(CH₃)₂), *sec*-butyl (*s*-Bu, -CH(CH₃)CH₂CH₃), *tert*-butyl (*t*-Bu, -C(CH₃)₃), *n*-pentyl (-CH₂CH₂CH₂CH₂CH₃), 2-pentyl (-CH(CH₃)CH₂CH₂CH₃), 3-pentyl (-CH(CH₂CH₃)₂), 2-methyl-2-butyl (-C(CH₃)₂CH₂CH₃), 3-methyl-2-butyl (-CH(CH₃)CH(CH₃)₂), 3-methyl-1-butyl (-CH₂CH₂CH(CH₃)₂), 2-methyl-1-butyl (-CH₂CH(CH₃)CH₂CH₃), *n*-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₃), 2-hexyl (-CH(CH₃)CH₂CH₂CH₂CH₃), 3-hexyl (-CH(CH₂CH₃)(CH₂CH₂CH₃)), 2-methyl-2-pentyl (-C(CH₃)₂CH₂CH₂CH₃), 3-methyl-2-pentyl (-CH(CH₃)CH(CH₃)CH₂CH₃), 4-methyl-2-pentyl (-CH(CH₃)CH₂CH(CH₃)₂), 3-methyl-3-pentyl (-C(CH₃)(CH₂CH₃)₂), 2-methyl-3-pentyl (-CH(CH₂CH₃)CH(CH₃)₂), 2,3-dimethyl-2-butyl (-C(CH₃)₂CH(CH₃)₂), 3,3-dimethyl-2-butyl (-CH(CH₃)C(CH₃)₃), *n*-heptyl and *n*-octyl, *etc.*

[0056] The term “alkenyl” refers to a linear or branched-chain monovalent hydrocarbon radical of 2 to 12 carbon atoms with at least one site of unsaturation, *i.e.*, a carbon-carbon, sp^2 double bond, wherein the alkenyl radical may be optionally substituted with one or more substituents described herein, and includes radicals having “cis” and “trans” orientations, or alternatively, “*E*” and “*Z*” orientations. In some embodiments, the alkenyl contains 2 to 8 carbon atoms. In other embodiments, the alkenyl contains 2 to 6 carbon atoms. In still other embodiments, the alkenyl contains 2 to 4 carbon atoms. In yet other embodiments, the alkenyl contains 2 to 3 carbon atoms. Examples of alkenyl groups include, but are not limited to, ethylenyl or vinyl ($-CH=CH_2$), allyl ($-CH_2CH=CH_2$), and the like.

[0057] The term “alkynyl” refers to a linear or branched monovalent hydrocarbon radical of 2 to 12 carbon atoms with at least one site of unsaturation, *i.e.*, a carbon-carbon, sp triple bond, wherein the alkynyl radical may be optionally substituted independently with one or more substituents described herein. In some embodiments, the alkynyl contains 2 to 8 carbon atoms. In other embodiments, the alkynyl contains 2 to 6 carbon atoms. In still other embodiments, the alkynyl contains 2 to 4 carbon atoms. In yet other embodiments, the alkynyl contains 2 to 3 carbon atoms. Examples of such groups include, but are not limited to, ethynyl ($-C\equiv CH$), propargyl ($-CH_2C\equiv CH$), 1-propynyl ($-C\equiv C-CH_3$), and the like.

[0058] The term “cycloalkyl” refers to a monovalent or multivalent saturated ring having 3 to 12 carbon atoms as a monocyclic, bicyclic, or tricyclic ring system. In some embodiments, the cycloalkyl group contains 3 to 12 carbon atoms. In other embodiments, the cycloalkyl group contains 3 to 10 carbon atoms. In other embodiments, the cycloalkyl group contains 3 to 8 carbon atoms. In still other embodiments, the cycloalkyl group contains 3 to 6 carbon atoms. The cycloalkyl group may be optionally substituted with one or more substituents disclosed herein.

[0059] The terms “heterocyclyl” and “heterocycle” as used interchangeably herein refer to a saturated or partially unsaturated, monocyclic, bicyclic or tricyclic ring containing 3-12 ring atoms of which at least one ring member is selected from nitrogen, sulfur and oxygen and at least one ring is nonaromatic. Unless otherwise specified, the heterocyclyl group may be carbon or nitrogen linked, and a $-CH_2-$ group can be optionally replaced by a $-C(=O)-$ group. In which, the sulfur can be optionally oxygenized to *S*-oxide and the nitrogen can be optionally oxygenized to *N*-oxide. Some non-limiting examples of the heterocyclyl group include oxiranyl, azetidiny, oxetanyl, thietanyl, pyrrolidiny, 2-pyrroliny, 3-pyrroliny, pyrazoliny, pyrazolidiny,

imidazoliny, imidazolidiny, tetrahydrofurany, dihydrofurany, tetrahydrothieny, dihydrothieny, 1,3-dioxolany, dithiolany, tetrahydropyrany, dihydropyrany, tetrahydrothiopyrany, piperidiny, morpholiny, thiomorpholiny, piperaziny, dioxany, dithiany, thioxany, homopiperaziny, homopiperidiny, oxepany, thiepany, oxazepiny, diazepiny, thiazepiny, indoliny, 1,2,3,4-tetrahydroisoquinolyl, 1,3-benzodioxolyl, 2-oxa-5-azabicyclo[2.2.1]hept-5-yl, and the like. Some non-limiting examples of heterocyclyl wherein -CH₂- group is replaced by -C(=O)- moiety include 2-oxopyrrolidiny, oxo-1,3-thiazolidiny, 2-piperidinonyl, 3,5-dioxopiperidiny and pyrimidinedione-yl. Some non-limited examples of heterocyclyl wherein the ring sulfur atom is oxidized is sulfolany, 1,1-dioxo-thiomorpholiny. The heterocyclyl group may be optionally substituted with one or more substituents disclosed herein.

[0060] In one embodiment, heterocyclyl may be 4-7 membered heterocyclyl, which refers to a saturated or partially unsaturated monocyclic ring containing 4-7 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur and oxygen. Unless otherwise specified, the heterocyclyl group containing 4-7 ring atoms may be carbon or nitrogen linked, and a -CH₂- group can be optionally replaced by a -C(=O)- group. In which, the sulfur can be optionally oxygenized to *S*-oxide and the nitrogen can be optionally oxygenized to *N*-oxide. Examples of the heterocyclyl group containing 4-7 ring atoms include, but are not limited to, azetidiny, oxetany, thietany, pyrrolidiny, 2-pyrroliny, 3-pyrroliny, pyrazoliny, pyrazolidiny, imidazoliny, imidazolidiny, tetrahydrofurany, dihydrofurany, tetrahydrothieny, dihydrothieny, 1,3-dioxolany, dithiolany, tetrahydropyrany, dihydropyrany, tetrahydrothiopyrany, piperidiny, morpholiny, thiomorpholiny, piperaziny, dioxany, dithiany, thioxany, homopiperaziny, homopiperidiny, oxepany, thiepany, oxazepiny, diazepiny and thiazepiny, and the like. Some non-limiting examples of heterocyclyl wherein -CH₂- group is replaced by -C(=O)- moiety include 2-oxopyrrolidiny, oxo-1,3-thiazolidiny, 2-piperidinonyl, 3,5-dioxopiperidiny and pyrimidinedione-yl. Some non-limited examples of heterocyclyl wherein the ring sulfur atom is oxidized is sulfolany, 1,1-dioxo-thiomorpholiny. The heterocyclyl group containing 4-7 ring atoms may be optionally substituted with one or more substituents disclosed herein.

[0061] In one embodiment, heterocyclyl may be 4- membered heterocyclyl, which refers to a saturated or partially unsaturated monocyclic ring containing 4 ring atoms, of which at least one

ring atom is selected from nitrogen, sulfur and oxygen. Unless otherwise specified, the heterocyclyl group containing 4 ring atoms may be carbon or nitrogen linked, and a -CH₂- group can be optionally replaced by a -C(=O)- group. In which, the sulfur can be optionally oxygenized to *S*-oxide and the nitrogen can be optionally oxygenized to *N*-oxide. Some non-limiting examples of the heterocyclyl containing 4 ring atoms include azetidiny, oxetanyl and thietanyl. The heterocyclyl group containing 4 ring atoms may be optionally substituted with one or more substituents disclosed herein.

[0062] In one embodiment, heterocyclyl may be 5- membered heterocyclyl, which refers to a saturated or partially unsaturated monocyclic ring containing 5 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur and oxygen. Unless otherwise specified, the heterocyclyl group containing 5 ring atoms may be carbon or nitrogen linked, and a -CH₂- group can be optionally replaced by a -C(=O)- group. In which, the sulfur can be optionally oxygenized to *S*-oxide and the nitrogen can be optionally oxygenized to *N*-oxide. Examples of 5-membered heterocyclyl include, but are not limited to, pyrrolidiny, 2-pyrroliny, 3-pyrroliny, pyrazoliny, pyrazolidiny, imidazoliny, imidazolidiny, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, 1,3-dioxolanyl, dithiolanyl, and the like. Some non-limiting examples of heterocyclyl wherein -CH₂- group is replaced by -C(=O)- moiety include 2-oxopyrrolidiny and oxo-1,3-thiazolidiny. Some non-limited examples of heterocyclyl wherein the ring sulfur atom is oxidized is sulfolanyl. The heterocyclyl group containing 5 ring atoms may be optionally substituted with one or more substituents disclosed herein.

[0063] In one embodiment, heterocyclyl may be 6- membered heterocyclyl, which refers to a saturated or partially unsaturated monocyclic ring containing 6 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur and oxygen. Unless otherwise specified, the heterocyclyl group containing 6 ring atoms may be carbon or nitrogen linked, and a -CH₂- group can be optionally replaced by a -C(=O)- group. In which, the sulfur can be optionally oxygenized to *S*-oxide and the nitrogen can be optionally oxygenized to *N*-oxide. Examples of the heterocyclyl group containing 6 ring atoms include, but are not limited to, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidiny, morpholiny, thiomorpholiny, piperaziny, dioxanyl, dithianyl and thioxanyl. Some non-limiting examples of heterocyclyl wherein -CH₂- group is replaced by -C(=O)- moiety include 2-piperidinonyl, 3,5-dioxopiperidiny and pyrimidinedionyl. Some non-limited examples of heterocyclyl wherein the ring sulfur atom is

oxidized is 1,1-dioxo-thiomorpholinyl. The heterocyclyl group containing 6 ring atoms may be optionally substituted with one or more substituents disclosed herein.

[0064] In other embodiment, heterocyclyl may be 7-12 membered heterocyclyl, which refers to a saturated or partially unsaturated spiro or fused bicyclic ring containing 7-12 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur and oxygen. Unless otherwise specified, the heterocyclyl group containing 7-12 ring atoms may be carbon or nitrogen linked, and a -CH₂- group can be optionally replaced by a -C(=O)- group. In which, the sulfur can be optionally oxygenized to *S*-oxide and the nitrogen can be optionally oxygenized to *N*-oxide. Some non-limiting examples of the heterocyclyl containing 7-12 ring atoms include indolyl, 1,2,3,4-tetrahydroisoquinolyl, 1,3-benzodioxolyl, 2-oxa-5-azabicyclo[2.2.1]hept-5-yl. The heterocyclyl group containing 7-12 ring atoms may be optionally substituted with one or more substituents disclosed herein.

[0065] The term “heterocyclylalkyl” refers to an alkyl group substituted with heterocyclyl. The term “heterocyclylalkoxy” refers to an alkoxy group substituted with heterocyclyl, attached to the rest of molecular through an oxygen atom. The term “heterocyclylalkylamino” refers to an alkylamino group substituted with heterocyclyl, attached to the rest of molecular through a nitrogen atom. Wherein the heterocyclyl group, alkyl, alkoxy and alkylamino group are as defined herein. Some non-limiting examples of such groups include pyrrol-2-yl-methyl, morpholin-4-yl-ethyl, morpholin-4-yl-ethoxy, piperazin-4-yl-ethoxy, piperazin-4-yl-ethylamino and the like.

[0066] The term “n- membered”, where n is an integer typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. For example, piperidinyl is an example of a 6 membered heterocycloalkyl and 1,2,3,4-tetrahydro-naphthalene is an example of a 10 membered cycloalkyl group.

[0067] The term “unsaturated” refers to a moiety having one or more units of unsaturation.

[0068] The term “heteroatom” refers to one or more of oxygen, sulfur, nitrogen, phosphorus and silicon, including any oxidized form of nitrogen, sulfur, or phosphorus; the quaternized form of any basic nitrogen; or a substitutable nitrogen of a heterocyclic ring, for example, N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR (as in *N*-substituted pyrrolidinyl).

[0069] The term “halogen” refers to fluorine (F), chlorine (Cl), bromine (Br) or iodine (I).

[0070] The term “aryl” refers to monocyclic, bicyclic and tricyclic carbocyclic ring systems

having a total of 6 to 14 ring members, or 6 to 12 ring members, or 6 to 10 ring members, wherein at least one ring in the system is aromatic, wherein each ring in the system contains 3 to 7 ring members and that has a single point or multipoint of attachment to the rest of the molecule. The term “aryl” and “aromatic ring” can be used interchangeably herein. Examples of aryl ring may include phenyl, naphthyl and anthracene. The aryl group may be optionally and independently substituted with one or more substituents disclosed herein.

[0071] The term “heteroaryl” refers to monocyclic, bicyclic and tricyclic ring systems having 1 to 9 carbon atoms, wherein at least one ring in the system is aromatic, and at least one ring system contains one or more heteroatoms selected from O, S and N, and wherein each ring in the system contains 5 to 7 ring members and that has a single point or multipoint of attachment to the rest of the molecule. The term “heteroaryl” and “heteroaromatic ring” or “heteroaromatic compound” can be used interchangeably herein. The heteroaryl group is optionally substituted with one or more substituents disclosed herein.

[0072] In some embodiments, the term “heteroaryl” refers to monocyclic, bicyclic and tricyclic ring systems having a total of 5 to 12 ring members, wherein at least one ring in the system is aromatic, and at least one ring system contains one or more heteroatoms selected from O, S and N, and wherein each ring in the system contains 5 to 7 ring members and that has a single point or multipoint of attachment to the rest of the molecule. In some embodiments, the term “heteroaryl” refers to monocyclic and bicyclic ring systems having a total of 5 to 10 ring members, wherein at least one ring in the system is aromatic, and at least one ring system contains one or more heteroatoms selected from O, S and N, and wherein each ring in the system contains 5 to 7 ring members and that has a single point or multipoint of attachment to the rest of the molecule. In some embodiments, the term “heteroaryl” refers to monocyclic aromatic ring system having a total of 5 to 6 ring members and containing 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, and that has a single point or multipoint of attachment to the rest of the molecule.

[0073] Some non-limiting examples of the heteroaryl group include 2-furanyl, 3-furanyl, *N*-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, *N*-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, pyridazinyl (*e.g.*, 3-pyridazinyl), 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, tetrazolyl (*e.g.*, 5-tetrazolyl), triazolyl (*e.g.*, 1,2,3-triazolyl

and 1,2,4-triazolyl), 2-thienyl, 3-thienyl, pyrazolyl (*e.g.*, 2-pyrazolyl), isothiazolyl, oxadiazolyl (*e.g.* 1,2,3-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), 1,2,3-triazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, pyrazinyl, 1,3,5-triazinyl, and the following bicycles: benzimidazolyl, benzofuryl, benzothiophenyl, indolyl (*e.g.*, 2-indolyl), purinyl, quinolinyl (*e.g.*, 2-quinolinyl, 3-quinolinyl, 4-quinolinyl), and isoquinolinyl (*e.g.*, 1-isoquinolinyl, 3-isoquinolinyl or 4-isoquinolinyl), imidazo[1,2-*a*]pyridyl, pyrazolo[1,5-*a*]pyridyl, pyrazolo[1,5-*a*]pyrimidyl, imidazo[1,2-*b*]pyridazinyl, [1,2,4]triazolo[4,3-*b*]pyridazinyl, [1,2,4]triazolo[1,5-*a*]pyrimidinyl, or [1,2,4]triazolo[1,5-*a*]pyridyl.

[0074] The terms “carboxy” or “carboxyl”, whether used alone or with other terms, such as “carboxyalkyl”, refer to -CO₂H. The term “carbonyl”, whether used alone or with other terms, such as “aminocarbonyl”, “acyloxy” denotes -(C=O)-.

[0075] The term “alkylamino” refers to “*N*-alkylamino” and “*N,N*-dialkylamino” wherein amino groups are independently substituted with one alkyl radical or two alkyl radicals, respectively. In some embodiments, the alkylamino group is lower alkylamino group having one or two alkyl groups of 1 to 6 carbon atoms attached to nitrogen atom. In other embodiments, the alkylamino group is lower alkylamino group having 1 to 3 carbon atoms. Some non-limiting examples of suitable alkylamino radical include mono or dialkylamino. Some examples include, but are not limited to, *N*-methylamino, *N*-ethylamino, *N,N*-dimethylamino and *N,N*-diethylamino, and the like.

[0076] The term “arylamino” refers to an amino group substituted with one or two aryl groups. Some non-limiting examples of such group included *N*-phenylamino. In some embodiments, the aryl group of the arylamino may be further substituted.

[0077] The term “aminoalkyl” refers to a C₁₋₁₀ linear or branched-chain alkyl group substituted with one or more amino groups. In some embodiments, the aminoalkyl is a C₁₋₆ lower aminoalkyl derived from C₁₋₆ lower alkyl substituted with one or more amino groups. Some non-limiting examples of the aminoalkyl group include aminomethyl, aminoethyl, aminopropyl, aminobutyl and aminohexyl.

[0078] The term “alkoxy” refers to an alkyl group, as previously defined, attached to the parent molecular moiety via an oxygen atom. Unless otherwise specified, the alkoxy group contains 1-12 carbon atoms. In one embodiment, the alkoxy group contains 1-6 carbon atoms. In other

embodiment, the alkoxy group contains 1-4 carbon atoms. In still other embodiment, the alkoxy group contains 1-3 carbon atoms. The alkoxy group may be optionally substituted with one or more substituents disclosed herein.

[0079] Some non-limiting examples of the alkoxy group include, but are not limited to, methoxy (MeO, -OCH₃), ethoxy (EtO, -OCH₂CH₃), 1-propoxy (*n*-PrO, *n*-propoxy, -OCH₂CH₂CH₃), 2-propoxy (*i*-PrO, *i*-propoxy, -OCH(CH₃)₂), 1-butoxy (*n*-BuO, *n*-butoxy, -OCH₂CH₂CH₂CH₃), 2-methyl-1-propoxy (*i*-BuO, *i*-butoxy, -OCH₂CH(CH₃)₂), 2-butoxy (*s*-BuO, *s*-butoxy, -OCH(CH₃)CH₂CH₃), 2-methyl-2-propoxy (*t*-BuO, *t*-butoxy, -OC(CH₃)₃), 1-pentoxy (*n*-pentoxy, -OCH₂CH₂CH₂CH₂CH₃), 2-pentoxy (-OCH(CH₃)CH₂CH₂CH₃), 3-pentoxy (-OCH(CH₂CH₃)₂), 2-methyl-2-butoxy (-OC(CH₃)₂CH₂CH₃), 3-methyl-2-butoxy (-OCH(CH₃)CH(CH₃)₂), 3-methyl-1-butoxy (-OCH₂CH₂CH(CH₃)₂), 2-methyl-1-butoxy (-OCH₂CH(CH₃)CH₂CH₃), and the like.

[0080] The term “alkylthio” refers to a group derived from an alkoxy group, the oxygen atom of which is replaced by a sulphur atom.

[0081] The terms “haloalkyl”, “haloalkenyl” or “haloalkoxy” refer to alkyl, alkenyl, or alkoxy, as the case may be, substituted with one or more halogen atoms. Some non-limiting examples of “haloalkyl”, “haloalkenyl” or “haloalkoxy” groups include trifluoromethyl, difluoroethyl (CHF₂CH₂-), trifluoromethoxy, and the like.

[0082] The terms “hydroxyalkyl” “hydroxy-substituted alkyl” refer to an alkyl group substituted with one or more hydroxy groups, wherein the alkyl is as defined herein. Some non-limiting examples include hydroxymethyl, hydroxyethyl, 1,2-dihydroxyethyl, and the like.

[0083] The term “amino” (used alone or in combination with other terms) refers to -NH₂.

[0084] The term “protecting group” or “PG” refers to a substituent that is commonly employed to block or protect a particular functionality while reacting with other functional groups on the compound. For example, an “amino-protecting group” is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include acetyl, trifluoroacetyl, *t*-butoxy-carbonyl (BOC, Boc), benzyloxycarbonyl (CBZ, Cbz) and 9-fluorenylmethylenoxy-carbonyl (Fmoc). Similarly, a “hydroxy-protecting group” refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable protecting groups include acetyl and silyl. A “carboxy-protecting group” refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Common

carboxy-protecting groups include $-\text{CH}_2\text{CH}_2\text{SO}_2\text{Ph}$, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl) ethoxy-methyl, 2-(*p*-toluenesulfonyl) ethyl, 2-(*p*-nitrophenylsulfonyl)-ethyl, 2-(diphenylphosphino)-ethyl, nitroethyl and the like. For a general description of protecting groups and their use, see T. W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, **1991**; and P. J. Kocienski, *Protecting Groups*, Thieme, Stuttgart, **2005**.

[0085] The term “prodrug” refers to a compound that is transformed *in vivo* into a compound of Formula (I). Such a transformation can be affected, for example, by hydrolysis of the prodrug form in blood or enzymatic transformation to the parent form in blood or tissue. Prodrugs of the compounds disclosed herein may be, for example, esters. Some common esters which have been utilized as prodrugs are phenyl esters, aliphatic (C_{1-24}) esters, acyloxymethyl esters, carbonates, carbamates and amino acid esters. For example, a compound disclosed herein that contains a hydroxy group may be acylated at this position in its prodrug form. Other prodrug forms include phosphates, such as, those phosphate compounds derived from the phosphonation of a hydroxy group on the parent compound. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, **1987**, J. Rautio *et al.*, *Prodrugs: Design and Clinical Applications*, *Nature Review Drug Discovery*, **2008**, 7, 255-270, and S. J. Hecker *et al.*, *Prodrugs of Phosphates and Phosphonates*, *Journal of Medicinal Chemistry*, **2008**, 51,2328-2345, all of which are incorporated herein by reference in their entireties.

[0086] A “metabolite” is a product produced through metabolism in the body of a specified compound or salt thereof. The metabolites of a compound may be identified using routine techniques known in the art and their activities determined using tests such as those described herein. Such products may result for example from oxidation, reduction, hydrolysis, amidation, deamidation, esterification, deesterification, enzyme cleavage, and the like, of the administered compound. Accordingly, the invention includes metabolites of compounds disclosed herein, including metabolites produced by contacting a compound disclosed herein with a mammal for a sufficient time period.

[0087] A “pharmaceutically acceptable salts” refers to organic or inorganic salts of a compound disclosed herein. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge *et al.*, describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*,

1977, 66: 1-19, which is incorporated herein by reference. Some non-limiting examples of pharmaceutically acceptable and nontoxic salts include salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid and malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, laurylsulfate, malate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, stearate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^{+}(C_{1-4} \text{ alkyl})_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil soluble or dispersable products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, C_{1-8} sulfonate or aryl sulfonate.

[0088] The term “solvate” refers to an association or complex of one or more solvent molecules and a compound disclosed herein. Examples of solvents that form solvates include, but are not limited to, water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid and ethanolamine. The term “hydrate” refers to the complex where the solvent molecule is water.

[0089] The term “hydrate” refers to the complex where the solvent molecule is water.

[0090] An “*N*-oxide” refers to one or more than one nitrogen atoms oxidised to form an *N*-oxide, where a compound contains several amine functions. Particular examples of *N*-oxides are the *N*-oxides of a tertiary amine or a nitrogen atom of a nitrogen-containing heterocycle. *N*-oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as hydrogen peroxide or a per-acid (*e.g.* a peroxy-carboxylic acid) (See, Advanced Organic

Chemistry, by Jerry March, 4th Edition, Wiley Interscience, pages). More particularly, *N*-oxides can be made by the procedure of L. W. Deady (Syn. Comm. **1977**, 7, 509-514) in which the amine compound is reacted with *m*-chloroperoxybenzoic acid (MCPBA), for example, in an inert solvent such as dichloromethane.

[0091] As used herein, the term “treat”, “treating” or “treatment” of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (*i.e.*, slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment “treat”, “treating” or “treatment” refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, “treat”, “treating” or “treatment” refers to modulating the disease or disorder, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter), or both. In yet another embodiment, “treat”, “treating” or “treatment” refers to preventing or delaying the onset or development or progression of the disease or disorder.

[0092] Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, *e.g.*, acetate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfonate, chloride/hydrochloride, chlorthalophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, stearate, succinate, subsalicylate, tartrate, tosylate and trifluoroacetate salts.

[0093] Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

[0094] Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, sulfosalicylic acid, and the like.

[0095] Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases.

[0096] Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts.

[0097] Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, choline, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

[0098] The pharmaceutically acceptable salts of the present invention can be synthesized from a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable. Lists of additional suitable salts can be found, *e.g.*, in “Remington's Pharmaceutical Sciences”, 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in “Handbook of Pharmaceutical Salts: Properties, Selection, and Use” by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

[0099] Furthermore, the compounds disclosed herein, including their salts, can also be obtained in the form of their hydrates, or include other solvents such as ethanol, DMSO, and the like, used for their crystallization. The compounds of the present invention may inherently or by design form solvates with pharmaceutically acceptable solvents (including water); therefore, it is intended that the invention embrace both solvated and unsolvated forms.

[00100] Any formula given herein is also intended to represent isotopically unenriched forms as well as isotopically enriched forms of the compounds. Any formula given herein is also intended to represent isotopically unenriched forms as well as isotopically enriched forms of the compounds. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, and chlorine, such as ^2H (deuterium, D), ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{18}F , ^{31}P , ^{32}P , ^{35}S , ^{36}Cl , ^{125}I ,

respectively.

[00101] In another aspect, the compounds of the invention include isotopically enriched compounds as defined herein, for example those into which radioactive isotopes, such as ^3H , ^{14}C and ^{18}F , or those into which non-radioactive isotopes, such as ^2H and ^{13}C are present. Such isotopically enriched compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^2H or ^3H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F -enriched compound may be particularly desirable for PET or SPECT studies. Isotopically-enriched compounds of Formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[00102] Further, substitution with heavier isotopes, particularly deuterium (*i.e.*, ^2H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound of Formula (I). The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation). Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O , acetone- d_6 , DMSO- d_6 .

[00103] In other aspect, provided herein is a compound for preparing the compound of Formula (I).

[00104] In other aspect, provided herein is a method of preparing, separating or purifying the compound of Formula (I).

[00105] The present invention provides a pharmaceutical composition comprising the compounds disclosed herein and pharmaceutically acceptable carrier, excipient, diluent, adjuvant, solvent and a combination thereof. In some embodiments, the pharmaceutical composition can be liquid, solid, semisolid, gel or spray.

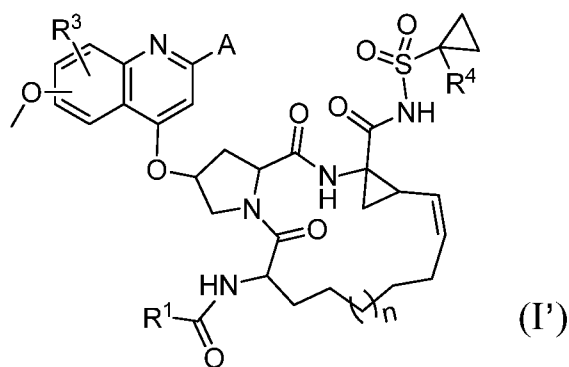
[00106] By “combination” according to the invention, there is meant either a fixed combination in one dosage unit form, or a kit of parts for the combined administration where a compound of the invention and a combination partner may be administered independently at the same time or separately within time intervals that especially allow that the combination partners show a cooperative, *e.g.* synergistic effect. The terms “co-administration” or “combined administration” or the like as used herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time. The term “pharmaceutical combination” as used herein refers to a product obtained from mixing or combining active ingredients, and includes both fixed and non-fixed combinations of the active ingredients. The term “fixed combination” means that the active ingredients, *e.g.* a compound of the invention and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term “non-fixed combination” means that the active ingredients, *e.g.* a compound of the invention and a co-agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the active ingredients in the body of the patient. The latter also applies to cocktail therapy, *e.g.* the administration of three or more active ingredients.

[00107] It should be noted that the term of “inhibiting HCV viral protein” should be broadly understood, which comprises inhibiting the expression level of HCV viral protein, inhibiting activity level of HCV viral protein, viral assembly and egress level. The expression level of HCV protein includes, but are not limited to translation level of the viral protein, posttranslational modification level of the viral protein, replication level of genetic material in offsprings and so on.

DESCRIPTION OF COMPOUNDS OF THE INVENTION

[00108] The present invention relates to a macrocyclic compound and a pharmaceutical preparation thereof, which can inhibit HCV infection effectively, especially HCV NS3/4A protein activity.

[00109] In one aspect, provided herein is a compound having Formula (I') or a stereoisomer, a tautomer, an enantiomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



wherein ring A is C₆₋₁₀ phenyl or C₁₋₉ heteroaryl; and ring A is optionally substituted with 1, 2, 3 or 4 independent R²;

R¹ is C₆₋₁₀ aryl or C₁₋₉ heteroaryl;

each of R² and R³ is independently H, F, Cl, Br, I, amino, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₂₋₁₀ heterocyclyl, C₆₋₁₀ aryl or C₁₋₉ heteroaryl;

R⁴ is H, deuterium or C₁₋₆ alkyl; and

n is 0, 1, 2, 3 or 4; and

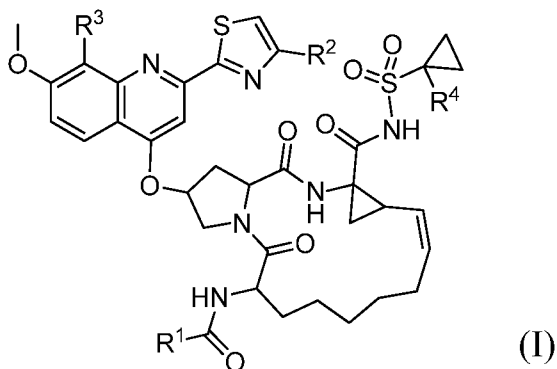
wherein each the C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₂₋₁₀ heterocyclyl, C₆₋₁₀ aryl, C₁₋₉ heteroaryl and amino is independently and optionally substituted with 1, 2, 3 or 4 substituents independently selected from deuterium, hydroxy, amino, F, Cl, Br, I, cyano, nitro, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ alkylamino, C₃₋₁₀ cycloalkyl, C₂₋₁₀ heterocyclyl, C₆₋₁₀ aryl and C₁₋₉ heteroaryl.

[00110] In some embodiments, wherein ring A is phenyl or 5-6 membered heteroaryl; and wherein each of the phenyl and 5-6 membered heteroaryl is independently and optionally substituted with 1, 2, 3 or 4 substituents independently selected from deuterium, hydroxy, amino, F, Cl, Br, I, cyano, nitro, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₁₋₃ alkylamino, C₃₋₁₀ cycloalkyl, C₂₋₁₀ heterocyclyl and C₆₋₁₀ aryl.

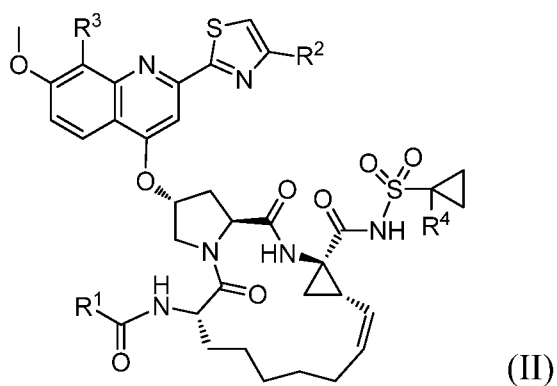
[00111] In other embodiments, ring A is phenyl, furyl, thienyl, thiazolyl, pyrrolyl, imidazolyl,

pyrazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyridyl, quinolyl, indolyl or acridinyl.

[00112] In some embodiments, provided herein is a compound having Formula (I), or a stereoisomer, a tautomer, an enantiomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof



[00113] In some embodiments, provided herein is a compound having Formula (II) or a stereoisomer, a tautomer, an enantiomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



[00114] In some embodiments, wherein R^1 of Formula (I'), (I) or (II) is phenyl or 5-6 membered heteroaryl; and wherein each of the phenyl and 5-6 membered heteroaryl is independently and optionally substituted with 1, 2, 3 or 4 substituents independently selected from deuterium, hydroxy, amino, F, Cl, Br, I, cyano, nitro, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{1-3} alkylamino, C_{3-10} cycloalkyl, C_{2-10} heterocyclyl and C_{6-10} aryl.

[00115] In some embodiments, wherein R^1 of Formula (I'), (I) or (II) is phenyl, furyl, thienyl, thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, oxadiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyridyl, quinolyl, indolyl or acridinyl, and wherein each R^1 is independently and optionally substituted with 1, 2, 3 or 4 substituents independently selected from deuterium, hydroxy, amino, F, Cl, Br, I, cyano, nitro, trifluoromethyl, difluoroethyl,

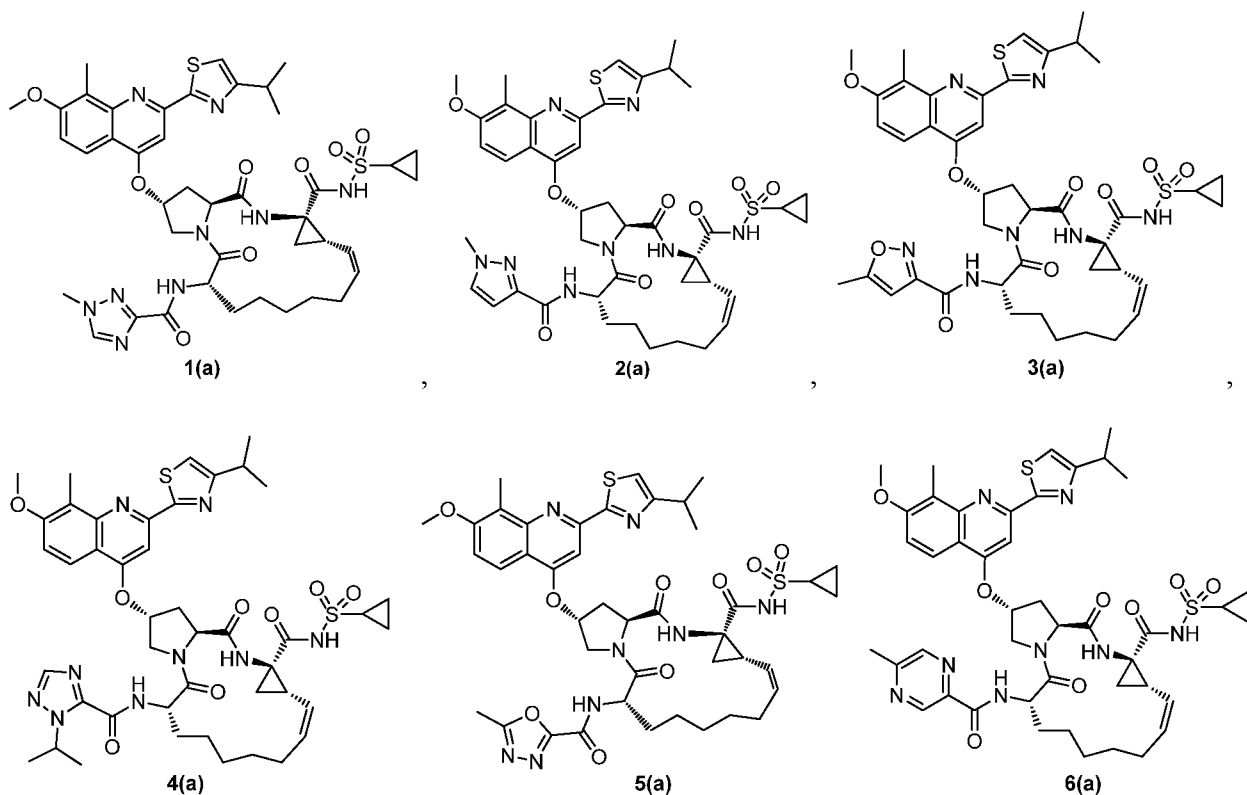
trifluoromethoxy, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *i*-butyl, *t*-butyl, vinyl, ethynyl, methoxy, ethoxy, cyclopropyl, cyclobutyl, cyclopentyl and phenyl.

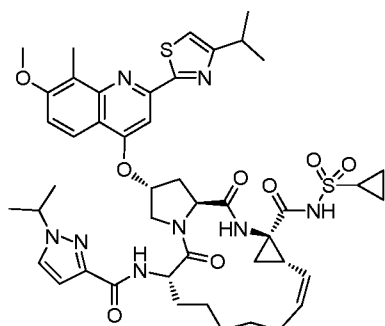
[00116] In some embodiments, each R² and R³ of Formula (I'), (I) or (II) is independently H, F, Cl, Br, I, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *i*-butyl, trifluoromethyl, trifluoromethoxy, *t*-butyl, vinyl, propenyl, ethynyl, propinyl, methoxy, ethoxy, cyclopropyl, cyclobutyl, cyclopentyl, phenyl, methylamino or ethylamino.

[00117] In some embodiments, wherein R⁴ of Formula (I'), (I) or (II) is H, deuterium, methyl, deuterated methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl or *t*-butyl.

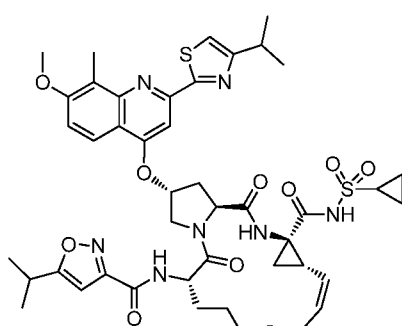
[00118] In some embodiments, wherein wherein R¹ of Formula (I'), (I) or (II) is 5-6 membered heteroaryl; and wherein the 5-6 membered heteroaryl is independently and optionally substituted with 1, 2, 3 or 4 substituents independently selected from deuterium, hydroxy, amino, F, Cl, Br, I, cyano, nitro, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy and C₁₋₃ alkylamino; R² of Formula (I'), (I) or (II) is C₁₋₆ alkyl; R³ of Formula (I'), (I) or (II) is C₁₋₃ alkyl; and R⁴ of Formula (I'), (I) or (II) is H or C₁₋₃ alkyl.

[00119] In some embodiments, provided herein is a compound having one of the following structures or a stereoisomer, a tautomer, an enantiomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof:

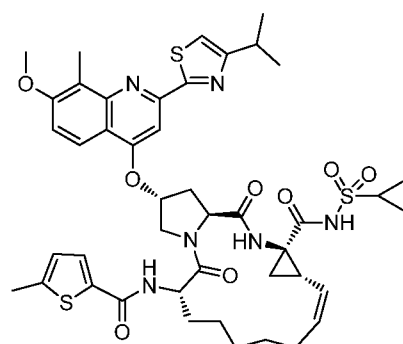




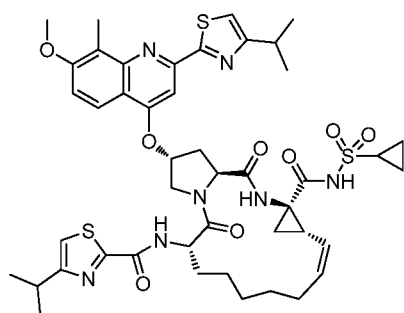
7(a)



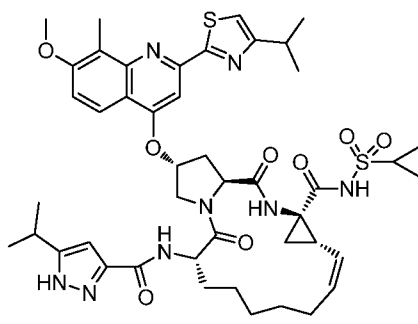
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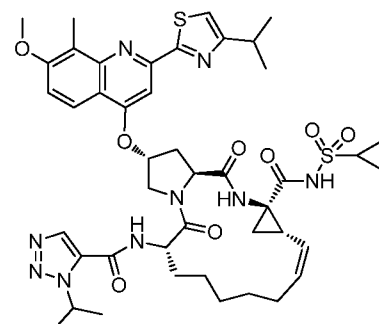
9(a)



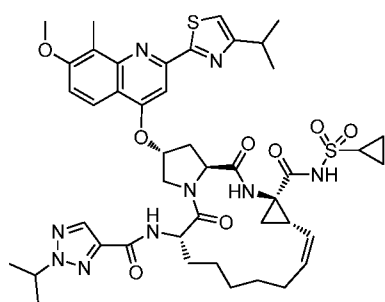
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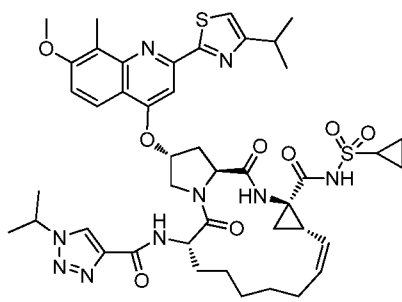
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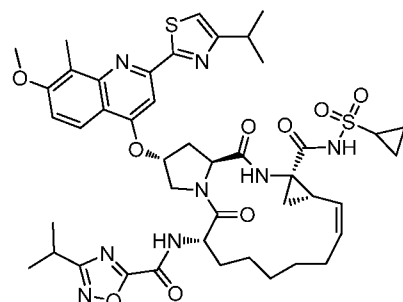
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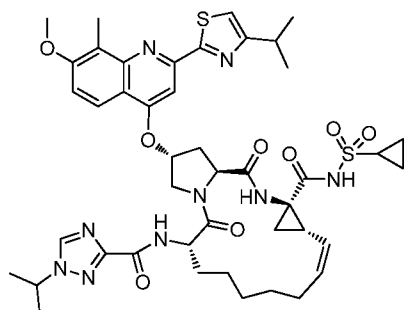
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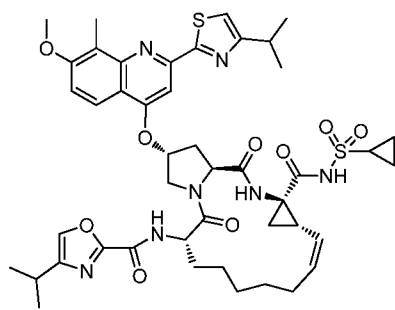
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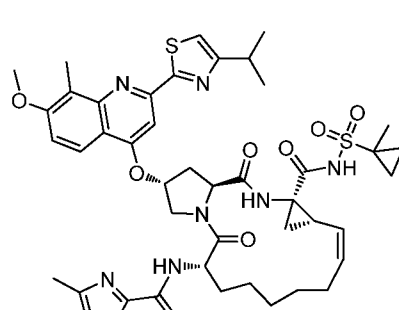
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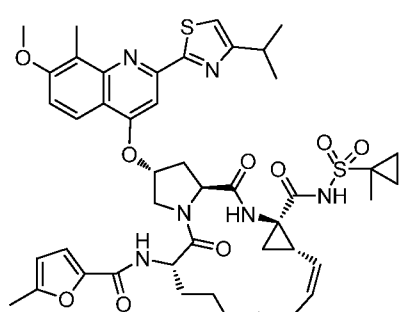
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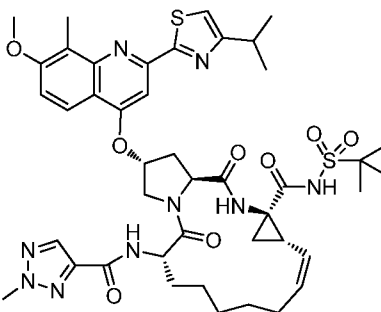
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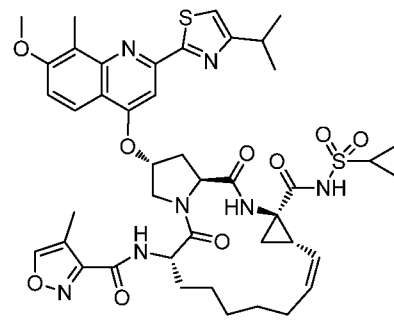
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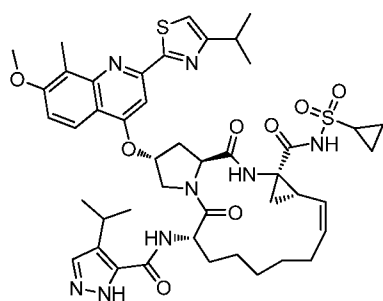
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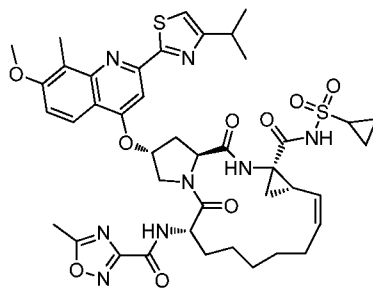
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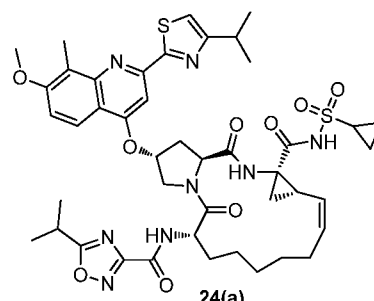
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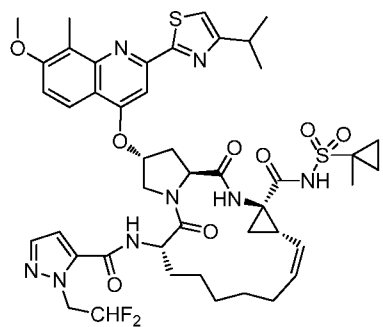
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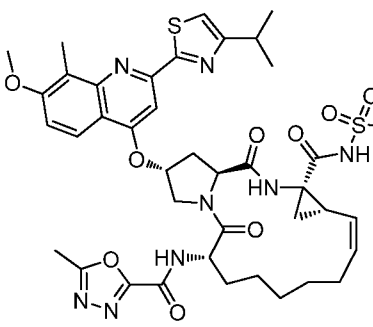
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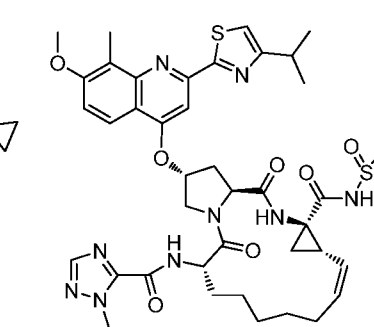
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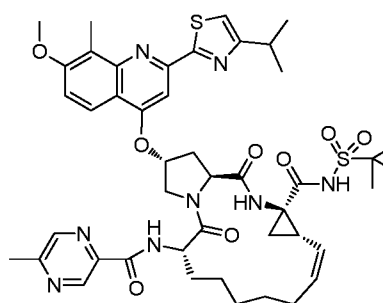
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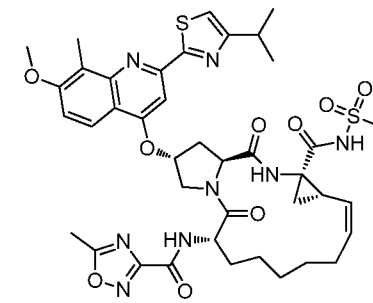
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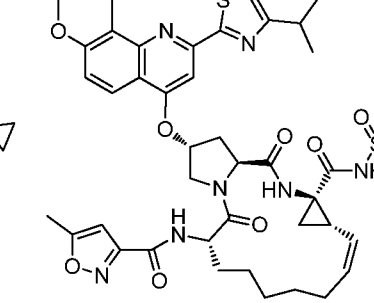
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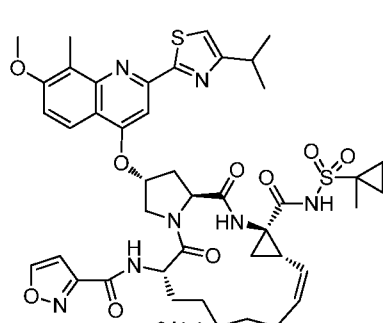
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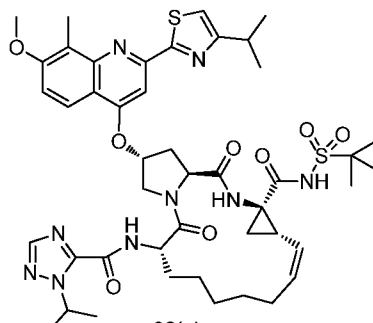
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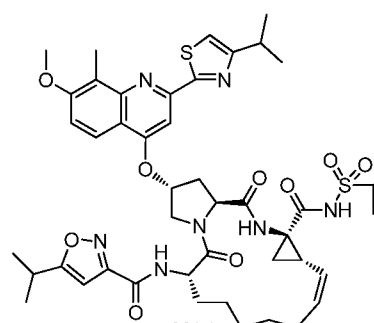
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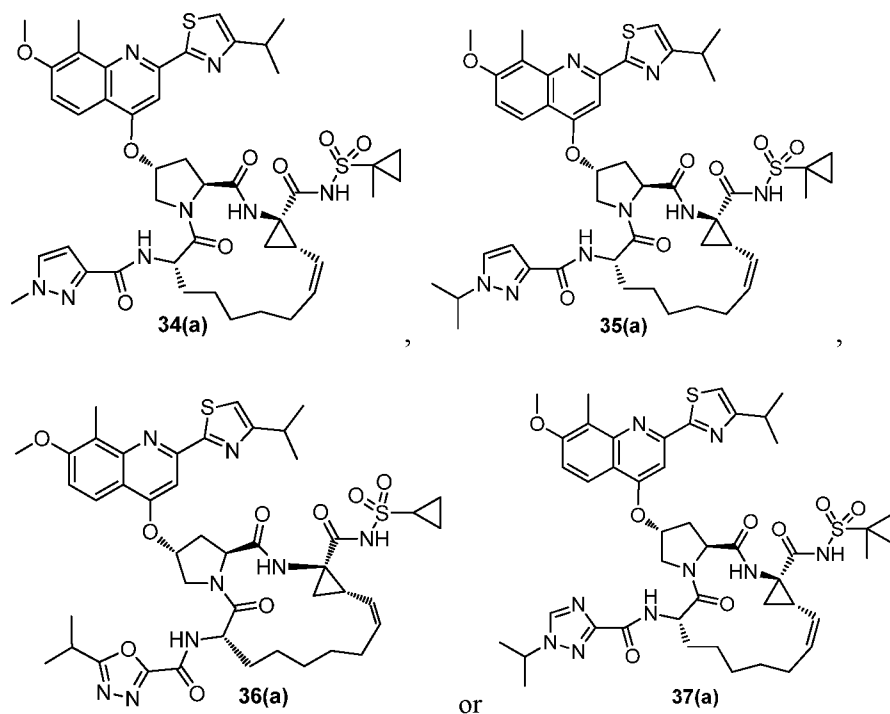
31(a)



32(a)



33(a)



[00120] In one aspect, the compound of the invention (comprising a compound having Formula (I'), (I) or (II), or a stereoisomer, a geometric isomer, a tautomer, an enantiomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof) can be used in the manufacture of a medicine for treatment of acute or chronic HCV infection including that described herein. Further more, the compound of the invention can be used in the manufacture of an anti-HCV drug. The compound disclosed herein also can be used in the manufacture of a medicine for lessening, preventing, managing or treating diseases mediated by HCV, especially HCV NS3/4A protein. Thus, the compound of the invention can act as an active ingredient of a pharmaceutical composition, the pharmaceutical composition may comprises the compound of Formula (I'), (I) or (II) and may further comprise at least one pharmaceutically acceptable carrier, adjuvant or diluent.

[00121] In certain embodiments, the salt is a pharmaceutically acceptable salt. The phrase “pharmaceutically acceptable” refers to that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith. The skills in the art could choose “pharmaceutically acceptable” substance or composition base on the other ingredients and the objects for treatment such as human.

[00122] The compounds disclosed herein also include salts of the compounds which are not necessarily pharmaceutically acceptable salts, and which may be useful as intermediates for

preparing and/or purifying compounds of Formula (I'), (I) or (II) and/or for separating enantiomers of compounds of Formula (I'), (I) or (II).

[00123] If the compound disclosed herein is a base, the desired salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid or organic acid, wherein the inorganic acid comprises hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Some non-limiting example of the organic acid include acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid and salicylic acid; a pyranosidyl acid, such as glucuronic acid and galacturonic acid; an alpha-hydroxy acid, such as citric acid and tartaric acid; an amino acid, such as aspartic acid and glutamic acid; an aromatic acid, such as benzoic acid and cinnamic acid; a sulfonic acid, such as *p*-toluenesulfonic acid, ethanesulfonic acid, and the like.

[00124] If the compound disclosed here in is an acid, the desired salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide, or alkaline earth metal hydroxide, and the like. Some non-limiting examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine; ammonia, such as primary, secondary and tertiary amine and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, lithium, and the like.

PHARMACEUTICAL COMPOSITION OF THE COMPOUND OF THE INVENTION AND PREPARATIONS AND ADMINISTRATION

[00125] The pharmaceutical composition disclosed herein comprises any one of the compounds. The pharmaceutical composition further comprises a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof. The pharmaceutical composition can be used for treating HCV infection or a HCV disorder, especially which has a good inhibitory effect on NS3/4A protein.

[00126] The pharmaceutical composition disclosed herein further comprises anti-HCV agents. The anti-HCV agent may be any other known anti-HCV agent except the compound described herein. For example, which can be an anti-HCV agent, wherein the anti-HCV agent is interferon, ribavirin, IL-2, IL-6, IL-12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, imiquimod, an inosine5'-monophosphate

dehydrogenase inhibitor, amantadine, rimantadine, bavituximab, CIVACIRTM, boceprevir, telaprevir, erlotinib, daclatasvir, simeprevir, asunaprevir, vaniprevir, faldaprevir, paritaprevir, danoprevir, sovalprevir, grazoprevir, vedoprevir, BZF-961, GS-9256, narlaprevir, ANA975, ombitasvir, EDP239, PPI-668, velpatasvir, samatasvir, elbasvir, MK-8325, GSK-2336805, PPI-461, BI-2013335, ciluprevir, ACH-1095, VX-985, IDX-375, VX-500, VX-813, PHX-1766, PHX-2054, IDX-136, IDX-316, modithromycin, VBY-376, TMC-649128, mericitabine, sofosbuvir, INX-189, IDX-184, IDX102, R-1479, UNX-08189, PSI-6130, PSI-938, PSI-879, nesbuvir, HCV-371, VCH-916, lomibuvir, MK-3281, dasabuvir, ABT-072, filibuvir, deleobuvir, tegobuvir, A-837093, JKT-109, GI-59728, GL-60667, AZD-2795, TMC647055, MK-3682, GS-9669, odalasvir, furaprevir, setrobuvir, alisporivir, BIT-225, AV-4025, ACH-3422, MK-2748, MK-8325, JNJ-47910382, ABP-560, TD-6450, TVB-2640, ID-12, PPI-383, A-848837, RG-7795, BC-2125 or a combination thereof. The interferon is interferon α -2b, pegylated interferon α , interferon α -2a, pegylated interferon α -2a, consensus interferon- α , interferon γ or a combination thereof. The pharmaceutical composition further comprise an HCV inhibitor, wherein the HCV inhibitor inhibits HCV replication process and/or a function of an HCV viral protein, and wherein the HCV replication process is a whole viral cycle consisting of HCV entry, uncoating, translation, replication, assembly and egress; and wherein the HCV viral proteins comprise metalloproteinase, non-structural protein NS2, NS3, NS4A, NS4B, NS5A or NS5B, an internal ribosome entry site (IRES) and inosine-5'-monophosphate dehydrogenase (IMPDH) required in HCV viral replication.

[00127] When it is possible that, for use in therapy, therapeutically effective amounts of the compound of formula (I) of the invention, as well as pharmaceutically acceptable salts thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. The invention further provides pharmaceutical compositions, which comprise therapeutically effective amounts of compounds of Formula (I) or pharmaceutically acceptable salts thereof, and one or more pharmaceutically acceptable carrier, diluent or excipient. The term "therapeutically effective amount," as used herein, refers to the total amount of each active component that is sufficient to show a meaningful patient benefit (*e.g.*, a reduction in viral load). When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in

combination, serially, or simultaneously. The compounds of Formula (I) and pharmaceutically acceptable salts thereof, are as described above. The carrier(s), diluent(s), or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the present disclosure there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable carriers, diluents, or excipients. The term “pharmaceutically acceptable,” as used herein, refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

[00128] Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Dosage levels of between about 0.01 and about 250 milligram per kilogram (“mg/kg”) body weight per day, preferably between about 0.05 and about 100 mg/kg body weight per day of the compounds of the present disclosure are typical in a mono therapy for the prevention and treatment of HCV mediated disease. Typically, the pharmaceutical compositions of this disclosure will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending on the condition being treated, the severity of the condition, the time of administration, the route of administration, the rate of excretion of the compound employed, the duration of treatment, and the age, gender, weight, and condition of the patient. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Treatment may be initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compound is most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

[00129] When the compositions of this disclosure comprise a combination of a compound of the

present disclosure and one or more additional therapeutic or prophylactic agent, both the compound and the additional agent are usually present at dosage levels of between about 10 to 150%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen. Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual, or transdermal), vaginal, or parenteral (including subcutaneous, intracutaneous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional, intravenous, or intradermal injections or infusions) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s). Oral administration and administration by injection are preferred.

[00130] Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solution or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil emulsions.

[00131] For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing, and coloring agent can also be present.

[00132] Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate, or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate, or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

[00133] Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or β -lactose, corn sweetener, natural and synthetic resin such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, and

the like. Lubricants used in these dosage forms include sodium oleate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, betonite, xanthan gum, and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant, and pressing into tablets. A powder mixture is prepared by mixing the compound, suitable comminuted, with a diluents or base as described above, and optionally, with a binder such as carboxymethylcellulose, an algininate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or and absorption agent such as betonite, kaolin, or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acacia mucilage, or solution of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulation, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc, or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present disclosure can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material, and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

[00134] Oral fluids such as solution, syrups, and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxyethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners, or saccharin or other artificial sweeteners, and the like can also be added.

[00135] Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating of embedding particulate material in polymers, wax, or the like.

[00136] The compounds of Formula (I), and pharmaceutically acceptable salts thereof, can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles,

large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

[00137] The compounds of Formula (I) and pharmaceutically acceptable salts thereof may also be delivered by the use of monoclonal antibodies as individual carrier to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers may encompass polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidophenol, polyhydroxy ethylaspartamidophenol or polyethylene oxide polylysine, substituted by palmitoyl radicals. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, poly(ϵ -caprolactone), polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

[00138] Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in *Pharmacol. Res.*, **1986**, 3(6), 318.

[00139] Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols, oils or transdermal patch.

[00140] Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

[00141] Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, *i.e.*, by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or nasal drops, include aqueous or oil solutions of the active ingredient.

[00142] Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered, dose pressurized aerosols, nebulizers, insufflators or other device which suitable for delivering aerosol spray.

[00143] Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulations.

[00144] Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain antioxidants, buffers, bacteriostats, and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

[00145] It should be understood that in addition to ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

USE OF THE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS

[00146] Provided herein is use of the compound or the pharmaceutical composition in the manufacture of a medicament for inhibiting HCV replication process and/or a function of an HCV viral protein, and wherein the HCV replication process is a whole viral cycle consisting of HCV entry, uncoating, translation, replication, assembly and egress; and wherein the HCV viral proteins comprise metalloproteinase, non-structural protein NS2, NS3, NS4A, NS4B, NS5A or NS5B, an internal ribosome entry site (IRES) and inosine-5'-monophosphate dehydrogenase (IMPDH) required in HCV viral replication. The pharmaceutical composition can be used for treating HCV infection or a HCV disorder, especially which has a good inhibitory effect on HCV NS3/4A protein.

[00147] The present invention also disclosed a therapeutic method comprising administering the compound or pharmaceutical composition disclosed herein, further comprising administering an other than anti-HCV agent, therefore, the method can comprise administering both the compound and the other than anti-HCV agent in a combination, wherein the anti-HCV agent is interferon, ribavirin, IL-2, IL-6, IL-12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, imiquimod, an inosine 5'-monophosphate

dehydrogenase inhibitor, amantadine, rimantadine, bavituximab, CIVACIRTM, boceprevir, telaprevir, erlotinib, daclatasvir, simeprevir, asunaprevir, vaniprevir, faldaprevir, paritaprevir, danoprevir, sovalprevir, grazoprevir, vedoprevir, BZF-961, GS-9256, narlaprevir, ANA975, ombitasvir, EDP239, PPI-668, velpatasvir, samatasvir, elbasvir, MK-8325, GSK-2336805, PPI-461, BI-2013335, ciluprevir, ACH-1095, VX-985, IDX-375, VX-500, VX-813, PHX-1766, PHX-2054, IDX-136, IDX-316, modithromycin, VBY-376, TMC-649128, mericitabine, sofosbuvir, INX-189, IDX-184, IDX102, R-1479, UNX-08189, PSI-6130, PSI-938, PSI-879, nesbuvir, HCV-371, VCH-916, lomibuvir, MK-3281, dasabuvir, ABT-072, filibuvir, deleobuvir, tegobuvir, A-837093, JKT-109, GI-59728, GL-60667, AZD-2795, TMC647055, MK-3682, GS-9669, odalasvir, furaprevir, setrobuvir, alisporivir, BIT-225, AV-4025, ACH-3422, MK-2748, MK-8325, JNJ-47910382, ABP-560, TD-6450, TVB-2640, ID-12, PPI-383, A-848837, RG-7795, BC-2125 or a combination thereof. The interferon is interferon α -2b, pegylated interferon α , interferon α -2a, pegylated interferon α -2a, consensus interferon- α , interferon γ or a combination thereof.

[00148] The treatment method that includes administering a compound or composition disclosed herein can further include administering to the patient an additional anti-HCV agent, wherein the additional anti-HCV drug is administered together with a compound or composition disclosed herein as a single dosage form or separately from the compound or composition as part of a multiple dosage form. The additional anti-HCV agent may be administered at the same time as a compound disclosed herein or at a different time. In the latter case, administration may be staggered by, for example, 6 hours, 12 hours, 1 day, 2 days, 3 days, 1 week, 2 weeks, 3 weeks, 1 month, or 2 months.

[00149] An “effective amount” or “effective dose” of the compound or pharmaceutically acceptable composition is an amount that is effective in treating or lessening the severity of one or more of the aforementioned disorders. The compounds and compositions, according to the method disclosed herein, may be administered using any amount and any route of administration which is effective for treating or lessening the severity of the disorder or disease. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. A compound or composition can also be administered with one or more other therapeutic agents as discussed above.

GENERAL SYNTHETIC PROCEDURES

[00150] Generally, the compounds disclosed herein may be prepared by methods described herein, wherein the substituents are as defined for Formula (I) above, except where further noted. The following non-limiting schemes and examples are presented to further exemplify the invention.

[00151] Persons skilled in the art will recognize that the chemical reactions described may be readily adapted to prepare a number of other compounds disclosed herein, and alternative methods for preparing the compounds disclosed herein are deemed to be within the scope disclosed herein. For example, the synthesis of non-exemplified compounds according to the invention may be successfully performed by modifications apparent to those skilled in the art, *e.g.*, by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, and/or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds disclosed herein.

[00152] In the examples described below, unless otherwise indicated all temperatures are set forth in degrees Celsius. Reagents were purchased from commercial suppliers such as Aldrich Chemical Company, Arco Chemical Company and Alfa Chemical Company, and were used without further purification unless otherwise indicated. Common solvents were purchased from commercial suppliers such as Shantou XiLong Chemical Factory, Guangdong Guanghua Reagent Chemical Factory Co. Ltd., Guangzhou Reagent Chemical Factory, Tianjin YuYu Fine Chemical Ltd., Qingdao Tenglong Reagent Chemical Ltd., and Qingdao Ocean Chemical Factory.

[00153] Anhydrous THF, dioxane, toluene, and ether were obtained by refluxing the solvent with sodium. Anhydrous CH_2Cl_2 and CHCl_3 were obtained by refluxing the solvent with CaH_2 . EtOAc, PE, hexane, DMAC and DMF were treated with anhydrous Na_2SO_4 prior to use.

[00154] The reactions set forth below were done generally under a positive pressure of nitrogen or argon or with a drying tube (unless otherwise stated) in anhydrous solvents, and the reaction flasks were typically fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried.

[00155] Column chromatography was conducted using a silica gel column. Silica gel (300-400 mesh) was purchased from Qingdao Ocean Chemical Factory. ^1H NMR spectra were obtained by

using CDCl_3 , $\text{DMSO}-d_6$, CD_3OD or $\text{acetone}-d_6$ solutions (reported in ppm), with TMS (0 ppm) or chloroform (7.25 ppm) as the reference standard. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets),. Coupling constants, when given, were reported in Hertz (Hz).

[00156] Low-resolution mass spectral (MS) data were determined by an Agilent 6320 Series LC-MS spectrometer equipped with a G1312A binary pump and a G1316A TCC (column was operated at 30 °C). G1329A autosampler and G1315B DAD detector were applied in the analysis, and an ESI source was used in the LC-MS spectrometer.

[00157] Low-resolution mass spectral (MS) data were determined by an Agilent 6120 Series LC-MS spectrometer equipped with a G1311A quaternary pump and a G1316A TCC (column was operated at 30 °C). G1329A autosampler and G1315D DAD detector were applied in the analysis, and an ESI source was used on the LC-MS spectrometer.

[00158] Both LC-MS spectrometers were equipped with an Agilent Zorbax SB-C18, 2.1 x 30 mm, 5 μm column. Injection volume was decided by the sample concentration. The flow rate was 0.6 mL/min. The HPLC peaks were recorded by UV-Vis wavelength at 210 nm and 254 nm. The mobile phase was 0.1% formic acid in acetonitrile (phase A) and 0.1% formic acid in ultrapure water (phase B). The gradient elution conditions were showed in Table 1:

Table 1

Time (min)	A (CH_3CN , 0.1% HCOOH)	B (H_2O , 0.1% HCOOH)
0-3	5-100	95-0
3-6	100	0
6-6.1	100-5	0-95
6.1-8	5	95

[00159] Purities of compounds were assessed by Agilent 1100 Series high performance liquid chromatography (HPLC) with UV detection at 210 nm and 254 nm (Zorbax SB-C18, 2.1 $\times$ 30 mm, 4 micorn, 10 min, 0.6 mL/min flow rate, 5 to 95 % (0.1% formic acid in CH_3CN) in (0.1% formic acid in H_2O). Column was operated at 40 °C.

[00160] The following abbreviations are used throughout the specification:

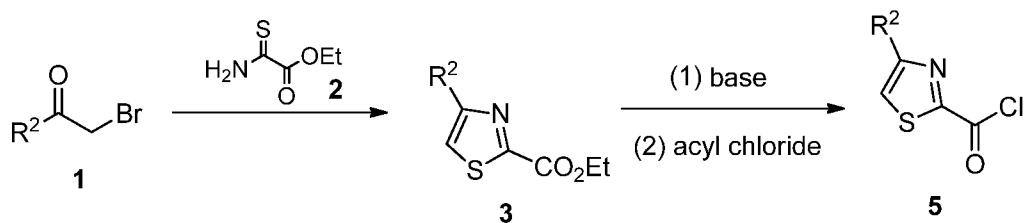
Ac	acetyl
Ac_2O	acetic anhydride
AcOH	acetic acid

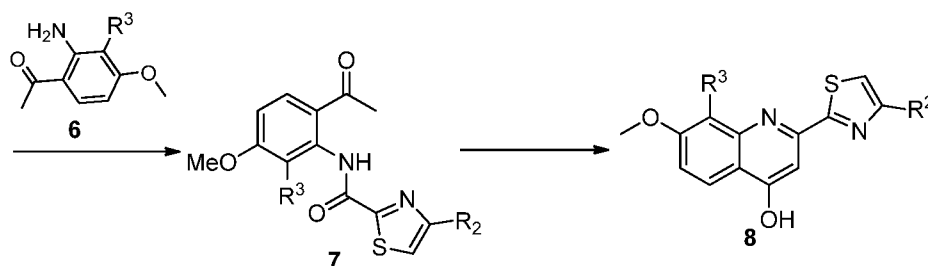
AcONa	sodium acetate
Boc	<i>tert</i> -butoxycarbonyl
Boc ₂ O	di- <i>tert</i> -butyl dicarbonate
Bn	benzyl
<i>t</i> -BuOLi	<i>tert</i> -butyllithium
Cbz	benzyloxy carbonyl
CH ₃ CN, MeCN, ACN	acetonitrile
CDI	1,1'-carbonyldiimidazole
CDCl ₃	chloroform- <i>d</i>
Cs ₂ CO ₃	cesium carbonate
CoCl ₂ ·6H ₂ O	cobalt chloride hexahydrate
CuSO ₄ ·5H ₂ O	copper sulfate pentahydrate
CO ₂	carbon dioxide
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DBAD	di- <i>tert</i> -butyl azodicarboxylate
DCM	dichloromethane
DMSO	dimethylsulfoxide
DIPEA	<i>N,N</i> -diisopropylethylamine
DIAD	diisopropyl azodicarboxylate
DMF	<i>N,N</i> -dimethylformamide
D ₂ O	water- <i>d</i> ₂
DTT	DL-dithiothreitol
DPPPy	diphenyl-2-pyridylphosphine
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EtOH	ethyl alcohol
EtOAc, EA	ethyl acetate
Et	ethyl
Et ₃ N	triethylamine
EP	eppendorf
Fmoc	fluorenylmethoxy carbonyl
HCl	hydrogen chloride
H ₂ O	water
HOAT	<i>N</i> -hydroxy-7-azabenzotriazole
HATU	2-(7-aza-1 <i>H</i> -benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

HCl/EA, HCl·EA	a solution of hydrogen chloride in ethyl acetate
HPLC	high performance liquid chromatography
IPA, <i>i</i> -PrOH	isopropanol
K ₂ CO ₃	potassium carbonate
KOH	potassium hydroxide
PMB	<i>p</i> -methoxybenzyl
LiOH	lithium hydroxide
Me	methyl
MeOH	methanol
MTBE	<i>tert</i> -butyl methyl ether
Na ₂ SO ₄	sodium sulfate
NaOH	sodium hydroxide
NaHCO ₃	sodium bicarbonate
NaHSO ₄	sodium bisulfate
NaCl	sodium chloride
NaN ₃	sodium azide
NADPH	nicotinamide adenine dinucleotide phosphate
N ₂	nitrogen
NH ₄ Cl	ammonia chloride
PE	petroleum ether (60 - 90 °C)
Py	pyridine
rt	room temperature
<i>p</i> -TSA	<i>p</i> -toluenesulfonic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TsCl	paratoluensulfonyl chloride

Scheme

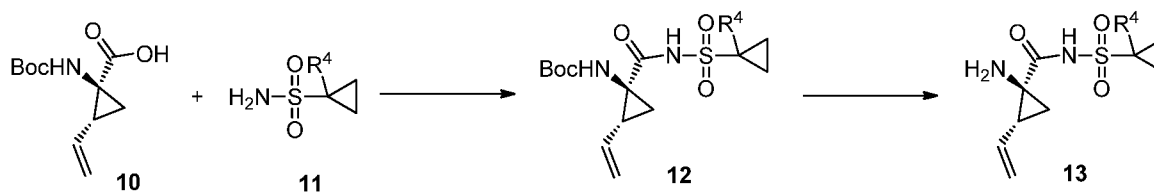
Scheme 1





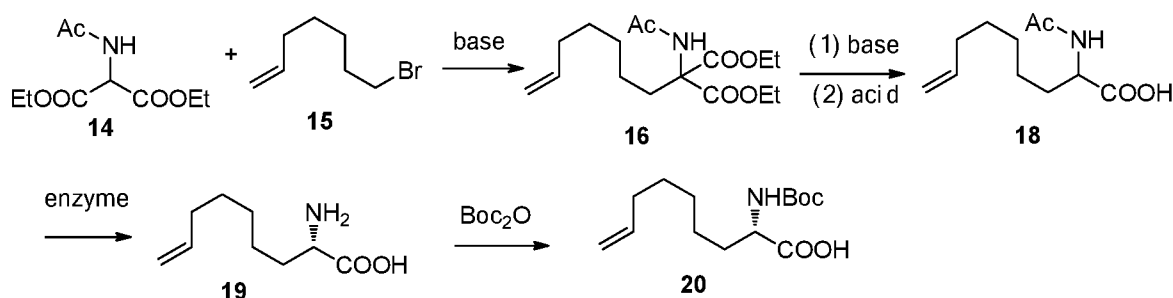
[00161] Compound **8** can be prepared by the process illustrated in Scheme 1, wherein R^2 and R^3 are as defined herein. Cyclization of compound **1** and compound **2** can afford compound **3**; compound **3** can be hydrolyzed under a base (such as lithium hydroxide, sodium hydroxide, and the like), the hydrolysis product can react with acyl chloride (such as oxalyl chloride, thionyl chloride, and the like) to afford compound **5**. Compound **5** can react with compound **6** to afford compound **7**; compound **7** can be cyclized under a base (such as potassium *tert*-butoxide, sodium *tert*-butoxide, and the like) to afford compound **8**.

Scheme 2



[00162] Compound **13** can be prepared by the process illustrated in Scheme 2, wherein R^4 is as defined herein; the condensation agent used herein is CDI, EDCI, HATU and so on, the acid used herein is hydrochloric acid, sulfuric acid, *p*-toluenesulfonic acid and so on. Compound **10** can be condensed with compound **11** in the present of a condensating agent to afford compound **12**; and then a protecting group of compound **12** can be removed under an acid condition to afford compound **13**.

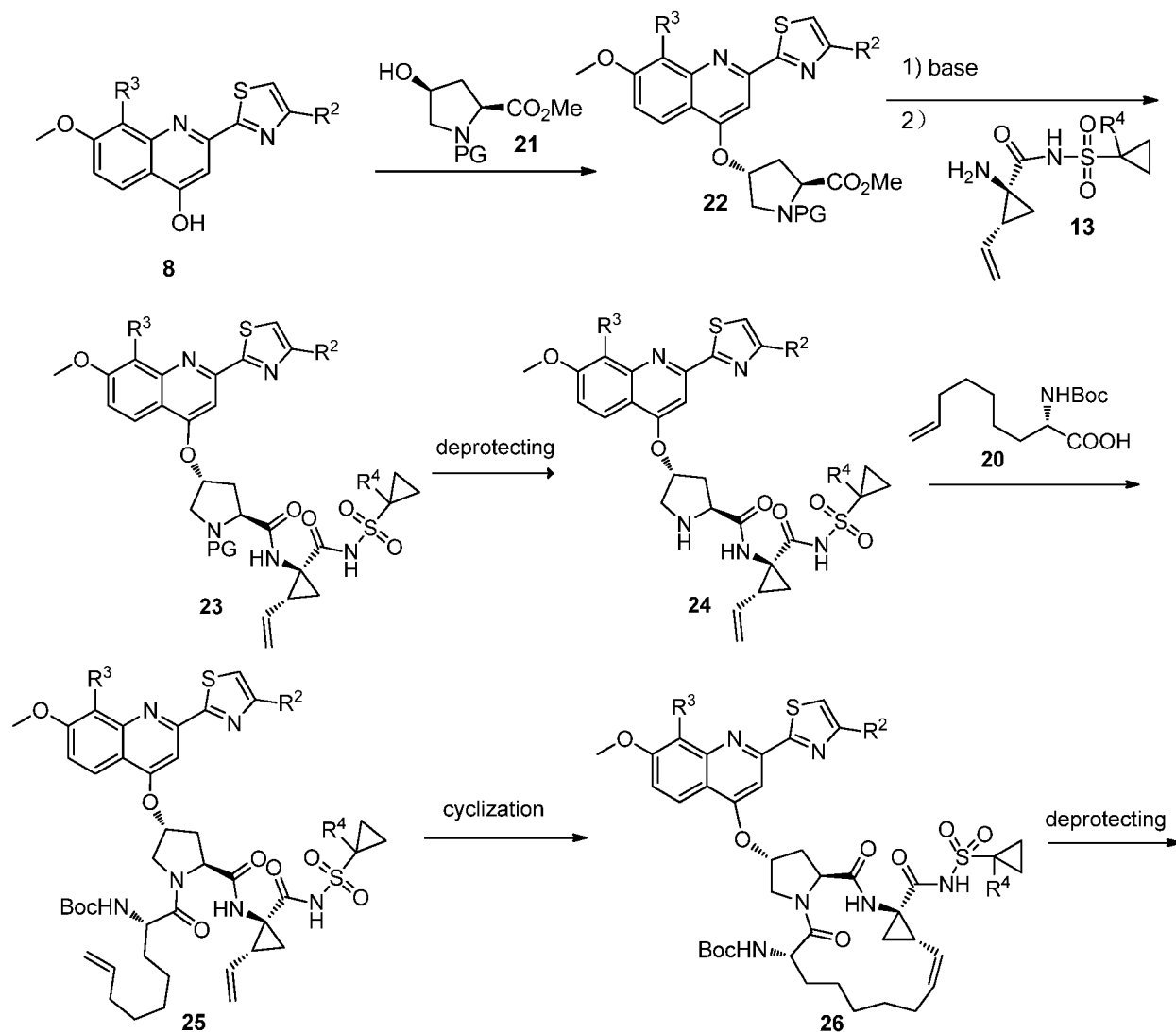
Scheme 3

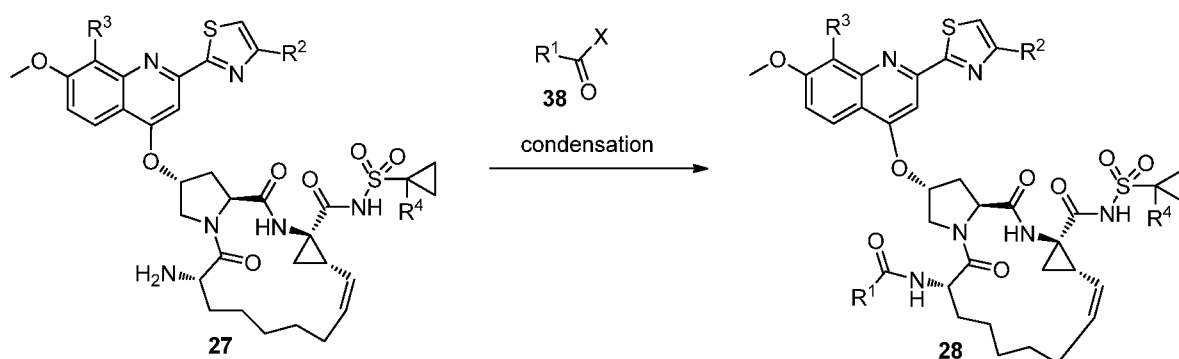


[00163] Compound **20** disclosed herein can be prepared by the process illustrated in scheme 3, Compound **14** can react with compound **15** under a base (such as lithium hydroxide, sodium hydroxide, potassium carbonate, sodium carbonate, cesium carbonate, and so on) to afford

compound **16**; compound **16** can be hydrolyzed under a base (such as lithium hydroxide, sodium hydroxide, potassium hydroxide, and the like), the hydrolysis product can be decarboxylated in the present of an acid (such as citric acid, hydrochloric acid, sulfuric acid, *p*-toluenesulfonic acid, and the like) to afford compound **18**. An acetyl group of compound **18** can be removed selectively in the present of an enzyme (such as deacetylase and so on) to afford compound **19**; compound **19** can be protected by a protecting group (such as Boc, Fmoc, and so on) to afford compound **20**.

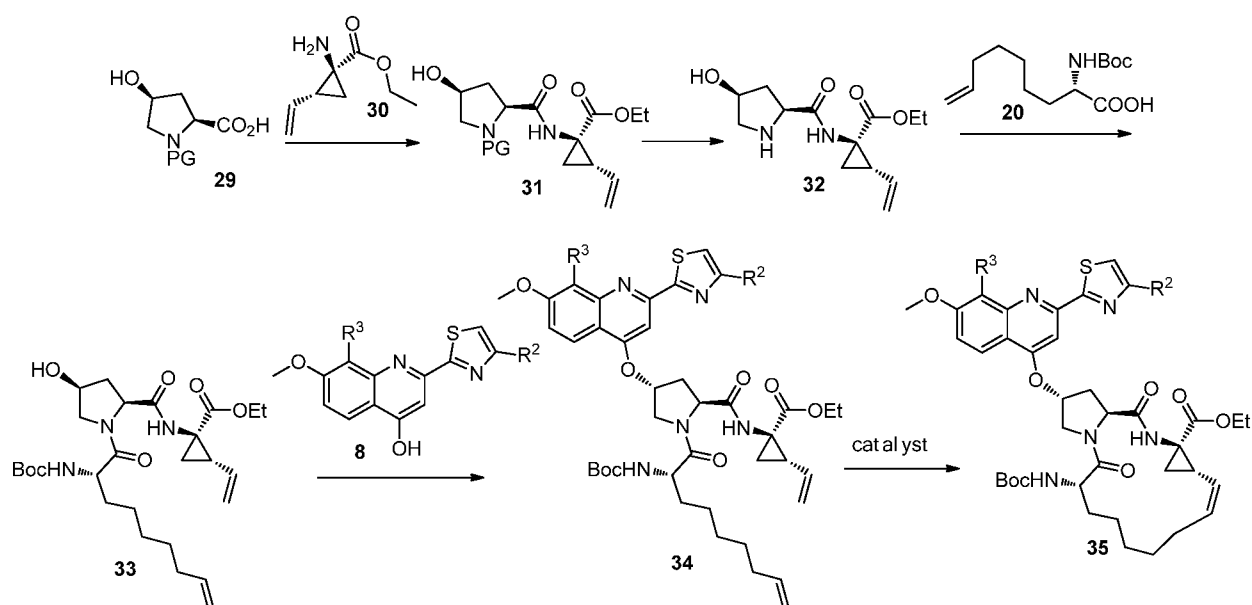
Scheme 4

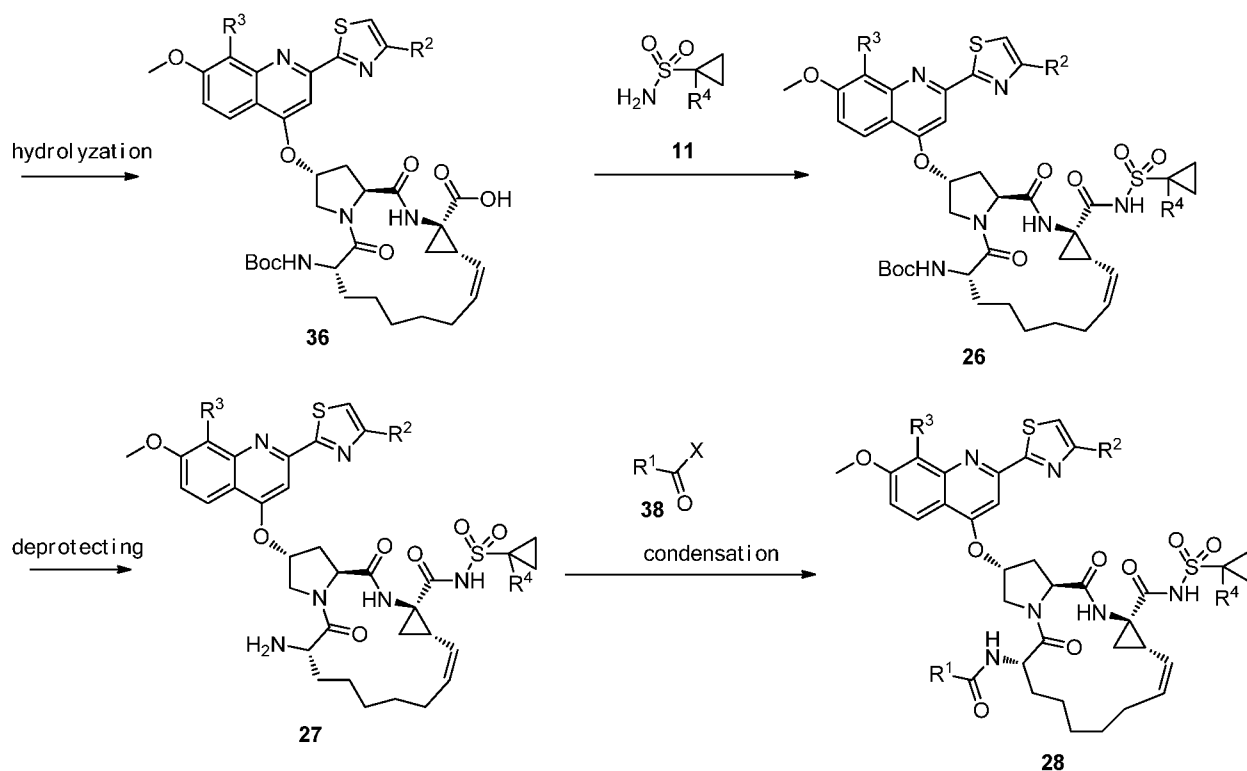




[00164] Compound **28** can be prepared by the process illustrated in Scheme 4, wherein R^1 , R^2 , R^3 and R^4 are as defined herein. The protecting group PG is Boc, Fmoc, Cbz, Bn, PMB, and so on; the base used herein is sodium hydroxide, sodium carbonate, potassium carbonate, potassium *tert*-butoxide, sodium *tert*-butoxide and so on; X is halogen or hydroxy; the condensation agent used herein is CDI, EDCI, HATU and so on; the catalyst used for cyclization is Grubb's Catalyst 2nd generation, ZHAN Catalyst-1B, ZHAN Catalyst-1C and so on. Compound **8** can react with compound **21** by Mitsunobu reaction to afford compound **22**; compound **22** can be hydrolyzed under a base, the hydrolysis product can be condensed with compound **13** in the present of a condensation agent to afford compound **23**. The protecting group of compound **23** can be removed to afford compound **24**; compound **24** can react with compound **20** in the present of a condensation agent to afford compound **25**. Compound **25** can convert to compound **26** catalyzed by a catalyst used for cyclization; the protecting group of compound **26** can be removed to afford compound **27**; compound **27** can react with compound **38** in the present of a condensation agent to afford compound **28**.

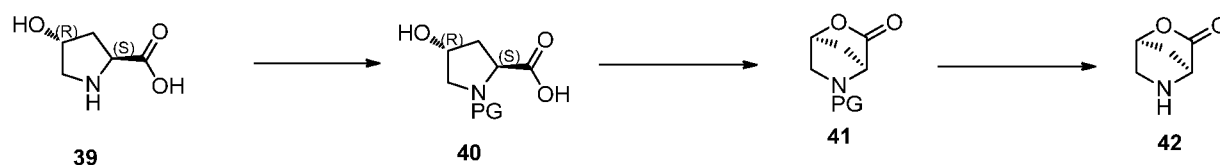
Scheme 5

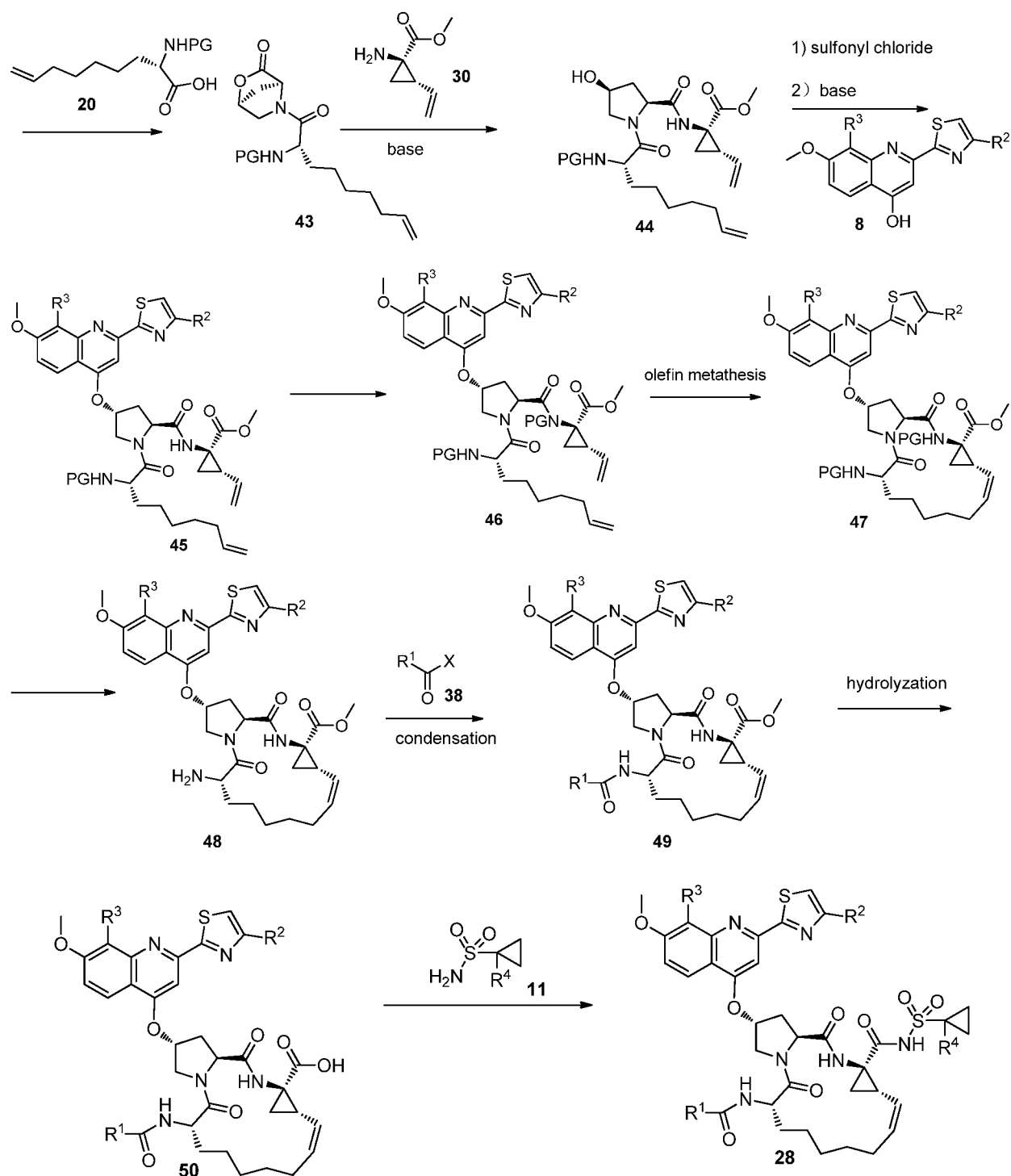




[00165] Compound **28** can be prepared by the process illustrated in Scheme 5, wherein R^1 , R^2 , R^3 and R^4 are as defined herein. The protecting group PG is Boc, Fmoc, Cbz, Bn, PMB, and so on; the base used herein is sodium hydroxide, sodium carbonate, potassium carbonate, potassium *tert*-butoxide, sodium *tert*-butoxide and so on; X is halogen or hydroxy; the catalyst used for cyclization is Grubb's Catalyst 2nd generation, ZHAN Catalyst-1B, ZHAN Catalyst-1C and so on. Compound **29** can react with compound **30** in the present of a condensation agent to afford compound **31**; the amino protecting group of compound **31** can be removed to afford compound **32**; compound **32** can react with compound **20** in the present of a condensation agent to afford compound **33**. Compound **33** can react with compound **8** by Mitsunobu reaction to afford compound **34**; compound **34** can convert to compound **35** catalyzed by a catalyst used for cyclization; compound **35** can be hydrolysed under a base to afford compound **36**. Compound **36** can react with compound **11** in the present of a condensation agent to afford compound **26**. The amino protecting group of compound **26** can be removed to afford compound **27**. Compound **27** can react with compound **38** in the present of a condensation agent to afford compound **28**.

Scheme 6



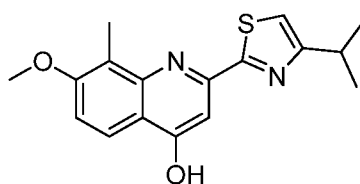


[00166] Compound **28** can be prepared by the process illustrated in Scheme 6, wherein R^1 , R^2 , R^3 and R^4 are as defined herein. The protecting group PG is Boc, Fmoc, Bn, Cbz, and so on. Compound **39** can be protected with an amino protecting group to afford compound **40**. Mitsunobu reaction of compound **40** can afford lactonic compound **41**; the protecting group of compound **41** can be removed to afford compound **42**. Condensation reaction of compound **42** with compound **20** can afford compound **43**, the condensation agent used herein is CDI, EDCI, HATU, and so on. Compound **43** can react with compound **30** under a base (such as sodium

iso-octoate, sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, and so on) to afford compound **44**. Compound **44** can react with sulfonyl chloride (such as methylsulfonyl chloride, *p*-toluenesulfonyl chloride, *p*-bromobenzenesulfonyl chloride, *p*-nitrobenzenesulfonyl chloride, and so on) to afford an intermediate having a better leaving group. The intermediate can react with compound **8** under a base (such as cesium carbonate, potassium carbonate, sodium carbonate and so on) to afford compound **45**; the amide group of compound **45** can be protected to afford compound **46**. Olefin metathesis of compound **46** in the presence of a catalyst (such as ZHAN Catalyst-1B, ZHAN Catalyst-1C, Grubb's Catalyst 2nd generation, and so on) can afford compound **47**. Deprotection reaction of compound **47** can afford compound **48**. Condensation reaction of compound **48** with compound **38** can afford compound **49**; compound **49** can be hydrolyzed under a base (such as lithium hydroxide, sodium hydroxide, potassium hydroxide, and the like) to afford compound **50**. Compound **50** can react with compound **11** to afford compound **28**.

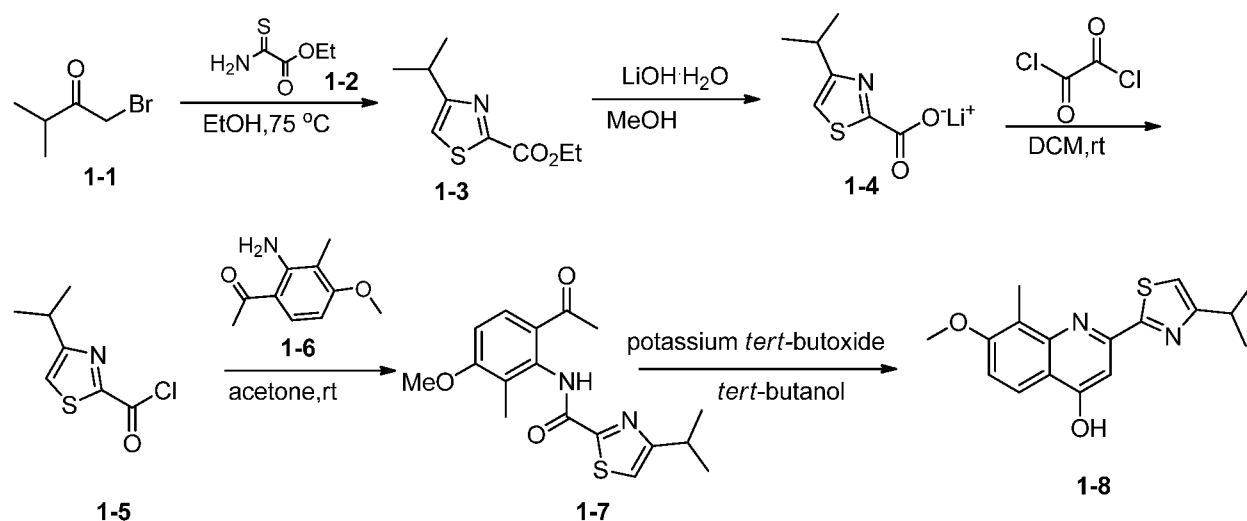
Example

Example 1



1-8

Synthesis route:



Step 1) preparation of compound **1-3**

[00167] A mixture of compound **1-2** (20 g, 150 mmol) and compound **1-1** (30 g, 170 mmol) in

ethanol (100 mL) was stirred at 75 °C for 2 hours. After the reaction was complete, the mixture was cooled to rt and concentrated *in vacuo*. The residue was diluted with water (100 mL), and the mixture was adjusted with ammonium hydroxide to pH between 6 and 8. The resulting mixture was extracted with MTBE (100 mL × 2). The combined organic layers were washed with water (50 mL × 2) and concentrated *in vacuo* to afford a brownish red crude product **1-3**, which was used in next step without further purification.

MS (ESI, pos.ion) *m/z*: 200.3[M+1]⁺.

Step 2) preparation of compound **1-4**

[00168] A solution of compound **1-3** (28 g, 140 mmol) in methanol (140 mL) was cooled to 0 °C, and then LiOH·H₂O (7 g, 168 mmol) was added. The mixture was stirred at 0 °C for 30 min and warmed up to rt, and further stirred for 3 hours. After the reaction was complete, the mixture was concentrated *in vacuo* and the residue was diluted with MTBE (140 mL). The mixture was stirred at 55 °C for 3 hours and cooled to rt, then further stirred for 2 hours. The mixture was filtered. The filter cake was washed with MTBE (50 mL) twice. The obtained solid was dried at 50 °C *in vacuo* to afford compound **1-4** (21.2 g, total yield of the two steps: 80%) as a pale yellow solid.

MS (ESI, pos.ion) *m/z*: 172.2[M+1]⁺.

Step 3) preparation of compound **1-5**

[00169] A solution of compound **1-4** (20 g, 113 mmol) in DCM (100 mL) was cooled to 0 °C, and then oxalyl chloride (30 g, 226 mmol) was added dropwise. The mixture was stirred at 0 °C for 30 min and warmed up to rt, and further stirred for 4 hours. After the reaction was complete, the mixture was filtered. The filtrate was concentrated *in vacuo* to afford a crude product **1-5**, which was used in next step without further purification.

Step 4) preparation of compound **1-7**

[00170] A solution of compound **1-5** (16 g, 84 mmol) in acetone (50 mL) was cooled to 0 °C, and then compound **1-6** (10 g, 55.8 mmol) was added. The mixture was stirred at 0 °C for 30 min and warmed up to rt, and further stirred for 4 hours. After the reaction was complete, the mixture was dropped in water (500 mL), there was a large amount of solid precipitated out after stirring. The mixture was filtered. The filter cake was washed with water (200 mL) twice. The obtained solid was dried at 55 °C *in vacuo* to afford compound **1-7** (14.8 g, 80%) as a pale yellow solid.

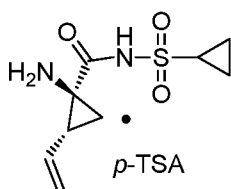
MS (ESI, pos.ion) *m/z*: 333.2[M+1]⁺.

Step 5) preparation of compound **1-8**

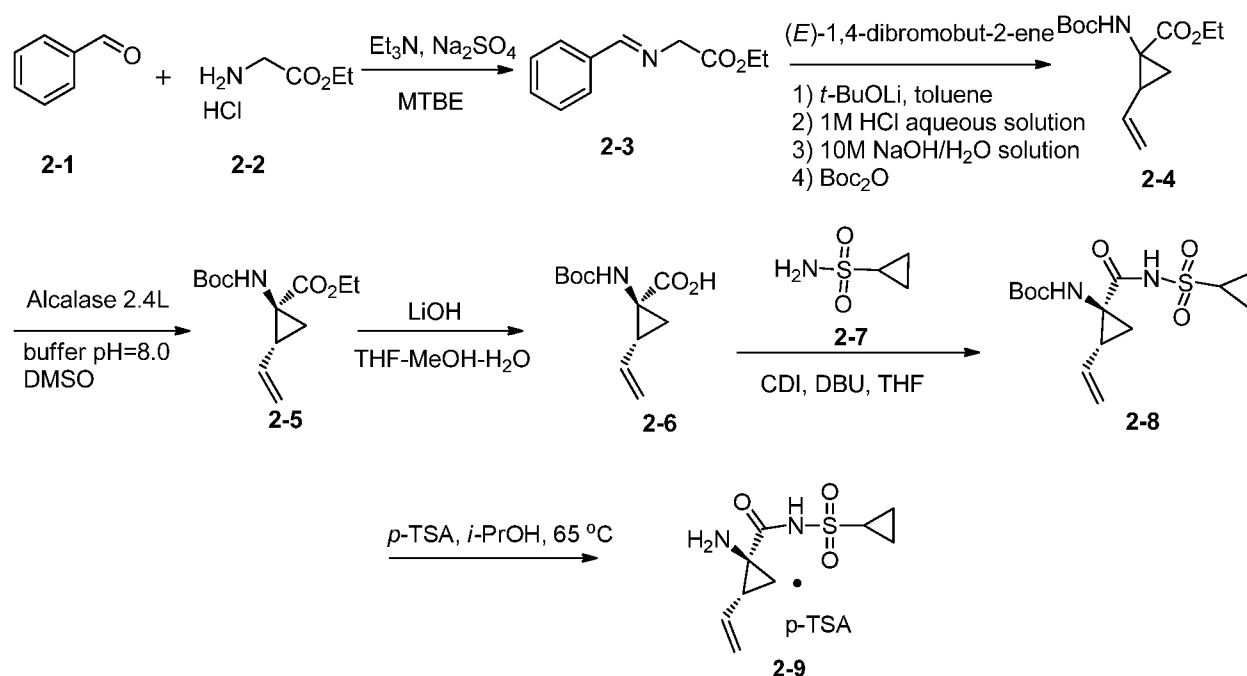
[00171] A mixture of compound **1-7** (5 g, 15 mmol) and potassium *tert*-butoxide (3.36 g, 30 mmol) in *tert*-butanol (50 mL) was stirred at 100 °C for 8 hours. After the reaction was complete, the mixture was cooled to rt and concentrated to remove *tert*-butanol (20 mL). The resulting mixture was poured into hydrochloric acid (0.5 M, 200 mL) at 0 °C. There was a large amount of yellow solid precipitated out after stirring. The mixture was filtered. The filter cake was washed with water (20 mL) and dried at 50 °C *in vacuo* to afford a pale yellow solid. The pale yellow solid was added into isopropyl ether (25 mL). The mixture was warmed to 60 °C and stirred for 2 hours. The mixture was cooled to rt and filtered. The filter cake was washed with isopropyl ether (5 mL × 2) to afford compound **1-8** (4.24g, 90%) as a white solid.

MS (ESI, pos.ion) m/z : 315.2[M+1]⁺.

Example 2



Synthesis route:

Step 1) preparation of compound **2-3**

[00172] A mixture of benzaldehyde **2-1** (95.6 mL, 943 mmol), glycine ethyl ester hydrochloride **2-2** (131 g, 943 mmol) and Na₂SO₄ (80 g, 565 mmol) in MTBE (900 mL) was cooled to 0 °C,

and then triethylamine (197 mL, 1414 mmol) was added slowly. After the addition, the mixture was warmed to 25 °C and stirred for 24 hours. The mixture was filtered by a diatomite filter. The filtrate was concentrated *in vacuo* to afford a crude product **2-3**, which was used in next step without further purification.

¹H NMR (600 MHz, CDCl₃): δ 8.28 (s, 1H), 7.86–7.71 (m, 2H), 7.50–7.32 (m, 3H), 4.47–4.32 (m, 2H), 4.29–4.18 (m, 2H), 1.32–1.22 (m, 3H) ppm.

Step 2) preparation of compound **2-4**

[00173] To a mixture of lithium *tert*-butoxide (17.60 g, 220 mmol) in toluene (250 mL) were added a solution of compound **2-3** (22.00 g, 117 mmol) in toluene (50 mL) and a solution of (*E*)-1,4-dibromobut-2-ene (20.00 g, 94 mmol) in toluene (50 mL) at 0 °C at the same time, the two solution was added at the same speed over 1 hour. The mixture was warmed to 30 °C and stirred for 2 hours, and then quenched with water (200 mL). The resulting mixture was extracted with MTBE (200 mL). To the combined organic layers were added hydrochloric acid (1 M, 200 mL), the mixture was stirred for 2 hours. The separated organic layer was extracted with water (150 mL). To the water layer was added sodium chloride (131.00 g, 2241 mmol) and MTBE (200 mL). The mixture was adjusted with aqueous NaOH solution (10 M) to pH between 12 and 13. The organic layer was separated; the water layer was extracted with MTBE (100 mL). To the combined organic layers was added Boc₂O (21 mL, 98 mmol). The mixture was stirred at rt overnight and then warmed to 60 °C, further stirred for 2 hours. The mixture was cooled to rt and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V : V) = 5 : 1 to afford compound **2-4** (12 g, 50%) as yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 5.17–5.80 (m, 1H), 5.29 (s, 1H), 5.06–5.09 (m, 1H), 4.12–4.19 (m, 2H), 2.17–2.14 (m, 1H), 1.77 (s, 1H), 1.43 (s, 1H), 1.41 (s, 9H), 1.24 (t, *J* = 7.2 Hz, 3H) ppm.

Step 3) preparation of compound **2-5**

[00174] Alcalase 2.4 L (52 mL) proteolytic enzyme was added into sodium phosphate buffer (0.1 M, 550 mL, pH = 8). The mixture was warmed to 39 °C, and 50% aqueous sodium hydroxide solution was added to adjusted pH 8.0. At this temperature, a solution of compound **2-4** (10.58 g, 42.5 mmol) in DMSO (100 mL) was added over 20 min. And then, the mixture was warmed to 40 °C and stirred for 24 hours. Aqueous sodium hydroxide solution (50%) was added

frequently to keep pH about 8.0 during the reaction process. The mixture was cooled to 30 °C and further stirred for 48 hours. The mixture was adjusted with aqueous sodium hydroxide solution (50%) to pH 8.5. The resulting mixture was extracted with MTBE (150 mL) twice. The combined organic layers were washed with aqueous NaHCO₃ solution (5%, 50 mL) thrice and with water (50 mL) thrice, and dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give compound **2-5** (5.01 g, 47%) as a yellow solid.

MS (ESI, pos.ion) *m/z*: 256.1[M+1]⁺.

Step 4) preparation of compound **2-6**

[00175] A solution of compound **2-5** (14.57 g, 57 mmol) in THF (100 mL) and methanol (50 mL) was cooled to 0 °C, and then a solution of lithium hydroxide (4.79 g, 114 mmol) in water (25 mL) was added dropwise. After the addition, the mixture was warmed to 30 °C and stirred overnight. The mixture was concentrated to afford solid; the solid was participated between ethyl acetate (50 mL) and water (50 mL). The water phase was adjusted with hydrochloric acid (1 M) to pH 4. The resulting mixture was extracted with ethyl acetate (50 mL) thrice. The combined organic layers were washed with saturated aqueous NaCl and dried over anhydrous Na₂SO₄, and concentrated *in vacuo* to afford a crude product **2-6** (12 g), which was used in next step without further purification.

MS (ESI, pos.ion) *m/z*: 228.1[M+1]⁺.

Step 5) preparation of compound **2-8**

[00176] To a solution of compound **2-6** (1.00 g, 4.4 mmol) in anhydrous tetrahydrofuran (20 mL) was added CDI (0.93 g, 5.7 mmol). The mixture was heated to reflux for 2 hours and then cooled to rt, compound **2-7** (0.80 g, 6.6 mmol) and DBU (1 mL, 6.6 mmol) were added. The resulting mixture was stirred at rt for 16 hours. After the reaction was complete, the mixture was concentrated *in vacuo*. The residue was diluted with ethyl acetate, the mixture was washed with hydrochloric acid (1 M) and saturated aqueous NaCl, dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to afford a crude product **2-8** (0.94 g, 65%).

MS (ESI, pos.ion) *m/z*: 331.1[M+1]⁺.

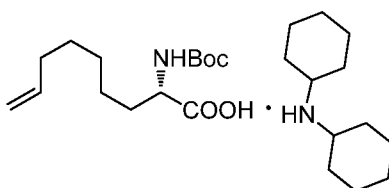
Step 6) preparation of compound **2-9**

[00177] To a solution of compound **2-8** (2.10 g, 6.3 mmol) in isopropanol (40 mL) was added *p*-toluenesulfonic acid (1.8 g, 9.4 mmol). The mixture was stirred at 65 °C for 4 hours and cooled to rt, and concentrated *in vacuo* to afford white solid. The solid was washed with ethyl acetate to

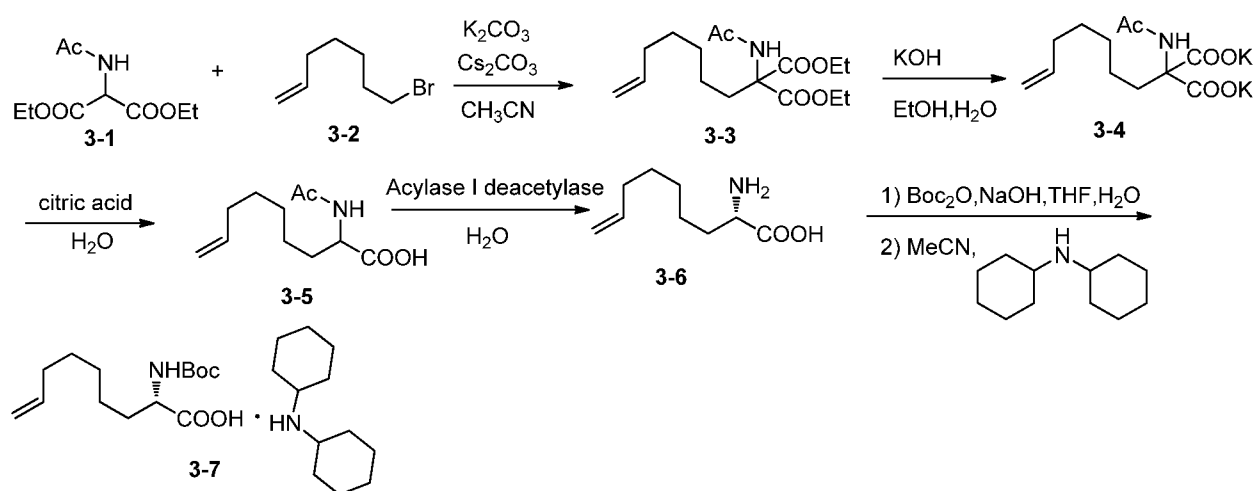
give compound **2-9**(1.49 g, 80%).

¹H NMR (400 MHz, CD₃OD): δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 7.9 Hz, 2H), 5.81–5.65 (m, 1H), 5.44 (d, *J* = 17.0 Hz, 1H), 5.36 (d, *J* = 10.3 Hz, 1H), 3.13–2.96 (m, 1H), 2.47–2.32 (m, 4H), 2.20 (t, *J* = 7.9 Hz, 1H), 1.72 (t, *J* = 9.0 Hz, 1H), 1.39–1.20 (m, 2H), 1.20–1.02 (m, 2H) ppm.

Example 3



Synthesis route:



Step 1) preparation of compound **3-3**

[00178] To a solution of compound **3-1** (100 g, 460.36 mmol) and compound **3-2** (100 g, 564.72 mmol) in acetonitrile (1 L) were added cesium carbonate (90 g, 276.219 mmol) and potassium carbonate (40 g, 289.427 mmol). The mixture was refluxed for 24 hours. The mixture was cooled to rt and filtered. The filtrate was concentrated *in vacuo* to afford a crude product **3-3**, which was used in next step without further purification.

MS (ESI, pos.ion) m/z : 314.4[M+1]⁺.

Step 2) preparation of compound 3-5

[00179] To a solution of compound **3-3** (150 g, 478.6 mmol) in ethanol (750 mL) was added aqueous KOH (81 g, 1443.72 mmol, 75 mL) solution dropwise. After the addition, the mixture was refluxed for 4 hours. After the reaction was complete, the mixture was concentrated *in vacuo*. The residue was diluted with water (500 mL). The resulting mixture was adjusted with citric acid (103 g, 536.118 mmol) to pH 4-5, and then refluxed overnight. After the reaction was complete,

the mixture was cooled to 0 °C and adjusted with hydrochloric acid (1 M) to pH 2-3, there was solid precipitated out. The mixture was filtered. The filter cake was washed with a little of water and dried to give a yellow solid **3-5** (70 g, 68.58%).

MS (ESI, pos.ion) m/z : 214.3[M+1]⁺.

Step 3) preparation of compound **3-6**

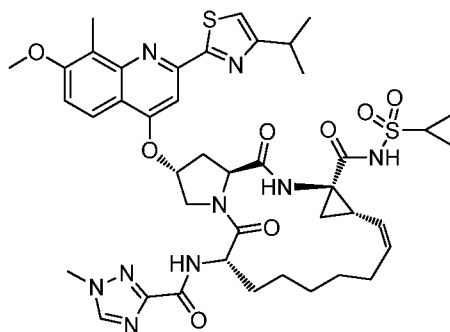
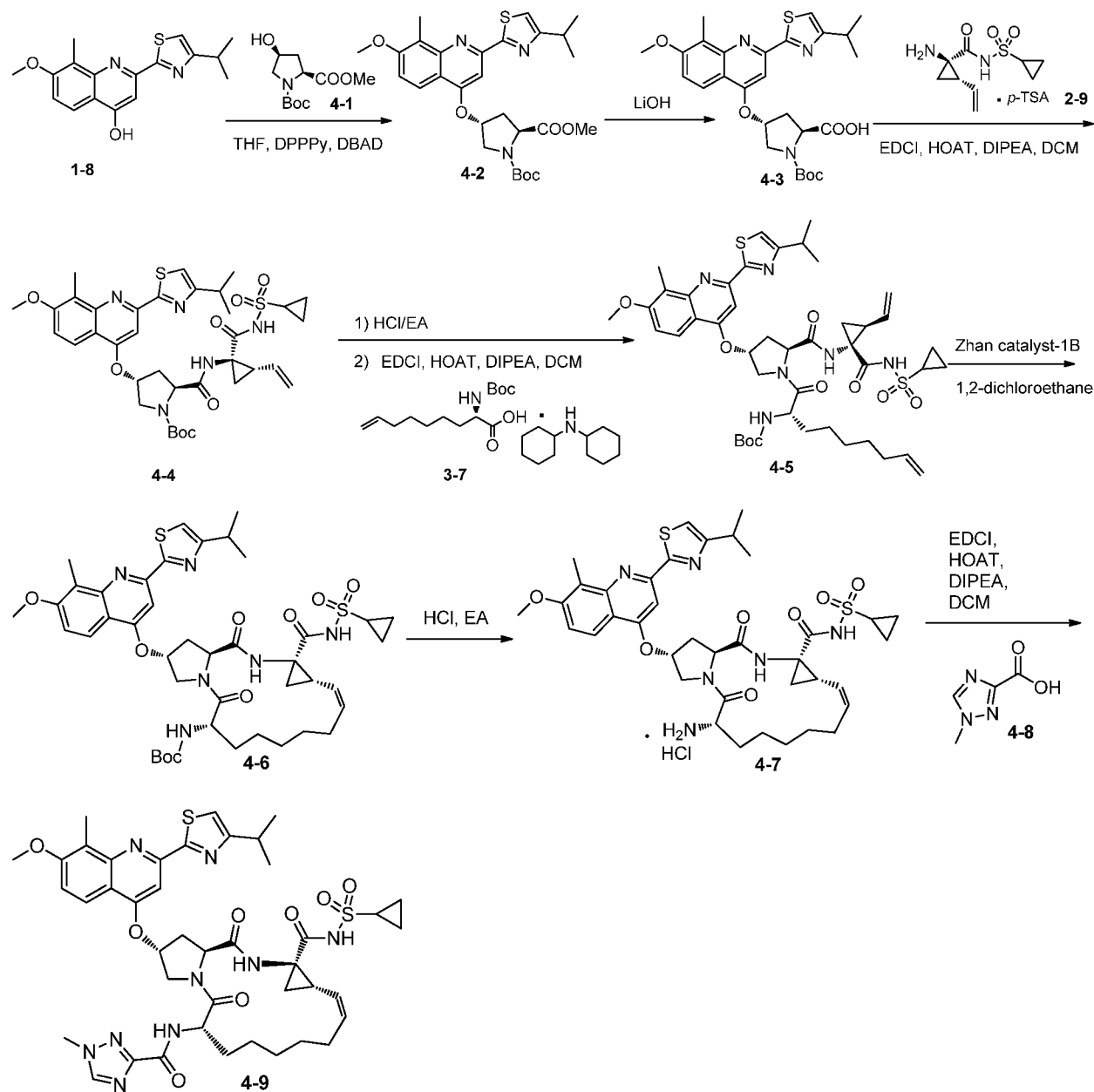
[00180] To a solution of compound **3-5** (70 g, 328.22 mmol) in H₂O (500 mL) was added sodium hydroxide (13.2 g, 330 mmol) and CoCl₂·6H₂O (0.05 g, 0.3 mmol) at rt. The mixture was stirred until dissolved completely. The mixture was adjusted with aqueous NaOH solution (0.1 M) to pH 7.8 and warmed to 38.5 °C, and then Acylase I deacetylase (350 mg, 0.5 U/mg) was added. The mixture was stirred at this temperature overnight. After the reaction was complete, the mixture was adjusted with hydrochloric acid (1 M) to pH 7.6 and cooled to rt and filtered. The filter cake was washed with water (1 L) and a mixed solvent of water and methanol (0.75 L, V : V = 10 : 1) in turn, and then dried at 55 °C *in vacuo* to give compound **3-6** (26 g, 46.2%) as a white solid.

Step 4) preparation of compound **3-7**

[00181] To a solution of compound **3-6** (250 g, 1.46 mol) in a mixed solvent of THF (1500 mL) and H₂O (1500 mL) was added NaOH (76 g, 1.9 mol) in an ice bath, and then Boc₂O (440 mL, 1900 mmol) was added dropwise. The mixture was stirred at rt overnight. After the reaction was complete, the mixture was concentrated *in vacuo* to remove THF. The residue was adjusted with saturated aqueous NaHSO₄ solution to pH 2-3. The resulting mixture was extracted with EtOAc (1000 mL × 3). The combined organic layers were washed with saturated aqueous NaCl solution, and dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give red oil. The red oil was diluted with MeCN (2500 mL), and dicyclohexylamine (340 mL, 1710 mmol) was added dropwise. The mixture was stirred at 50 °C for 30 min and cooled to rt, and then further stirred for 4 hours. The mixture was concentrated *in vacuo* to remove acetonitrile to give a white solid. The solid was triturated with PE (1 L) and filtered. The filter cake was dried at 50 °C *in vacuo* to give compound **3-7** (500 g, 96.70%).

MS (ESI, pos.ion) m/z : 172.3[M+1-100]⁺.

Example 4

**Synthesis route:****Step 1) preparation of compound 4-2**

[00182] A mixture of compound **1-8** (0.30 g, 1 mmol), compound **4-1** (0.23 g, 0.94 mmol), diphenyl-2-pyridylphosphine (DPPPy, 0.4 g, 2 mmol) and di-*tert*-butyl azodicarboxylate (DBAD,

0.3 g, 2 mmol) in THF (15 mL) was stirred at rt under N₂ for 24 hours. After the reaction was complete, the mixture was concentrated *in vacuo*. The residue was diluted with EtOAc (30 mL). The mixture was washed with hydrochloric acid (1 M, 20 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V : V) = 5 : 1 to afford a yellow product **4-2** (0.4 g, 80%) as oil.

MS (ESI, pos.ion) *m/z*: 541.8[M+1]⁺.

Step 2) preparation of compound **4-3**

[00183] To a solution of compound **4-2** (0.7 g, 1 mmol) in methanol (10 mL) was added a solution of LiOH (0.06 g, 3 mmol) in water (5 mL). The mixture was stirred at rt for 3 hours. After the reaction was complete, the mixture was concentrated *in vacuo*. The residue was adjusted with hydrochloric acid (1 M) to pH = 3. The resulting mixture was extracted with EtOAc (20 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (20 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo* to give compound **4-3** (0.7 g, 100%) as a white solid.

MS (ESI, pos.ion) *m/z*: 528.3 [M+1]⁺.

Step 3) preparation of compound **4-4**

[00184] A round-bottom flask was charged with compound **4-3** (0.7 g, 1 mmol), compound **2-9** (0.6 g, 1 mmol), EDCI (0.3 g, 2 mmol) and HOAT (0.2 g, 1 mmol), and then DCM (30 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (0.7 mL, 3 mmol) was added. The resulting mixture was stirred at 30 °C for 4 hours. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with EtOAc (20 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (20 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **4-4** (0.54 g, 60%) as a white solid.

MS (ESI, pos.ion) *m/z*: 739[M+1]⁺.

Step 4) preparation of compound **4-5**

[00185] A solution of compound **4-4** (0.54 g, 0.73 mmol) in EtOAc (2 mL) was cooled to 0 °C, and a solution of HCl in EtOAc (30%, 20 mL) was added. The mixture was stirred at rt until no more gas evolution. The mixture was filtered to afford a white solid; the solid was washed with EtOAc (20 mL). A round-bottom flask was charged with the white solid, compound **3-7** (0.32 g,

0.71 mmol), EDCI (0.15 g, 0.78 mmol) and HOAT (0.1 g, 0.7 mmol), and then DCM (20 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (0.3 mL, 2 mmol) was added. The resulting mixture was stirred at 30 °C for 4 hours. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with EtOAc (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (20 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **4-5** (0.32 g, 61%) as a white solid.

Step 5) preparation of compound **4-6**

[00186] To a solution of compound **4-5** (0.32 g, 0.35 mmol) in 1,2-dichloroethane (300 mL) was added Zhan catalyst-1B (0.05 g). The mixture was stirred at 65 °C for 48 hour. The mixture was cooled to rt and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V : V) = 2 : 1 to afford a white solid **4-6** (0.18 g, 58%).

MS (ESI, pos.ion) *m/z*: 865[M+1]⁺.

Step 6) preparation of compound **4-9**

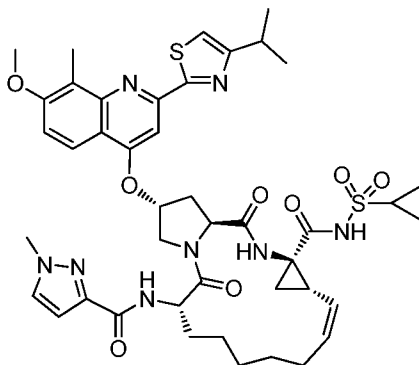
[00187] A solution of compound **4-6** (0.18 g, 0.2 mmol) in EtOAc (2 mL) was cooled to 0 °C, and a solution of HCl in EtOAc (30%, 20 mL) was added. The mixture was stirred at rt until no more gas evolution. The mixture was filtered to afford compound **4-7** as a white solid; the solid was washed with EtOAc (20 mL). A round-bottom flask was charged with compound **4-7**, compound **4-8** (0.02 g, 0.16 mmol), EDCI (0.04 g, 0.21 mmol) and HOAT (0.03 g, 0.22 mmol), and then DCM (20 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (0.1 mL, 0.6 mmol) was added slowly. After the addition, the resulting mixture was stirred at 30 °C for 4 hours. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with EtOAc (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (20 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **4-9** (0.03 g, 23%) as a white solid.

MS (ESI, pos.ion) *m/z*: 874[M+1]⁺; and

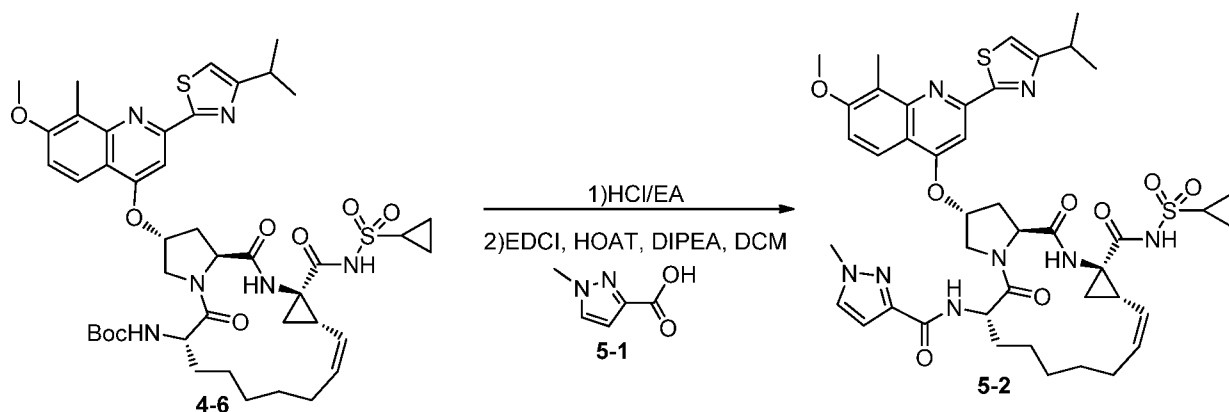
¹H NMR (400 MHz, CDCl₃): δ 10.22 (s, 1H), 7.88 (d, *J* = 9.2 Hz, 1H), 7.77 (s, 1H), 7.71 (d, *J* = 7.2 Hz, 1H), 7.56 (s, 1H), 7.10–6.95 (m, 3H), 5.74 (d, *J* = 9.2 Hz, 1H), 5.58 (s, 1H), 5.04–4.97 (m, 1H), 4.72–4.66 (m, 2H), 4.63–4.55 (m, 1H), 4.11–4.06 (m, 1H), 3.93 (s, 3H), 3.79

(s, 3H), 3.26–3.15 (m, 1H), 2.96–2.89 (m, 1H), 2.67 (s, 3H), 2.37–2.18 (m, 2H), 1.98–1.87 (m, 3H), 1.53–1.39 (m, 16H), 0.93–0.87 (m, 4H) ppm.

Example 5



Synthesis route:



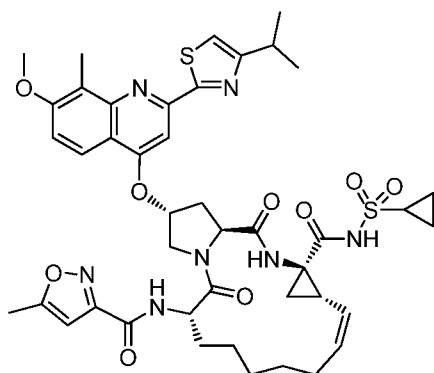
Synthesis steps:

[00188] A solution of compound **4-6** (0.26 g, 0.30 mmol) in EtOAc (2 mL) was cooled to 0 °C, and a solution of HCl in EtOAc (30%, 2 mL) was added. The mixture was stirred at rt until no more gas evolution. The mixture was filtered to afford compound **4-7** as a white solid; the solid was washed with EtOAc (20 mL). A round-bottom flask was charged with compound **4-7**, 5-methylpyrazole-3-carboxylic acid (0.05 g, 0.4 mmol), EDCI (0.13 g, 2.8 mmol) and HOAT (0.1 g, 3.0 mmol), and then DCM (20 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (0.5 mL, 10 mmol) was added slowly. The mixture was stirred at 30 °C for 6 hours. The mixture was quenched with water (10 mL). The resulting mixture was extracted with DCM (20 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (20 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **5-2** (0.135 g, 51.9%) as a white solid.

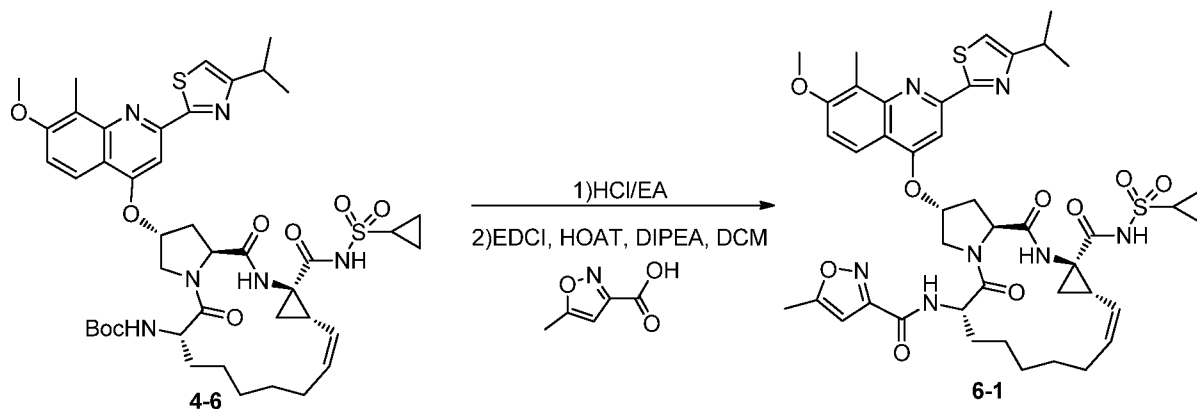
MS (ESI, pos.ion) *m/z*: 873.3[M+1]⁺; and

^1H NMR (600 MHz, CDCl_3): δ 7.99 (s, 1H), 7.89 (t, $J = 7.3$ Hz, 1H), 7.50 (s, 1H), 7.35 (dd, $J = 10.7, 4.3$ Hz, 2H), 7.04 (d, $J = 4.4$ Hz, 1H), 7.00 (d, $J = 9.2$ Hz, 1H), 6.65 (d, $J = 2.2$ Hz, 1H), 5.69 (dd, $J = 18.2, 8.5$ Hz, 1H), 5.49 (s, 1H), 4.98–4.94 (m, 1H), 4.64 (t, $J = 7.4$ Hz, 2H), 4.48 (d, $J = 11.4$ Hz, 1H), 4.16 (dd, $J = 11.3, 4.4$ Hz, 1H), 3.90 (d, $J = 6.8$ Hz, 3H), 3.77 (s, 3H), 3.23 (dt, $J = 13.6, 6.8$ Hz, 1H), 2.87 (dq, $J = 8.1, 4.9$ Hz, 1H), 2.69 (dd, $J = 13.7, 7.8$ Hz, 1H), 2.62 (s, 3H), 2.58–2.52 (m, 2H), 2.25 (dd, $J = 17.4, 8.7$ Hz, 1H), 2.04 (s, 1H), 1.93–1.87 (m, 1H), 1.82 (dd, $J = 8.0, 5.9$ Hz, 1H), 1.74–1.69 (m, 1H), 1.65 (dd, $J = 9.3, 5.8$ Hz, 1H), 1.52–1.44 (m, 5H), 1.35–1.25 (m, 6H), 1.10 (dddd, $J = 24.1, 15.7, 7.6, 5.3$ Hz, 3H), 0.93–0.84 (m, 2H) ppm.

Example 6



Synthesis route:



Synthesis steps:

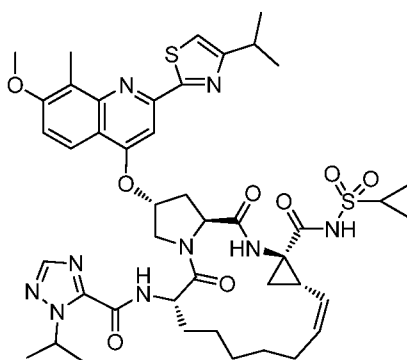
[00189] A solution of compound **4-6** (0.21 g, 0.24 mmol) in EtOAc (2 mL) was cooled to 0 °C, and a solution of HCl in EtOAc (30%, 2 mL) was added. The mixture was stirred at rt until no more gas evolution. The mixture was filtered to afford compound **4-7** as a white solid; the solid was washed with EtOAc (20 mL). A round-bottom flask was charged with compound **4-7**, 5-methylisoxazole-3-carboxylic acid (0.05 g, 0.4 mmol), EDCI (0.13 g, 2.8 mmol) and HOAT (0.1 g, 3.0 mmol), and then DCM (20 mL) was added under N_2 . The mixture was cooled to 0 °C, and DIPEA (0.5 mL, 10 mmol) was added slowly. The mixture was stirred at 30 °C for 6 hours.

After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with DCM (20 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (20 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **6-1** (0.203 g, 88.6%) as a white solid.

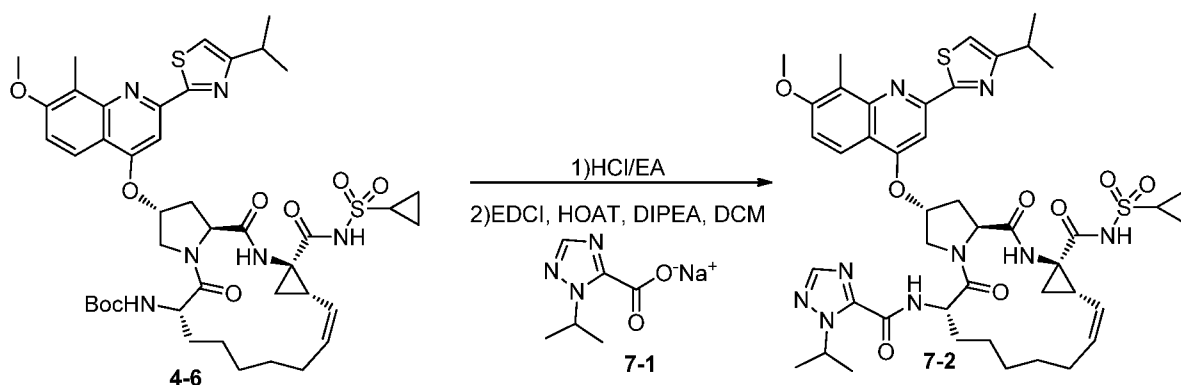
MS (ESI, pos.ion) m/z : 874.3[M+1]⁺; and

¹H NMR (600 MHz, CDCl₃): δ 10.44 (s, 1H), 8.09 (d, J = 7.8 Hz, 1H), 8.00 (s, 1H), 7.84 (d, J = 9.1 Hz, 1H), 7.57 (s, 1H), 7.03 (d, J = 9.1 Hz, 2H), 6.13 (d, J = 16.7 Hz, 1H), 5.64 (dd, J = 17.9, 8.8 Hz, 1H), 5.54 (s, 1H), 4.95–4.87 (m, 1H), 4.74 (ddd, J = 23.5, 13.1, 5.3 Hz, 2H), 4.63 (d, J = 11.5 Hz, 1H), 4.12 (dd, J = 11.5, 3.7 Hz, 1H), 3.87 (s, 3H), 3.21 (dq, J = 13.6, 6.8 Hz, 1H), 2.90–2.85 (m, 1H), 2.75 (dd, J = 13.8, 7.7 Hz, 1H), 2.66 (s, 3H), 2.61–2.54 (m, 1H), 2.36 (s, 3H), 2.24 (q, J = 8.5 Hz, 1H), 2.09 (dd, J = 23.2, 11.2 Hz, 1H), 1.85–1.80 (m, 1H), 1.77 (dd, J = 7.6, 6.2 Hz, 1H), 1.65–1.58 (m, 1H), 1.48–1.38 (m, 12H), 1.28–1.22 (m, 3H), 1.14–1.09 (m, 1H), 1.08–1.03 (m, 1H), 0.89 (dd, J = 10.5, 5.5 Hz, 1H) ppm.

Example 7



Synthesis route:



Synthesis steps:

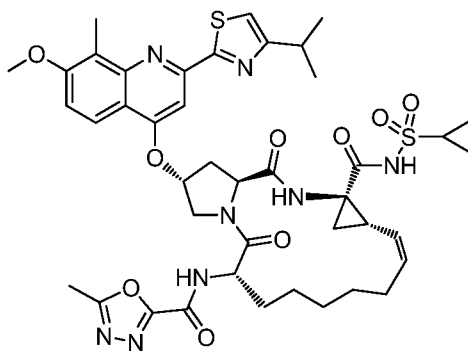
[00190] A solution of compound **4-6** (0.21 g, 0.24 mmol) in EtOAc (2 mL) was cooled to 0 °C,

and a solution of HCl in EtOAc (30%, 6 mL) was added. The mixture was stirred at rt until no more gas evolution. The mixture was filtered to afford compound **4-7** as a white solid; the solid was washed with EtOAc (20 mL) and dried *in vacuo*. A round-bottom flask was charged with compound **4-7**, compound **7-1** (0.05 g, 0.4 mmol), EDCI (0.13 g, 2.8 mmol) and HOAT (0.1 g, 3.0 mmol), and then DCM (20 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (0.5 mL, 10 mmol) was added slowly. After the addition, the resulting mixture was stirred at 30 °C for 6 hours. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with DCM (20 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (20 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **7-2** (0.203 g, 88.6%) as a white solid.

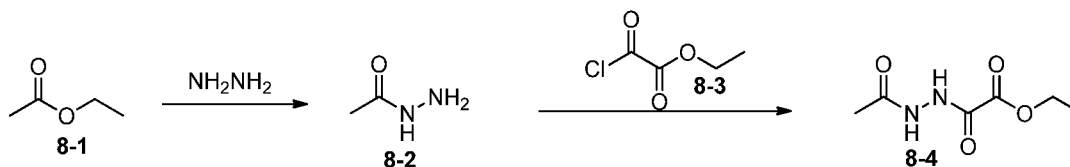
MS (ESI, pos.ion) m/z : 902.3[M+1]⁺; and

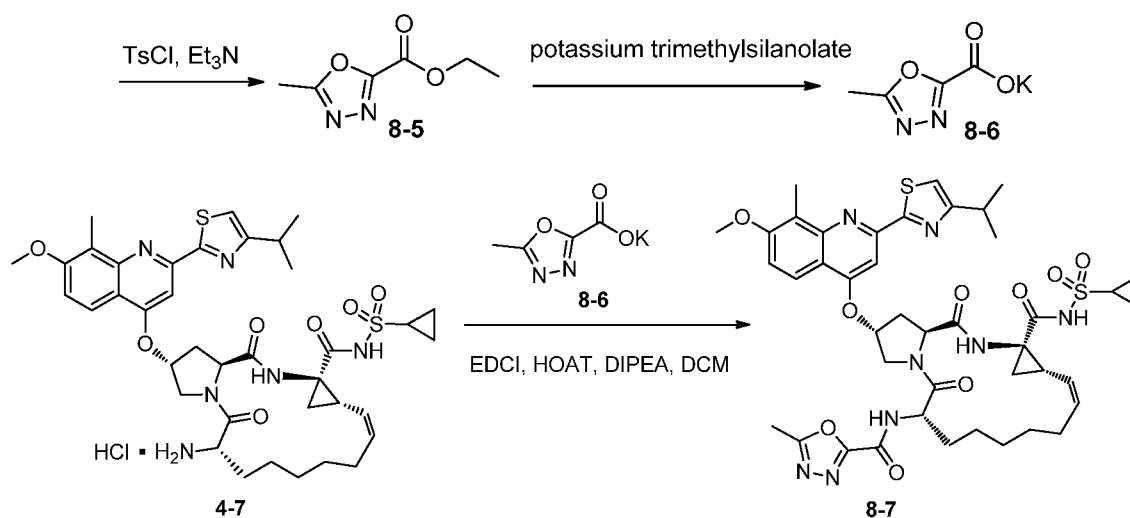
¹H NMR (600 MHz, CDCl₃): δ 10.44 (s, 1H), 8.08 (d, J = 7.4 Hz, 1H), 8.01 (s, 1H), 7.86–7.82 (m, 2H), 7.52 (s, 1H), 7.06–7.03 (m, 2H), 5.69 (dd, J = 17.9, 8.8 Hz, 1H), 5.49 (s, 1H), 5.06 (dt, J = 13.1, 6.5 Hz, 1H), 4.98–4.94 (m, 1H), 4.74 (t, J = 8.3 Hz, 2H), 4.67–4.63 (m, 1H), 4.13 (dd, J = 11.7, 2.7 Hz, 1H), 3.89 (s, 3H), 3.22 (dd, J = 13.4, 6.3 Hz, 1H), 2.89 (td, J = 8.0, 4.1 Hz, 1H), 2.73 (dd, J = 13.8, 7.4 Hz, 1H), 2.67 (s, 3H), 2.31 (q, J = 8.5 Hz, 1H), 2.07 (d, J = 5.9 Hz, 1H), 1.85 (ddd, J = 13.9, 8.8, 5.3 Hz, 2H), 1.66 (dd, J = 16.5, 7.2 Hz, 1H), 1.55–1.40 (m, 10H), 1.29 (dd, J = 18.7, 15.0 Hz, 9H), 1.15–1.04 (m, 4H), 0.92 – 0.87 (m, 2H) ppm.

Example 8



Synthesis route:





Step 1) preparation of compound **8-2**

[00191] A mixture of EtOAc (10 g, 113.5 mmol) and hydrazine hydrate (10 mL, 257.3 mmol, 25.73 mol/L) in ethanol (15 mL) was refluxed for 4 hours. After the reaction was complete, the mixture was cooled to rt and concentrated *in vacuo* to afford a white product **8-2** (8.2 g, 98%) as a solid.

MS (ESI, pos.ion) m/z : 75 $[\text{M}+1]^+$.

Step 2) preparation of compound **8-4**

[00192] To a solution of compound **8-2** (1.0 g, 13 mmol) in DCM (20 mL) was added triethylamine (2 mL, 14.3 mmol) in an ice bath, and then compound **8-3** (1.8 g, 13 mmol) was added dropwise slowly. After the addition, the mixture was stirred at rt overnight. After the reaction was complete, the mixture was diluted with EtOAc (100 mL) and filtered to remove salt. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with $\text{PE} : \text{EtOAc}$ (V : V) = 5 : 1 to afford a white solid **8-4** (2.2 g, 13 mmol, 94%).

MS (ESI, neg.ion) m/z : 173 $[\text{M}-1]^-$.

Step 3) preparation of compound **8-5**

[00193] To a solution of compound **8-4** (2.2 g, 13 mmol) in DCM (45 mL) were added triethylamine (2.5 mL, 18 mmol) and paratoluensulfonyl chloride (3.0 g, 16 mmol) in an ice bath. The mixture was stirred at rt for 8 hours. After the reaction was complete, the mixture was quenched with water (50 mL) and filtered. The filtrate was dried over anhydrous Na_2SO_4 , and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with $\text{PE} : \text{EtOAc}$ (V:V) = 2:1 to give compound **8-5** (1.1 g, 56%) as a white solid.

MS (ESI, pos.ion) m/z : 157[M+1]⁺.

Step 4) preparation of compound **8-6**

[00194] To a solution of compound **8-5** (1.1 g, 7.0 mmol) in ether (25 mL) was added potassium trimethylsilanolate (0.9 g, 7 mmol) with stirring. The mixture was stirred at rt overnight, there was white solid precipitated out during the reaction process. After the reaction was complete, the mixture was filtered. The filter cake was washed with a little ethanol and dried *in vacuo* to afford a white solid **8-6** (0.85 g, 73%).

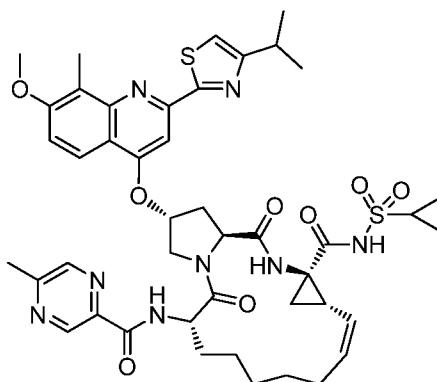
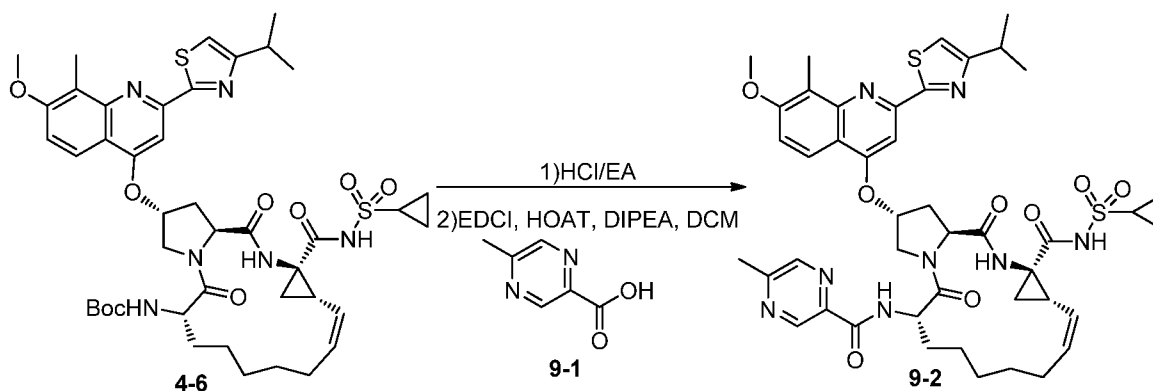
Step 5) preparation of compound **8-7**

[00195] A round-bottom flask was charged with compound **4-7** (0.15 g, 0.19 mmol), compound **8-6** (0.04 g, 0.23 mmol), EDCI (0.04 g, 0.21 mmol) and HOAT (0.03 g, 0.22 mmol), and then DCM (20 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (0.1 mL, 0.6 mmol) was added slowly. The resulting mixture was stirred at 30 °C for 4 hours. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with EtOAc (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (20 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **8-7** (0.05 g, 30%) as a white solid.

MS (ESI, pos.ion) m/z : 874[M+1]⁺; and

¹H NMR (600 MHz, CDCl₃): δ 10.37 (s, 1H), 8.59 (s, 1H), 7.98–7.85 (m, 2H), 7.62–7.54 (m, 1H), 7.15–7.03 (m, 2H), 5.76 (dd, J = 17.6, 9.0 Hz, 1H), 5.59 (s, 1H), 5.07–4.98 (m, 1H), 4.84 (t, J = 8.0 Hz, 1H), 4.71 (t, J = 7.6 Hz, 1H), 4.64 (d, J = 11.5 Hz, 1H), 4.20 (d, J = 8.8 Hz, 1H), 3.91 (s, 3H), 3.30–3.18 (m, 1H), 2.99–2.88 (m, 1H), 2.79 (s, 2H), 2.70 (s, 4H), 2.53 (s, 3H), 2.33–2.28 (m, 1H), 2.24–2.17 (m, 1H), 1.79–1.68 (m, 3H), 1.42 (d, J = 6.9 Hz, 6H), 1.33–1.27 (m, 7H), 0.98–0.85 (m, 4H) ppm.

Example 9

**Synthesis route:****Synthesis steps:**

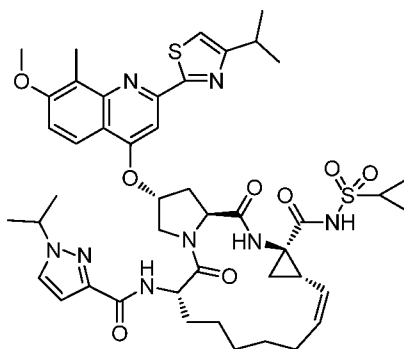
[00196] A solution of compound **4-6** (0.2 g, 0.3 mmol) in EtOAc (2 mL) was cooled to 0 °C, and a solution of HCl in EtOAc (30%, 2 mL) was added. The mixture was stirred at rt until no more gas evolution. The mixture was filtered to afford compound **4-7** as a white solid; the solid was washed with EtOAc (20 mL). A round-bottom flask was charged with compound **4-7**, compound **9-1** (0.06 g, 0.4 mmol), EDCI (0.13 g, 0.66 mmol) and HOAT (0.1 g, 0.7 mmol), and then DCM (10 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (0.2 mL, 1 mmol) was added slowly. After the addition, the resulting mixture was stirred at 30 °C for 6 hours. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **9-2** (0.180 g, 80%) as a white solid.

MS (ESI, pos.ion) *m/z*: 885.3[M+1]⁺; and

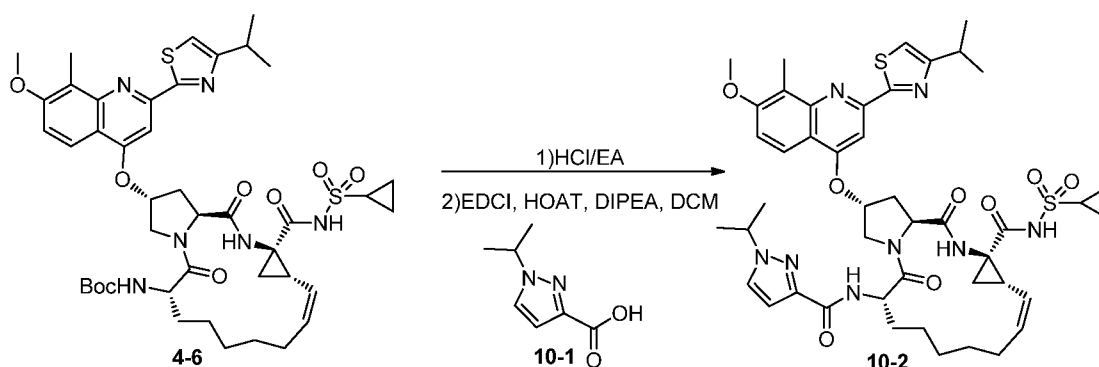
¹H NMR (600 MHz, CDCl₃): δ 10.38 (s, 1H), 9.07 (d, *J* = 0.8 Hz, 1H), 8.44 (s, 1H), 8.15 (d, *J* = 6.7 Hz, 1H), 7.85 (d, *J* = 9.1 Hz, 2H), 7.47 (s, 1H), 7.04 (s, 1H), 6.95 (d, *J* = 9.2 Hz, 1H), 5.73 (dd, *J* = 18.2, 8.7 Hz, 1H), 5.50 (s, 1H), 5.02–4.97 (m, 1H), 4.69–4.64 (m, 2H), 4.49 (d, *J* =

11.5 Hz, 1H), 4.10 (dd, $J = 11.6, 3.9$ Hz, 1H), 3.77 (s, 3H), 3.22 (dt, $J = 13.7, 6.8$ Hz, 1H), 2.92–2.86 (m, 1H), 2.71 (dd, $J = 13.8, 7.7$ Hz, 1H), 2.65 (s, 3H), 2.60 (s, 4H), 2.29–2.25 (m, 1H), 2.04–2.00 (m, 1H), 1.91 (dd, $J = 7.8, 6.1$ Hz, 2H), 1.78–1.71 (m, 1H), 1.66 (dd, $J = 9.4, 5.9$ Hz, 1H), 1.53–1.45 (m, 5H), 1.39 (t, $J = 13.5$ Hz, 7H), 1.16–1.07 (m, 3H), 0.94–0.86 (m, 2H) ppm.

Example 10



Synthesis route:



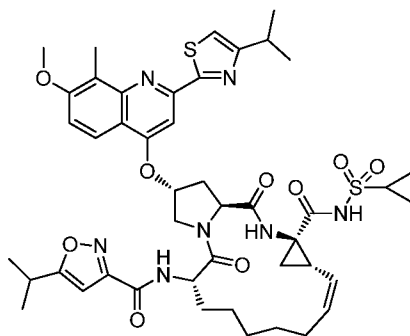
Synthesis steps:

[00197] A solution of compound **4-6** (0.2 g, 0.3 mmol) in EtOAc (2 mL) was cooled to 0 °C, and a solution of HCl in EtOAc (30%, 2 mL) was added. The mixture was stirred at rt until no more gas evolution. The mixture was filtered to afford compound **4-7** as a white solid; the solid was washed with EtOAc (20 mL). A round-bottom flask was charged with compound **4-7**, compound **10-1** (0.1 g, 0.6 mmol), EDCI (0.13 g, 0.66 mmol) and HOAT (0.1 g, 0.7 mmol), and then DCM (10 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (0.2 mL, 1 mmol) was added slowly. After the addition, the resulting mixture was stirred at 30 °C for 6 hours. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **10-2** (0.166 g, 70%) as a white solid.

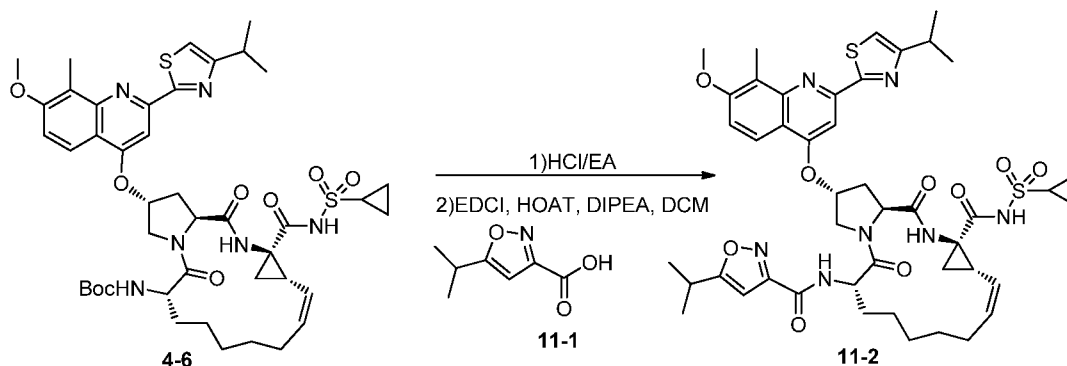
MS (ESI, pos.ion) m/z : 901.3[M+1]⁺; and

¹H NMR (600 MHz, CDCl₃): δ 10.37 (s, 1H), 7.98 (d, J = 9.1 Hz, 1H), 7.54 (s, 1H), 7.41 (d, J = 2.3 Hz, 1H), 7.37 (d, J = 7.3 Hz, 1H), 7.10 (t, J = 6.8 Hz, 1H), 7.04 (s, 1H), 6.68 (d, J = 2.3 Hz, 1H), 5.71 (dd, J = 18.3, 8.5 Hz, 1H), 5.53 (s, 1H), 4.98–4.94 (m, 1H), 4.75 (ddd, J = 10.5, 7.4, 3.1 Hz, 1H), 4.65 (d, J = 11.4 Hz, 1H), 4.60 (t, J = 7.8 Hz, 1H), 4.49 (dd, J = 13.4, 6.7 Hz, 1H), 4.19–4.11 (m, 3H), 3.89 (s, 3H), 3.23 (dt, J = 13.8, 6.8 Hz, 1H), 2.92–2.87 (m, 1H), 2.66 (d, J = 10.1 Hz, 4H), 2.61–2.55 (m, 2H), 2.33 (q, J = 8.7 Hz, 1H), 2.06 (s, 3H), 2.04–1.90 (m, 4H), 1.86 (dd, J = 8.0, 6.0 Hz, 1H), 1.75–1.69 (m, 1H), 1.50 (dt, J = 10.2, 5.1 Hz, 9H), 1.41 (s, 3H), 1.19–1.05 (m, 3H), 0.95–0.86 (m, 2H) ppm.

Example 11



Synthesis route:



Synthesis steps:

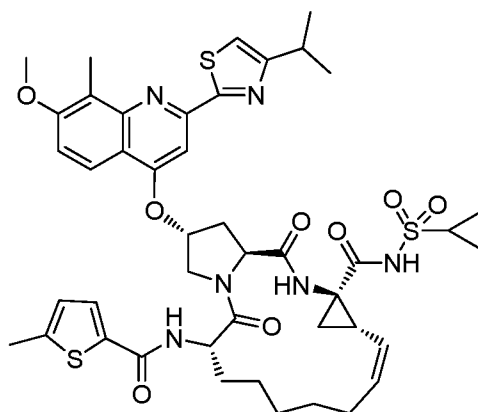
[00198] A solution of compound **4-6** (0.16 g, 0.2 mmol) in EtOAc (2 mL) was cooled to 0 °C, and a solution of HCl in EtOAc (30%, 2 mL) was added. The mixture was stirred at rt until no more gas evolution. The mixture was filtered to afford compound **4-7** as a white solid; the solid was washed with EtOAc (20 mL). A round-bottom flask was charged with compound **4-7**, compound **11-1** (0.1 g, 0.6 mmol), EDCI (0.2 g, 1.5 mmol) and HOAT (0.15 g, 1.1 mmol), and then DCM (10 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (0.5 mL, 3 mmol) was added slowly. After the addition, the resulting mixture was stirred at 30 °C for 6

hours. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **11-2** (0.09 g, 50%) as a white solid.

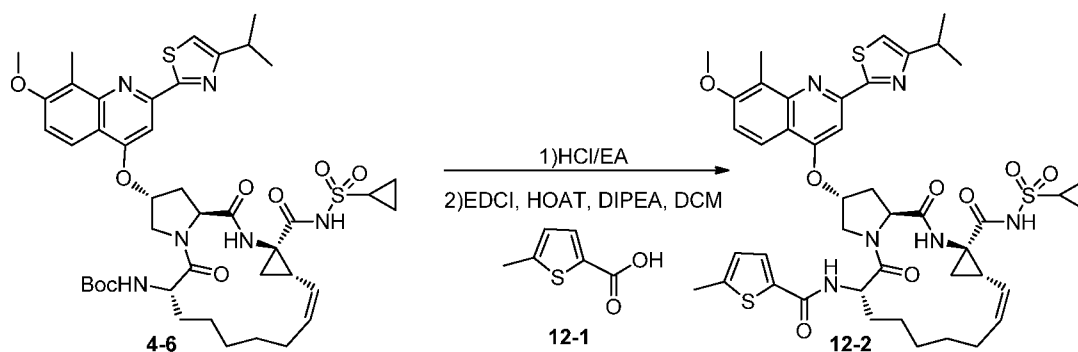
MS (ESI, pos.ion) m/z : 902.3[M+1]⁺; and

¹H NMR (600 MHz, CDCl₃): δ 10.39 (s, 1H), 8.05 (d, J = 7.4 Hz, 1H), 7.89 (d, J = 9.1 Hz, 1H), 7.76 (s, 1H), 7.57 (s, 1H), 7.09–7.04 (m, 2H), 6.16 (s, 1H), 5.71 (dd, J = 17.7, 9.0 Hz, 1H), 5.57 (s, 1H), 4.99–4.94 (m, 1H), 4.81 (dd, J = 13.3, 5.3 Hz, 1H), 4.72–4.67 (m, 2H), 4.18–4.14 (m, 1H), 3.91 (s, 3H), 3.27–3.20 (m, 1H), 3.02 (dt, J = 13.8, 6.9 Hz, 1H), 2.91 (ddd, J = 12.9, 8.2, 4.9 Hz, 1H), 2.79–2.73 (m, 2H), 2.70 (s, 3H), 2.65 (d, J = 4.8 Hz, 1H), 2.29 (dd, J = 17.0, 8.4 Hz, 1H), 2.14 (dd, J = 22.8, 10.8 Hz, 1H), 2.04 (d, J = 23.2 Hz, 1H), 1.85 (dd, J = 14.1, 7.9 Hz, 2H), 1.71–1.65 (m, 1H), 1.49 (ddd, J = 17.2, 9.9, 5.8 Hz, 5H), 1.42 (t, J = 7.0 Hz, 8H), 1.30 (s, 2H), 1.13 (ddt, J = 21.0, 15.4, 6.6 Hz, 3H), 0.92 (dt, J = 13.9, 7.6 Hz, 2H) ppm.

Example 12



Synthesis route:



Synthesis steps:

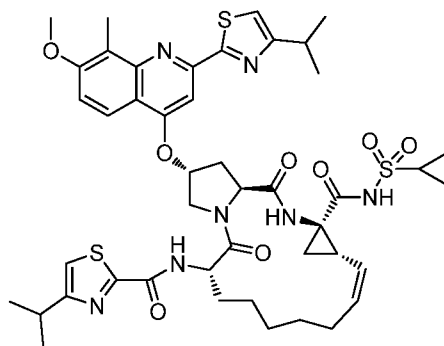
[00199] A solution of compound **4-6** (0.3 g, 0.4 mmol) in EtOAc (2 mL) was cooled to 0 °C, and

a solution of HCl in EtOAc (30%, 2 mL) was added. The mixture was stirred at rt until no more gas evolution. The mixture was filtered to afford compound **4-7** as a white solid; the solid was washed with EtOAc (20 mL). A round-bottom flask was charged with compound **4-7**, compound **12-1** (0.06 g, 0.4 mmol), EDCI (0.2 g, 1.5 mmol) and HOAT (0.15 g, 1.1 mmol), and then DCM (20 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (0.5 mL, 3 mmol) was added slowly. After the addition, the resulting mixture was stirred at 30 °C for 6 hours. After the reaction was complete, the mixture was quenched with water (20 mL). The resulting mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **12-2** (0.2 g, 60%) as a white solid.

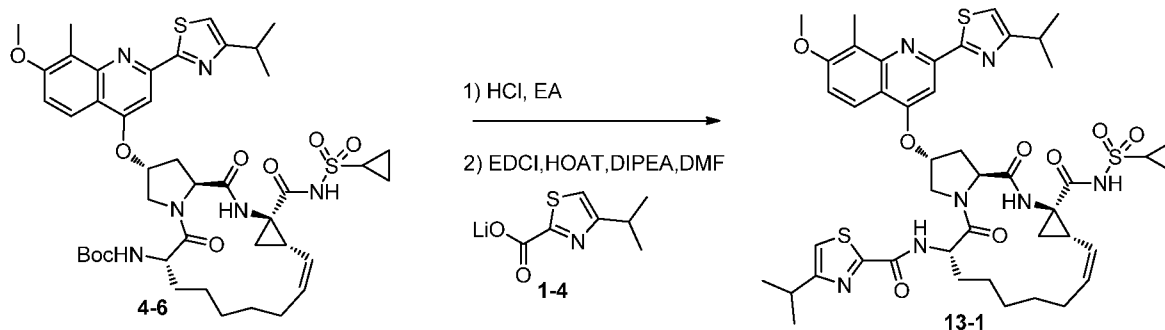
MS (ESI, pos.ion) m/z : 889.3[M+1]⁺; and

¹H NMR (600 MHz, CDCl₃): δ 10.49 (s, 1H), 9.09 (s, 3H), 8.37 (s, 1H), 8.17 (s, 1H), 7.44 (s, 1H), 7.40 (s, 1H), 7.26 (d, J = 9.0 Hz, 1H), 7.21 (s, 1H), 6.97 (s, 1H), 6.65 (s, 1H), 5.67–5.53 (m, 2H), 4.94–4.69 (m, 3H), 4.45 (s, 1H), 4.04 (d, J = 6.8 Hz, 1H), 3.92 (d, J = 38.0 Hz, 3H), 3.31 (dt, J = 13.6, 6.8 Hz, 1H), 2.81 (d, J = 29.5 Hz, 2H), 2.57 (s, 2H), 2.45 (d, J = 10.5 Hz, 6H), 2.18 (s, 1H), 1.91 (s, 1H), 1.76 (s, 1H), 1.64 (d, J = 39.2 Hz, 3H), 1.44 (dd, J = 6.7, 2.4 Hz, 7H), 1.29–1.21 (m, 3H), 1.14 (s, 1H), 1.04–0.85 (m, 3H) ppm.

Example 13



Synthesis route:



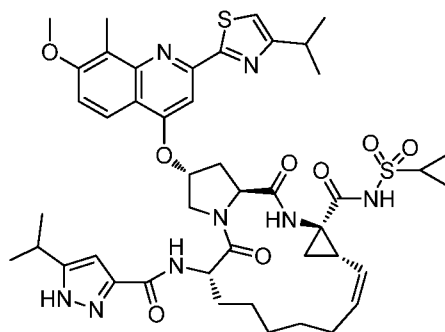
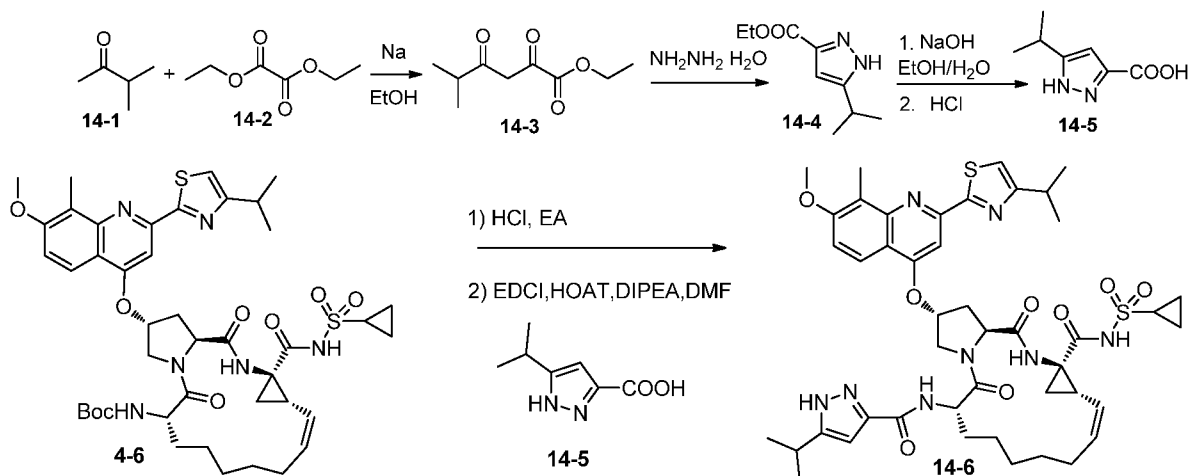
Step 1) preparation of compound **13-1**

[00200] A solution of compound **4-6** (0.3 g, 0.4 mmol) in EtOAc (2 mL) was cooled to 0 °C, and a solution of HCl in EtOAc (30%, 2 mL) was added. The mixture was stirred at rt until no more gas evolution. The mixture was filtered to afford compound **4-7** as a white solid; the solid was washed with EtOAc (20 mL). To a mixture of compound **4-7**, compound **1-4** (0.05 g, 0.3 mmol), EDCI (0.05 g, 0.3 mmol) and HOAT (0.040 g, 0.29 mmol) in DMF (20 mL) was added DIPEA (0.1 mL, 0.6 mmol) dropwise in an ice bath. The mixture was stirred at this temperature for 0.5 hour and further stirred at rt overnight. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **13-1** (164 mg, 60%) as a white solid.

MS (ESI, pos.ion) m/z : 918.4[M+1]⁺; and

¹H NMR (600 MHz, CDCl₃): δ 10.32 (s, 1H), 8.16 (d, J = 6Hz, 1H), 7.66 (s, 1H), 7.25 (d, J = 12Hz, 2H), 7.12 (s, 1H), 5.75 (dd, J_1 = 18Hz, J_2 = 12Hz, 1H), 5.68 (s, 1H), 5.32 (s, 1H), 5.05 (t, J_1 = 12Hz, J_2 = 6Hz, 1H), 4.73 (d, J = 6Hz, 1H), 4.69 (d, J = 6Hz, 2H), 4.33 (t, J_1 = 6Hz, J_2 = 6Hz, 1H), 4.16–4.15 (m, 1H), 3.98 (s, 3H), 3.35–3.31 (m, 1H), 3.14–3.08 (m, 1H), 2.94–2.86 (m, 1H), 2.80–2.73 (m, 2H), 2.65 (s, 2H), 2.37–2.33 (m, 1H), 2.10–2.04 (m, 1H), 1.94–1.93 (m, 2H), 1.79–1.72 (m, 2H), 1.57–1.47 (m, 3H), 1.44 (d, J = 6Hz, 6H), 1.33 (d, J = 6Hz, 6H), 1.20–1.13 (m, 1H), 1.08–1.06 (m, 1H), 1.00–0.86 (m, 6H) ppm.

Example 14

**Synthesis route:****Step 1) preparation of compound 14-3**

[00201] Na (2.63 g, 0.11 mmol) was added to EtOH (65 mL). The mixture was refluxed under N₂ until the reaction was complete. The mixture was cooled to 0 °C, and then compound **14-1** (10 g, 116.1 mmol) and compound **14-2** (16.98 g, 116.2 mmol) were added. The resulting mixture was stirred at rt for 1 hour and further stirred at 80 °C for 0.75 hour. After the reaction was complete, the mixture was cooled to rt. The mixture was adjusted with hydrochloric acid to pH 2 and diluted with water (100 mL). The resulting mixture was extracted with ether (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl solution, and dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give product **14-3** as oil (19.4 g, 89.7%).

MS (ESI, pos.ion) *m/z*: 187.1[M+1]⁺; and

¹H NMR (600 MHz, CDCl₃): δ 6.31–6.30 (m, 1H), 4.26–4.23 (m, 2H), 2.58–2.55 (m, 2H), 1.28–1.26 (m, 3H), 1.09–1.08 (m, 6H) ppm.

Step 2) preparation of compound 14-4

[00202] A mixture of compound **14-3** (1 g, 5.37 mmol) and hydrazine hydrate (10.7 mmol, 9.64 mol/L) in ethanol (20 mL) was stirred at 75 °C under N₂ for 1 hour. After the reaction was complete, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column

chromatography eluted with PE : EtOAc (V : V) = 2 : 1 to afford a pale yellow solid **14-4** (0.55 g, 56%).

MS (ESI, pos.ion) m/z : 183.1[M+1]⁺; and

¹H NMR (600 MHz, CDCl₃): δ 11.37 (b, 1H), 6.63 (s, 1H), 4.40–4.37 (m, 2H), 3.07–3.05 (m, 1H), 1.43–1.40 (m, 3H), 1.39–1.30 (m, 6H) ppm.

Step 3) preparation of compound **14-5**

[00203] To a mixture of compound **14-4** (2.2 g, 12 mmol) in a mixed solvent of ethanol (10 mL) and water (5 mL) was added NaOH (1.9 g, 48 mmol). The mixture was stirred at rt for 3 hours. After the reaction was complete, the mixture was adjusted with hydrochloric acid (1 M) to pH 2 and concentrated *in vacuo* to remove ethanol. The mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were washed with saturated aqueous NaCl solution, and dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give product **14-5** as a white solid (1.64 g, 88%).

Step 4) preparation of compound **14-6**

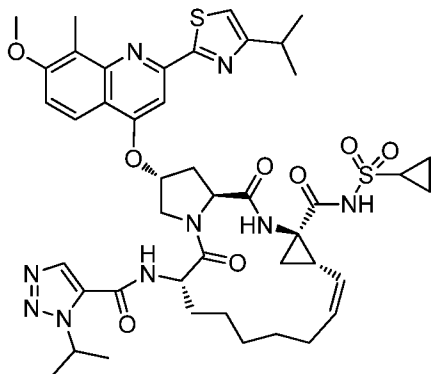
[00204] A solution of compound **4-6** (0.3 g, 0.4 mmol) in EtOAc (2 mL) was cooled to 0 °C, and a solution of HCl in EtOAc (30%, 2 mL) was added. The mixture was stirred at rt until no more gas evolution. The mixture was filtered to afford compound **4-7** as a white solid; the solid was washed with EtOAc (20 mL). To a mixture of compound **4-7**, compound **14-5** (0.04 g, 0.3 mmol), EDCI (0.05 g, 0.3 mmol) and HOAT (0.040 g, 0.29 mmol) in DMF (5 mL) was added DIPEA (0.1 mL, 0.6 mmol) dropwise at 0 °C under N₂. The mixture was stirred at 0 °C for 0.5 hour and further stirred at rt overnight. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **14-6** (150 mg, 0.17 mmol) as a white solid.

MS (ESI, pos.ion) m/z : 901.4[M+1]⁺; and

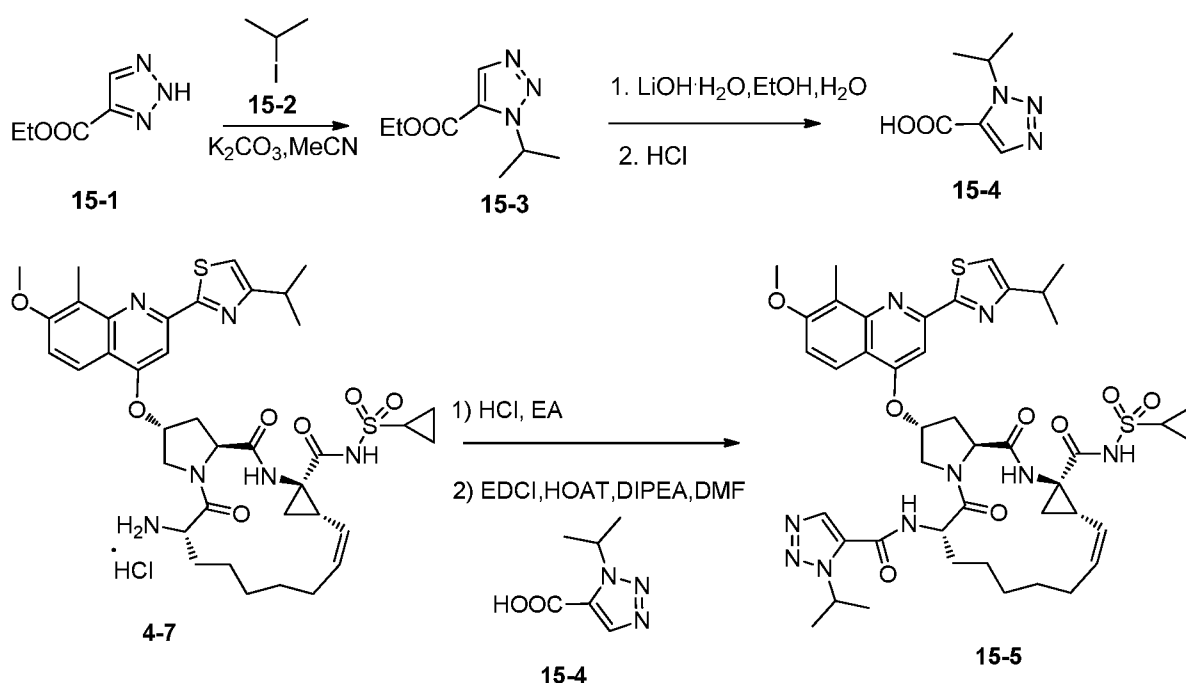
¹H NMR (600 MHz, CDCl₃): δ 10.73 (s, 1H), 8.92 (s, 1H), 7.90 (s, 1H), 7.49 (s, 1H), 7.31 (s, 1H), 6.95 (d, J = 6Hz, 1H), 6.42 (s, 1H), 5.81 (d, J = 6Hz, 1H), 5.60 (s, 1H), 5.12–5.09 (m, 1H), 4.69–4.65 (m, 2H), 4.52 (s, 1H), 4.20–4.12 (m, 1H), 4.04 (d, J = 12Hz, 1H), 3.68 (s, 3H), 3.38–3.32 (m, 1H), 3.04–3.03 (m, 1H), 2.68–2.63 (m, 1H), 2.52 (s, 1H), 2.40 (s, 3H), 2.25–2.21

(m, 1H), 2.07 (s, 1H), 2.00 (s, 1H), 1.91 (s, 1H), 1.74–1.71 (m, 1H), 1.59–1.56 (m, 1H), 1.47–1.43 (m, 11H), 1.30–1.26 (m, 7H), 1.22–1.08 (m, 4H), 1.02–0.97 (m, 1H), 0.93–0.87 (m, 1H) ppm.

Example 15



Synthesis route:



Step 1) preparation of compound 15-3

[00205] A mixture of compound **15-1** (1.5 g, 11 mmol), compound **15-2** (1.91 mL) and K_2CO_3 (2.46 g, 17.8 mmol) in acetonitrile (15 mL) was stirred at rt under N_2 for 4 days. After the reaction was complete, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V : V) = 2 : 1 to afford compound **15-3** (70 mg, 3.6%) as colorless oil.

MS (ESI, pos.ion) m/z : 184.3[M+1]⁺.

Step 2) preparation of compound 15-4

[00206] To a mixture of compound **15-3** (0.2 g, 1 mmol) in a mixed solvent of ethanol (4 mL) and water (2 mL) was added LiOH·H₂O (84 mg, 2 mmol). The mixture was stirred at rt for 12 hours. After the reaction was complete, the mixture was concentrated *in vacuo* to remove ethanol. The mixture was diluted with water (10 mL). The resulting mixture was adjusted with hydrochloric acid (2 M) to pH 5 and extracted with DCM (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl solution, dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give compound **15-4** as a white solid (0.1 g, 60%).

MS (ESI, pos.ion) *m/z*: 156.2[M+1]⁺.

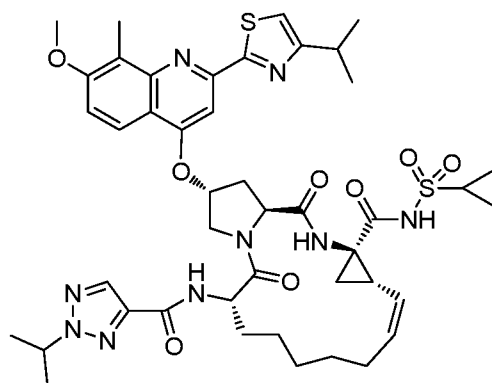
Step 3) preparation of compound **15-5**

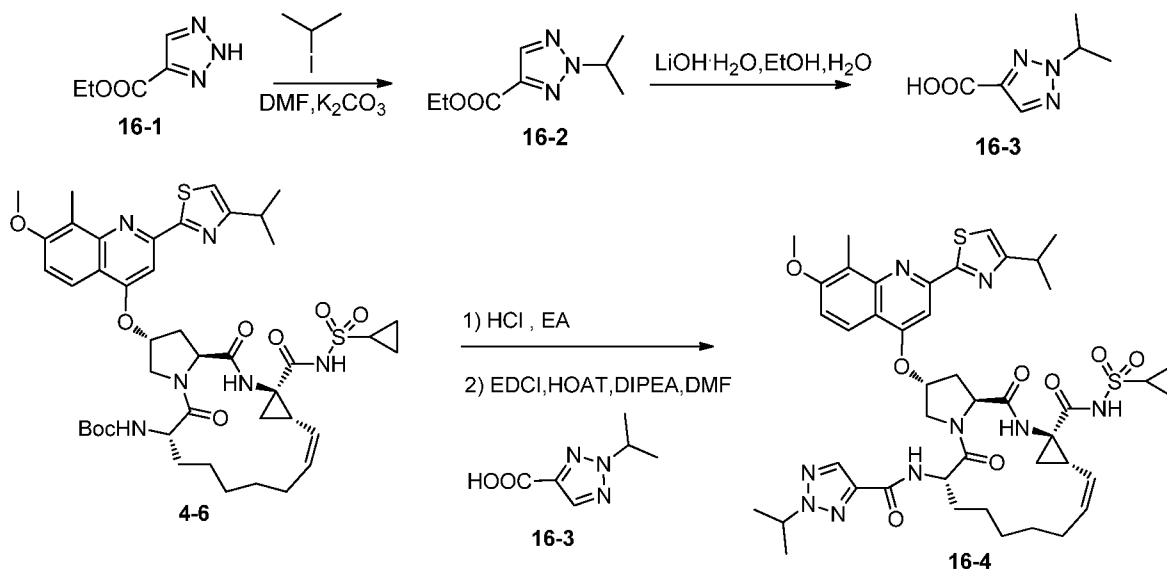
[00207] To a mixture of compound **4-7** (0.2 g, 0.25 mmol), compound **15-4** (0.05 g, 0.3 mmol), EDCI (0.05 g, 0.3 mmol) and HOAT (0.040 g, 0.29 mmol) in DMF (5 mL) was added DIPEA (0.1 mL, 0.75 mmol) dropwise at 0 °C. After the addition, the mixture was warmed to rt and further stirred overnight. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **15-5** as a white solid (112 mg, 50%).

MS (ESI, pos.ion) *m/z*: 901.6[M+1]⁺; and

¹H NMR (600 MHz, CDCl₃): δ 10.30 (s, 1H), 7.98–7.97 (m, 1H), 7.87 (d, *J* = 12Hz, 1H), 7.07–7.05 (m, 2H), 6.85–6.76 (m, 1H), 5.77–5.70 (m, 1H), 5.59–5.52 (m, 1H), 5.32 (s, 2H), 5.13–5.06 (m, 1H), 5.02–4.98 (m, 1H), 4.79–4.63 (m, 4H), 3.93 (s, 3H), 3.27–3.20 (m, 1H), 2.96–2.90 (m, 1H), 2.78–2.73 (m, 1H), 2.70 (s, 3H), 1.94–1.89 (m, 2H), 1.70 (d, *J* = 6Hz, 6H), 1.33–1.24 (m, 9H), 1.19–1.09 (m, 3H), 0.90–0.84 (m, 6H) ppm.

Example 16



Synthesis route:**Step 1) preparation of compound 16-2**

[00208] To a mixture of compound **16-1** (1 g, 7.09 mmol) and 2-iodopropane (2.4 g, 14.2 mmol) in acetonitrile (15 mL) was added K₂CO₃ (1.955 g, 14.17 mmol). The mixture was stirred at 80 °C under N₂ overnight. After the reaction was complete, the mixture was cooled to rt and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V : V) = 5 : 1 to afford compound **16-2** (0.4 g, 30%) as colorless oil.

MS (ESI, pos.ion) *m/z*: 184.1[M+1]⁺.

Step 2) preparation of compound 16-3

[00209] To a mixture of compound **16-2** (0.4 g, 2 mmol) in a mixed solvent of ethanol (4 mL) and water (2 mL) was added LiOH·H₂O (168 mg, 4 mmol). The mixture was stirred at rt for 12 hours. After the reaction was complete, the mixture was concentrated *in vacuo* to remove ethanol. The mixture was diluted with water (10 mL). The resulting mixture was adjusted with hydrochloric acid (2 M) to pH 5 and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with saturated aqueous NaCl solution, and dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give compound **16-3** as a white solid (0.29 g, 90%).

MS (ESI, pos.ion) *m/z*: 156.2[M+1]⁺.

Step 4) preparation of compound 16-4

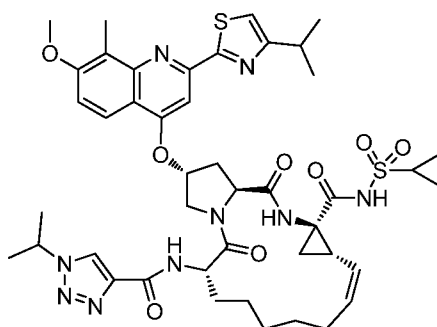
[00210] A solution of compound **4-6** (0.3 g, 0.4 mmol) in EtOAc (2 mL) was cooled to 0 °C, and a solution of HCl in EtOAc (30%, 4 mL) was added. The mixture was stirred at rt until no more gas evolution. The mixture was filtered to afford a white solid; the solid was washed with EtOAc (20 mL). To a mixture of compound **4-7**, compound **16-3** (0.05 g, 0.3 mmol), EDCI (0.05 g, 0.3

mmol) and HOAT (0.040 g, 0.29 mmol) in DMF (5 mL) was added DIPEA (97 mg, 0.75 mmol) dropwise at 0 °C. After the addition, the mixture was stirred at rt overnight. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2 : 1 to give compound **16-4** (162 mg, 60%) as a white solid.

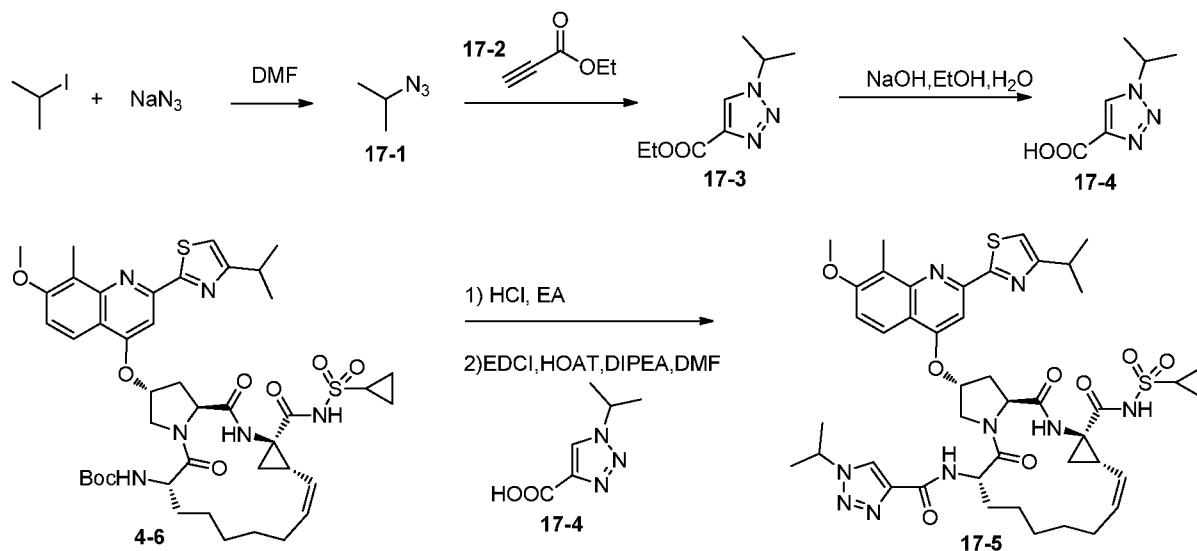
MS (ESI, pos.ion) m/z : 901.6[M+1]⁺; and

¹H NMR (600 MHz, CDCl₃): δ 10.33 (s, 1H), 7.96 (d, J = 6Hz, 1H), 7.92 (s, 1H), 7.24 (d, J = 12Hz, 1H), 7.17 (s, 1H), 7.09 (d, J = 12Hz, 1H), 7.03 (s, 1H), 5.72–5.68 (m, 1H), 5.52 (m, 1H), 4.97 (t, J = 6Hz, J = 12Hz, 1H), 4.86–4.81 (m, 1H), 4.80–4.76 (m, 1H), 4.60 (t, J = 6Hz, J = 12Hz, 2H), 3.91 (s, 3H), 3.24–3.18 (m, 1H), 2.92–2.84 (m, 1H), 2.73–2.69 (m, 1H), 2.67 (s, 3H), 2.63–2.56 (m, 2H), 2.37–2.33 (m, 1H), 2.07–2.01 (m, 2H), 1.74–1.68 (m, 5H), 1.58 (d, J = 6Hz, 6H), 1.50–1.48 (m, 2H), 1.47–1.42 (m, 4H), 1.40–1.39 (m, 6H), 0.96 (m, 4H) ppm.

Example 17



Synthesis route:



Step 1) preparation of compound **17-1**

[00211] A mixture of 2-iodopropane (3 g, 17.648 mmol) and sodium azide (4.589 g, 70.59 mmol) in DMF (20 mL) was stirred at rt for 48 hours. After the reaction was complete, the mixture was filtered. To the filtrate were added compound **17-2** (0.2 g, 2 mmol) and CH₃CN (20 mL), followed by the addition of CuSO₄·5H₂O (0.05 g, 0.2 mmol) and Cu (0.03 g, 0.5 mmol) at rt. The mixture was stirred at rt under N₂ for 72 hours. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was diluted with EtOAc (30 mL). The mixture was washed with saturated aqueous NH₄Cl (30 mL), the water phased was extracted with EtOAc (30 mL × 2). The combined organic layers were washed with saturated aqueous NaCl and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 6:1 to give compound **17-3** (2 g, 85.63%) as a white solid.

MS (ESI, pos.ion) *m/z*: 184.3[M+1]⁺; and

¹H NMR (600 MHz, CDCl₃): δ 8.08 (s, 1H), 4.87–4.80 (m, 1H), 4.39–4.31 (m, 2H), 1.57–1.53 (m, 6H), 1.35–1.30 (m, 3H) ppm.

Step 3) preparation of compound **17-4**

[00212] To a mixture of compound **17-3** (1.4 g, 7.6 mmol) in a mixed solvent of ethanol (10 mL) and water (2 mL) was added NaOH (1.2 g, 31 mmol). The mixture was stirred at rt overnight. After the reaction was complete, the mixture was concentrated *in vacuo* to remove ethanol. The mixture was adjusted with hydrochloric acid (2 M) to pH 5 and extracted with DCM (30 mL × 3). The combined organic layers were washed with saturated aqueous NaCl solution, and dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give a product as a white solid **17-4** (0.7 g, 80%).

MS (ESI, neg.ion) *m/z*: 154.1[M-1]⁻; and

¹H NMR (600 MHz, CDCl₃): δ 8.47 (s, 1H), 8.18 (s, 1H), 4.83–4.75 (m, 1H), 1.47 (d, *J* = 12Hz, 6H) ppm.

Step 4) preparation of compound **17-5**

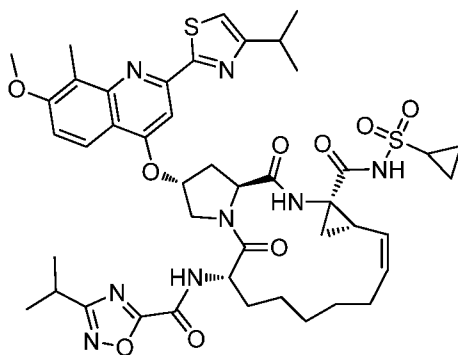
[00213] A solution of compound **4-6** (0.3 g, 0.4 mmol) in EtOAc (2 mL) was cooled to 0 °C, and a solution of HCl in EtOAc (30%, 4 mL) was added. The mixture was stirred at rt until no more gas evolution. The mixture was filtered to afford a white solid; the solid was washed with EtOAc (20 mL). To a mixture of compound **4-7**, compound **17-4** (0.04 g, 0.3 mmol), EDCI (0.05 g, 0.3

mmol) and HOAT (0.040 g, 0.29 mmol) in DMF (20 mL) was added DIPEA (97 mg, 0.75 mmol) dropwise at 0 °C. After the addition, the mixture was stirred at rt overnight. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **17-5** (135 mg, 50%) as a white solid.

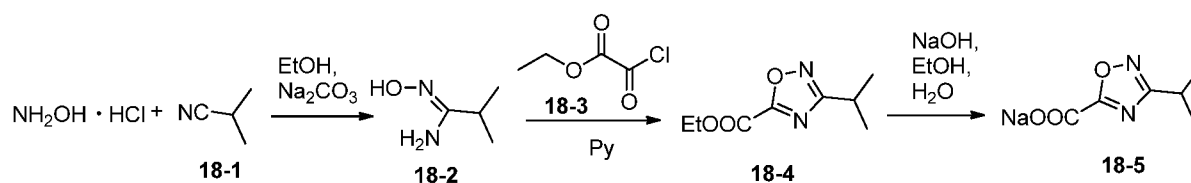
MS (ESI, pos.ion) m/z : 901.6 [M+1]⁺; and

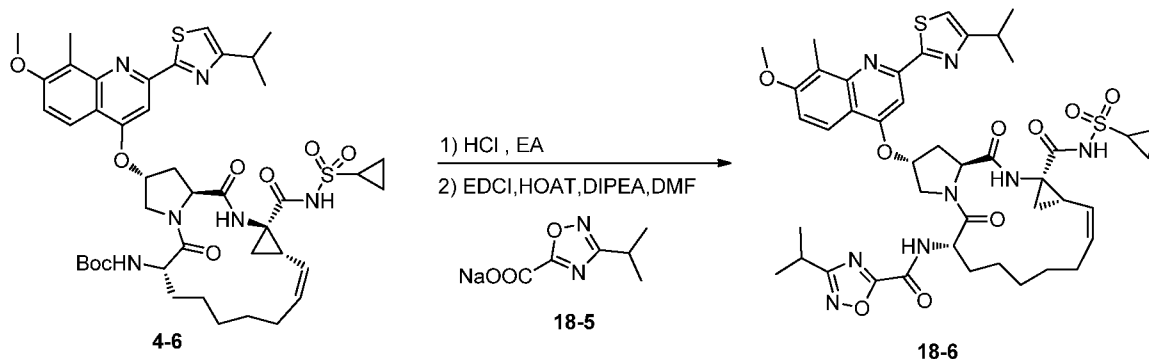
¹H NMR (600 MHz, CDCl₃): δ 10.41 (s, 1H), 8.04 (d, J = 12Hz, 1H), 7.97 (s, 1H), 7.86 (s, 1H), 7.68 (s, 1H), 7.31 (s, 1H), 7.25 (d, J = 12Hz, 1H), 6.42 (s, 1H), 5.76–5.69 (m, 1H), 5.05 (t, J_1 = 6Hz, J_2 = 12Hz, 1H), 4.83–4.76 (m, 1H), 4.69 (d, J = 12Hz, 1H), 4.22 (d, J = 6Hz, 1H), 3.98 (s, 3H), 3.38–3.31 (m, 1H), 2.96–2.90 (m, 1H), 2.81–2.74 (m, 2H), 2.65 (s, 3H), 2.62–2.54 (m, 1H), 2.37–2.32 (m, 1H), 2.14–2.09 (m, 1H), 1.96–1.88 (m, 2H), 1.76–1.73 (m, 1H), 1.56–1.54 (m, 6H), 1.43 (d, 6H), 1.39–1.33 (m, 2H), 1.32–1.28 (m, 1H), 1.26–1.17 (m, 2H), 1.16–1.07 (m, 1H), 0.91–0.84 (m, 6H) ppm.

Example 18



Synthesis route:





Step 1) preparation of compound **18-2**

[00214] To a mixture of compound **18-1** (0.7 mL, 8 mmol) in EtOH (40 mL) were added Na_2CO_3 (1 g, 9.434 mmol) and hydroxylamine hydrochloride (0.65 g, 9.4 mmol). The mixture was refluxed for 7 hours. The mixture was cooled to rt, and additional Na_2CO_3 (1 g, 9.434 mmol) and hydroxylamine hydrochloride (0.65 g, 9.4 mmol) were added. The mixture was refluxed overnight. After the reaction was complete, the mixture was cooled to rt and filtered. The filtrate was concentrated *in vacuo* to remove ethanol. The residue was dissolved in ether (20 mL). The resulting mixture was washed with hydrochloric acid (1 M, 10 mL) and adjusted with ammonium hydroxide to neutral. The water phase was extracted with ether (30 mL $\times$ 3). The combined organic layers were washed with saturated aqueous NaCl and dried over anhydrous Na_2SO_4 , and then concentrated *in vacuo* to afford compound **18-2** (0.6 g, 70%) as a white solid.

MS (ESI, pos.ion) m/z : 103.3[M+1]⁺.

Step 2) preparation of compound **18-4**

[00215] A mixture of compound **18-2** (4 g, 39.2 mmol) in pyridine (20 mL, 247 mmol) was stirred at 0 °C for 10 min, and then compound **18-3** (5.3 mL, 47 mmol) was added dropwise. After the addition, the mixture was stirred at 80 °C for 2 hours. The reaction mixture was poured into ice water (100 mL). The mixture was extracted with DCM (30 mL). The organic layer was washed with hydrochloric acid (1 M, 10 mL) and saturated aqueous NaCl (20 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford compound **18-4** (6.1 g, 85%) as a white solid.

MS (ESI, pos.ion) m/z : 185.1[M+1]⁺; and

¹H NMR (600 MHz, CDCl_3): δ 4.49–4.41 (m, 2H), 3.18–3.05 (m, 1H), 1.41–1.35 (m, 3H), 1.32–1.27 (m, 6H) ppm.

Step 3) preparation of compound **18-5**

[00216] To a mixture of compound **18-4** (5.6 g, 30 mmol) in ethanol (10 mL) was added a

solution of NaOH (1.3 g, 33 mmol) in water (5 mL) in an ice bath. The mixture was stirred at 60 °C for 1.5 hours. After the reaction was complete, the mixture was concentrated *in vacuo* to afford compound **18-5** (5.0 g, 92%) as a white solid.

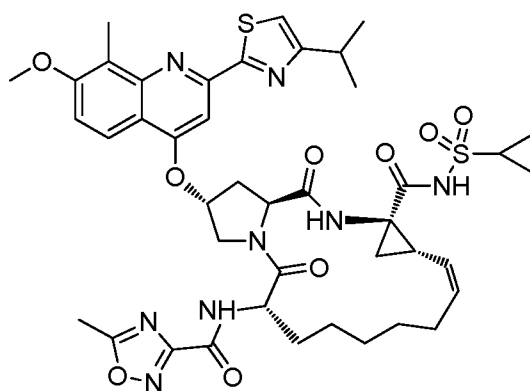
Step 4) preparation of compound **18-6**

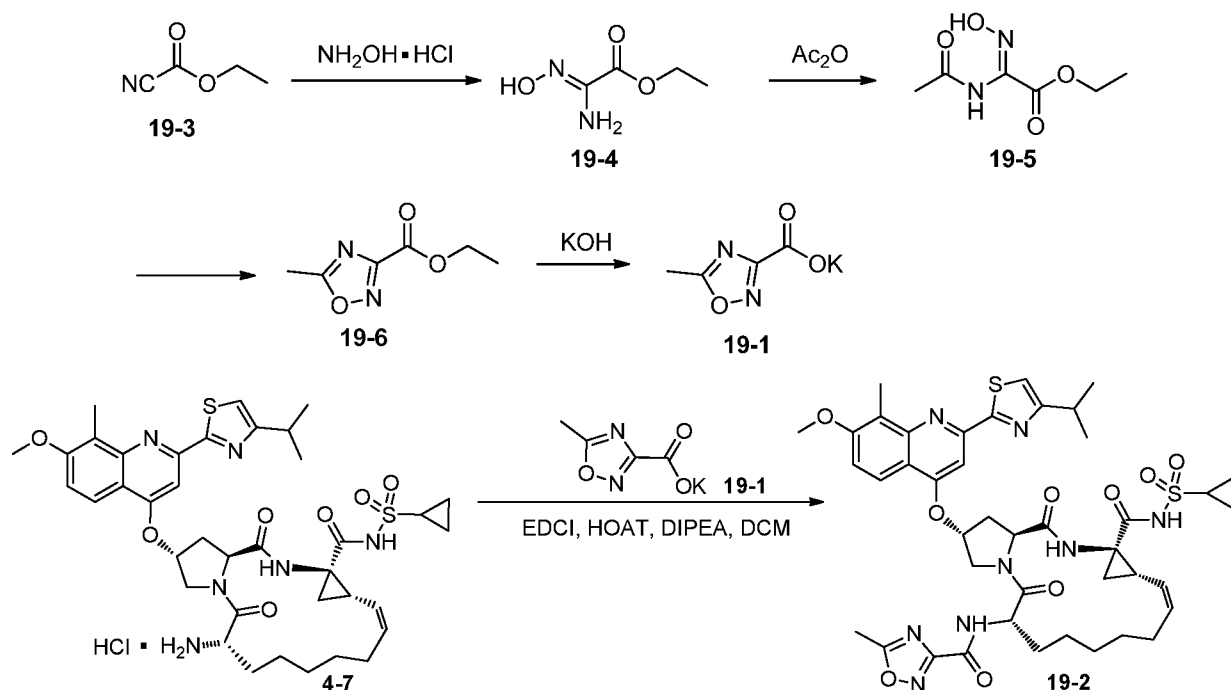
[00217] A solution of compound **4-6** (0.3 g, 0.4 mmol) in EtOAc (2 mL) was cooled to 0 °C, and a solution of HCl in EtOAc (30%, 4 mL) was added. The mixture was stirred at rt until no more gas evolution. The mixture was filtered to afford a white solid; the solid was washed with EtOAc (20 mL). To a mixture of compound **4-7**, compound **18-5** (0.05 g, 0.3 mmol), EDCI (0.05 g, 0.3 mmol) and HOAT (0.040 g, 0.29 mmol) in DMF (5 mL) was added DIPEA (97 mg, 0.75 mmol) dropwise at 0 °C. After the addition, the mixture was stirred at rt overnight. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **18-6** as a white solid (135 mg, 50%).

MS (ESI, pos.ion) *m/z*: 902.6[M+1]⁺; and

¹H NMR (600 MHz, CDCl₃): δ 10.15 (s, 1H), 8.03 (d, *J* = 12Hz, 1H), 7.59 (s, 1H), 7.11 (s, 1H), 6.74 (s, 1H), 5.80–5.76 (m, 1H), 5.60 (s, 1H), 5.40–5.33 (m, 1H), 5.06–5.03 (m, 1H), 4.82–4.80 (m, 1H), 4.65–4.63 (m, 1H), 4.56 (d, *J* = 12Hz, 1H), 4.18 (d, *J* = 12Hz, 1H), 4.00 (s, 3H), 3.31–3.26 (m, 1H), 3.21–3.15 (m, 1H), 2.97–2.92 (m, 1H), 2.79 (s, 3H), 2.61–2.53 (m, 1H), 2.37–2.31 (m, 1H), 2.28–2.26 (m, 1H), 2.07–2.04 (m, 2H), 2.02–1.99 (m, 2H), 1.86–1.81 (m, 1H), 1.73–1.63 (m, 1H), 1.43–1.41 (d, 6H), 1.41–1.35 (d, 5H), 1.20–1.15 (m, 2H), 1.15–1.05 (m, 2H), 1.21–1.18 (m, 2H), 1.15–1.10 (m, 2H), 1.02–0.95 (m, 2H), 0.91–0.86 (m, 2H) ppm.

Example 19



Synthesis route:**Step 1) preparation of compound 19-6**

[00218] To an AcOH (25 mL) solution in flask were added hydroxylamine hydrochloride (4.6 g, 66 mmol) and compound **19-3** (5.0 g, 50 mmol) in turn, and then AcONa (5.4 g, 66 mmol) was added in portions. The mixture was stirred at rt for 2 hours. The reaction was monitored by TLC until compound **19-3** was consumed, then the product was intermediate **19-4**. To the reaction mixture was added Ac₂O (7.2 mL, 76 mmol) slowly. The resulting mixture was stirred for 30 min. The reaction was monitored by TLC until compound **19-4** was consumed; the product was intermediate **19-5**. The mixture was stirred at 100 °C for 12 hours. The reaction was monitored by TLC until compound **19-5** was consumed. The mixture was concentrated *in vacuo* to remove acetic acid. The residue was dissolved in EtOAc (150 mL). The solution was washed with water (30 mL) and saturated aqueous NaCl (30 mL) in turn, dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to afford compound **19-6** (3.1 g) as a white solid, which was used in next step without further purification.

MS (ESI, pos.ion) *m/z*: 157[M+1]⁺.

Step 2) preparation of compound 19-1

[00219] To a solution of compound **19-6** (3.1 g, 20 mmol) in EtOH (40 mL) was added an aqueous potassium hydroxide solution (11.68 mol/L, 2 mL, 23.36 mmol); there was solid precipitated out immediately, the mixture was stirred overnight. The reaction mixture was filtered. The filter cake was washed with a little of EtOH and dried *in vacuo* to give compound

19-1 (2.4 g, 14 mmol, 73%) as a white solid.

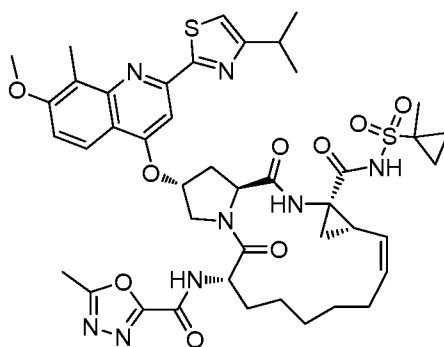
Step 3) preparation of compound **19-2**

[00220] A round-bottom flask was charged with compound **4-7** (0.15 g, 0.19 mmol), compound **19-1** (0.04 g, 0.23 mmol), EDCI (0.04 g, 0.21 mmol) and HOAT (0.03 g, 0.22 mmol), and then DCM (20 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (0.1 mL, 0.6 mmol) was added slowly. After the addition, the resulting mixture was stirred at 30 °C for 4 hours. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with EtOAc (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (20 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **19-2** (0.07 g, 42%) as a white solid.

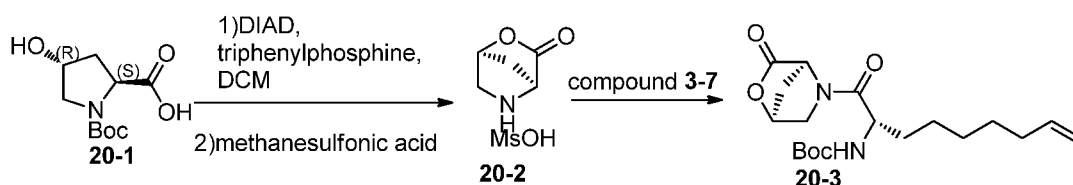
MS (ESI, pos.ion) *m/z*: 875[M+1]⁺; and

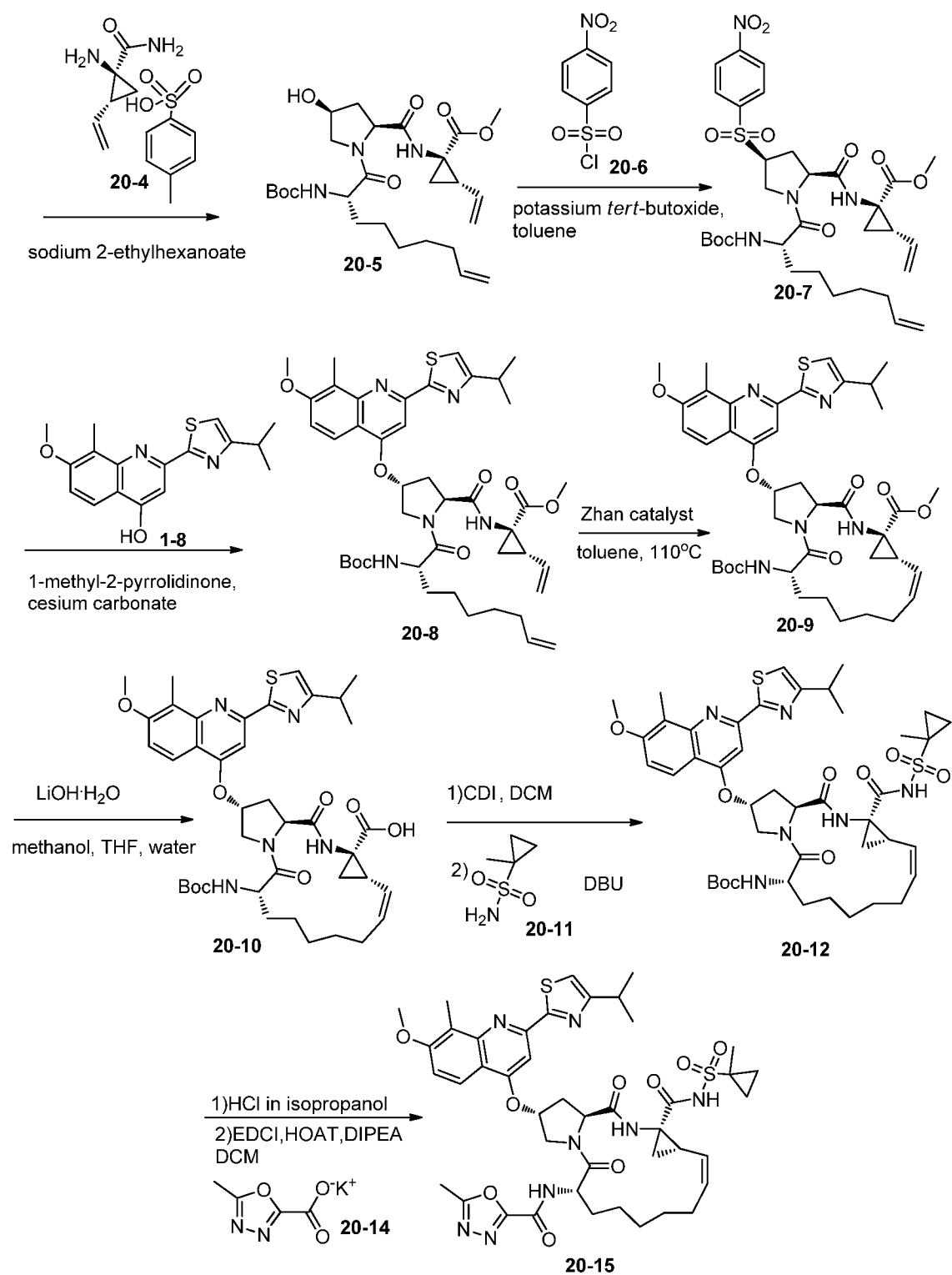
¹H NMR (600 MHz, CDCl₃) δ 10.32 (s, 1H), 7.93 (d, *J* = 8.9 Hz, 1H), 7.71 (d, *J* = 6.7 Hz, 1H), 7.63 (s, 1H), 7.50 (s, 1H), 7.13 (d, *J* = 9.2 Hz, 1H), 7.04 (s, 1H), 5.69 (dd, *J* = 18.0, 8.7 Hz, 1H), 5.52 (s, 1H), 4.94 (t, *J* = 9.4 Hz, 1H), 4.77 (s, 1H), 4.69 (t, *J* = 7.7 Hz, 1H), 4.42 (d, *J* = 11.3 Hz, 1H), 4.13 (d, *J* = 8.2 Hz, 1H), 3.86 (s, 3H), 3.27 – 3.17 (m, 1H), 2.90 – 2.77 (m, 2H), 2.64 (d, *J* = 11.7 Hz, 6H), 2.56 – 2.47 (m, 1H), 2.28 – 2.19 (m, 1H), 2.06 – 1.93 (m, 2H), 1.87 – 1.81 (m, 1H), 1.73 (s, 1H), 1.58 – 1.52 (m, 1H), 1.46 – 1.44 (m, 2H), 1.41 (d, *J* = 6.9 Hz, 6H), 1.33 – 1.25 (m, 4H), 1.14 – 1.04 (m, 2H), 0.92 – 0.85 (m, 3H) ppm.

Example 20



Synthesis route:





Step 1) preparation of compound **20-2**

[00221] A mixture of compound **20-1** (50 g, 216 mmol), triphenylphosphine (68 g, 259 mmol) and DCM (375 mL) in a flask was cooled to -10 °C under N₂, and then DIAD (52.5 g, 260 mmol) was added dropwise. After the addition, the mixture was stirred at -10 °C for 3 hours. After the reaction was complete, methanesulfonic acid (62.5 g, 650 mmol) was added, and the mixture was stirred at 40 °C for 2 hours. After the reaction was complete, the mixture was cooled to rt

and filtered. The filter cake was washed with a little of DCM and dried at 40 °C *in vacuo* for 4 hours to give compound **20-2** (40 g, 88.4%) as a white solid.

Step 2) preparation of compound **20-3**

[00222] To a mixture of compound **20-2** (10 g, 47.8 mmol), compound **3-7** (10 g, 36.8 mmol), ethyl cyanoglyoxylate-2-oxime (1.3 g, 9.1 mmol), DIPEA (9.0 mL, 54 mmol) and DCM (250 mL) in a flask was added EDCI (0.85 g, 4.4 mmol) under N₂. The mixture was stirred at rt for 3 hours. After the reaction was complete, to the mixture was added water (250 mL). The organic layer was washed with aqueous citric acid solution (10%, 250 mL), saturated aqueous sodium bicarbonate solution (250 mL) and saturated aqueous sodium chloride solution (250 mL) in turn, and dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give compound **20-3** (12.7 g, 94.1%) as brownish red oil.

Step 3) preparation of compound **20-5**

[00223] A 250 mL of flask was charged with compound **20-3** (13.37 g, 36.49 mmol), toluene (13 mL) and water (130 mL), and then followed by the addition of compound **20-4** (11.66 g, 37.20 mmol) and sodium 2-ethylhexanoate (10.00 g, 54.85 mmol). The mixture was stirred at rt overnight. After the reaction was complete, the mixture was extracted with EtOAc (150 mL × 2). The organic layers were combined. The combined organic layers were washed with saturated aqueous sodium bicarbonate (150 mL), hydrochloric acid (1 mol/L, 150 mL) and saturated aqueous sodium chloride, dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give compound **20-5** (18.52 g, 100%) as brownish red oil.

Step 4) preparation of compound **20-7**

[00224] A 250 mL of flask were charged with compound **20-5** (18.5 g, 36.4 mmol), compound **20-6** (10.48 g, 47.3 mmol) and toluene (100 mL). The mixture was cooled to -10 °C, and a solution of potassium *tert*-butoxide (6.12 g, 54.6 mmol) in anhydrous tetrahydrofuran (20 mL) was added slowly, the reaction temperature was maintained not higher than -5 °C. After the addition, the mixture was further stirred at -5 °C for 3 hours. After the reaction was complete, to the mixture was added hydrochloric acid (1 mol/L, 100 mL). The resulting mixture was stirred at rt for 30 min. The aqueous phase was extracted with toluene (100 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (100 mL), hydrochloric acid (1 mol/L, 150 mL) and saturated aqueous sodium chloride, dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give compound **20-7** (24.0 g, 97.6%) as brownish red oil.

Step 5) preparation of compound **20-8**

[00225] A 250 mL of flask were charged with compound **20-7** (24 g, 35.4 mmol), compound **1-8** (10 g, 31.8 mmol), cesium carbonate (15 g, 46 mmol) and 1-methyl-2-pyrrolidinone (70 mL). The mixture was stirred at 50 °C overnight. After the reaction was complete, the mixture was participated between water (100 mL) and *tert*-butyl methyl ether (70 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (70 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate (70 mL) and saturated aqueous sodium chloride, and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo* to give brownish red oil. The oil was suspended in isopropanol (210 mL) and the mixture was warmed and stirred until dissolved completely. The mixture was cooled to rt and then compound **20-8** (20.0 g, 80%) precipitated out as a white solid.

Step 6) preparation of compound **20-9**

[00226] A mixture of compound **20-8** (20 g, 24.8 mmol) and toluene (1400 mL) was refluxed at 110 °C for 1 hour. To the mixture was added a solution of Zhan catalyst-1B (0.08 g, 0.1 mmol) in toluene (200 mL) under N₂ over 3 hours. After the addition, the mixture was refluxed for 2 hours. After the reaction was complete, the mixture was concentrated *in vacuo* to give brownish grey oil, the oil was suspended in methyl *tert*-butyl ether (80 mL) and the mixture was refluxed and stirred until dissolved completely. And then the mixture was cooled to rt and compound **20-9** (15.0 g, 80%) precipitated out as a white solid.

Step 7) preparation of compound **20-10**

[00227] A mixture of compound **20-9** (10 g, 12.89 mmol), monohydrate lithium hydroxide (1.1 g, 26 mmol), methanol (40 mL), tetrahydrofuran (40 mL) and water (20 mL) in a 250 mL of one neck flask was stirred at rt overnight. After the reaction was complete, the mixture was concentrated *in vacuo*. The residue was participated between hydrochloric acid (1mol/L, 50 mL) and EtOAc (50 mL). The water phase was extracted with EtOAc (50 mL). The organic phases were combined. The combined organic phases were washed with saturated aqueous sodium chloride (50 mL), dried over anhydrous Na₂SO₄, and concentrated *in vacuo* to give compound **20-10** (9.15 g, 93.2%) as a white solid.

Step 8) preparation of compound **20-12**

[00228] A mixture of compound **20-10** (2 g, 2.625 mmol), CDI (0.87 g, 5.3 mmol) and DCM (20 mL) was stirred at rt for 3 hours, and DBU (0.82 g, 5.3 mmol) and compound **20-11** (0.72 g, 5.3

mmol) were added. The resulting mixture was stirred at rt overnight. After the reaction was complete, to the mixture was added hydrochloric acid (1 mol/mL, 40 mL). The aqueous phase was extracted with DCM (10 mL). The combined organic phases were washed with saturated aqueous sodium chloride (50 mL), dried over anhydrous Na₂SO₄, and concentrated *in vacuo* to give compound **20-12** (2.2 g, 94.42%) as a yellow solid.

MS (ESI, pos.ion) *m/z*: 880.8[M+1]⁺; and

¹H NMR (600 MHz, CDCl₃): δ 10.31 (s, 1H), 8.03 (d, *J* = 7.5 Hz, 1H), 7.93 (s, 1H), 7.84 – 7.79 (m, 2H), 7.54 (s, 1H), 7.06 – 7.01 (m, 2H), 5.70 (dd, *J* = 17.9, 8.7 Hz, 1H), 5.52 (s, 1H), 5.03 – 4.98 (m, 1H), 4.76 – 4.69 (m, 2H), 4.65 – 4.60 (m, 1H), 4.13 – 4.09 (m, 1H), 3.89 (s, 3H), 3.73 (s, 3H), 3.26 – 3.19 (m, 2H), 2.75 (dd, *J* = 13.8, 7.4 Hz, 1H), 2.65 (s, 3H), 2.31 (d, *J* = 8.6 Hz, 1H), 2.07 – 2.04 (m, 1H), 1.85 (dd, *J* = 15.5, 9.2 Hz, 2H), 1.78 (dd, *J* = 10.5, 5.1 Hz, 1H), 1.66 – 1.62 (m, 1H), 1.50 (d, *J* = 7.3 Hz, 4H), 1.40 (d, *J* = 6.9 Hz, 7H), 1.26 (d, *J* = 4.2 Hz, 3H), 1.20 (s, 3H), 0.86 – 0.77 (m, 3H) ppm.

Step 9) preparation of compound **20-15**

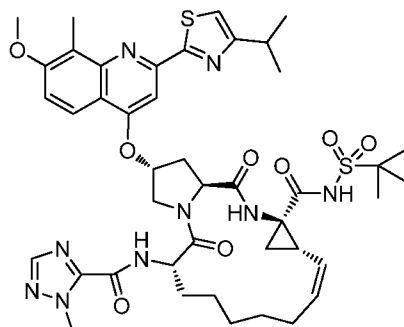
[00229] A solution of compound **20-12** (0.2 g, 0.2 mmol) in isopropanol (2 mL) was cooled to 0°C, and a solution of HCl in isopropanol (40%, 5 mL) was added. The mixture was stirred at rt until no more gas evolution. The mixture was filtered; the filter cake was washed with EtOAc (5 mL) and dried *in vacuo* to give a white solid. A round-bottom flask was charged with the white solid, compound **20-14** (0.1 g, 0.6 mmol), EDCI (0.2 g, 1.5 mmol) and HOAT (0.15 g, 1.1 mmol), and then DCM (10 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (0.5 mL, 3 mmol) was added slowly. The mixture was stirred at 30 °C for 6 hours. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **20-15** as a white solid (0.140 g, 60%).

MS (ESI, pos.ion) *m/z*: 890.8[M+1]⁺; and

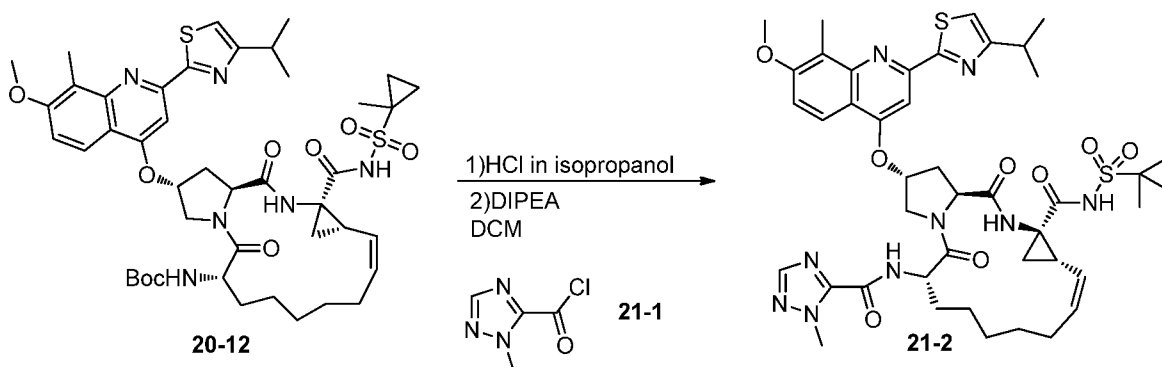
¹H NMR (600 MHz, CDCl₃): δ 10.31 (s, 1H), 8.03 (d, *J* = 7.5 Hz, 1H), 7.93 (s, 1H), 7.84 – 7.79 (m, 2H), 7.54 (s, 1H), 7.06 – 7.01 (m, 2H), 5.70 (dd, *J* = 17.9, 8.7 Hz, 1H), 5.52 (s, 1H), 5.03 – 4.98 (m, 1H), 4.76 – 4.69 (m, 2H), 4.65 – 4.60 (m, 1H), 4.13 – 4.09 (m, 1H), 3.89 (s, 3H), 3.73 (s, 3H), 3.26 – 3.19 (m, 2H), 2.75 (dd, *J* = 13.8, 7.4 Hz, 1H), 2.65 (s, 3H), 2.31 (d, *J* = 8.6

Hz, 1H), 2.07 – 2.04 (m, 1H), 1.85 (dd, $J = 15.5, 9.2$ Hz, 2H), 1.78 (dd, $J = 10.5, 5.1$ Hz, 1H), 1.66 – 1.62 (m, 1H), 1.50 (d, $J = 7.3$ Hz, 4H), 1.40 (d, $J = 6.9$ Hz, 7H), 1.26 (d, $J = 4.2$ Hz, 3H), 1.20 (s, 3H), 0.86 – 0.77 (m, 3H).

Example 21



Synthesis route:



Synthesis steps:

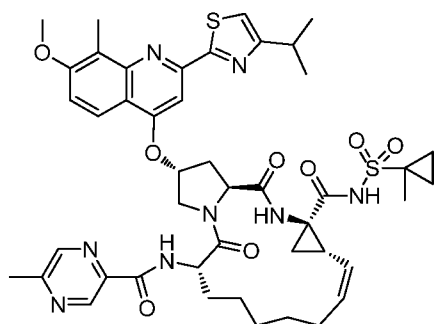
[00230] A solution of compound **20-12** (0.2 g, 0.2 mmol) in isopropanol (2 mL) was cooled to 0 °C, and a solution of HCl in isopropanol (40%, 5 mL) was added. The mixture was stirred at rt until no more gas evolution. The mixture was filtered to afford a white solid; the solid was washed with EtOAc (5 mL) and dried at rt *in vacuo*. A round-bottom flask was charged with the white solid, compound **21-1** (0.1 g, 0.6 mmol) and DCM (10 mL). The mixture was cooled to 0 °C, and DIPEA (0.5 mL, 3 mmol) was added slowly under N₂. The mixture was stirred at 30 °C for 4 hours. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **21-2** (0.130 g, 60 %) as a white solid.

MS (ESI, pos.ion) m/z : 889.4[M+1]⁺; and

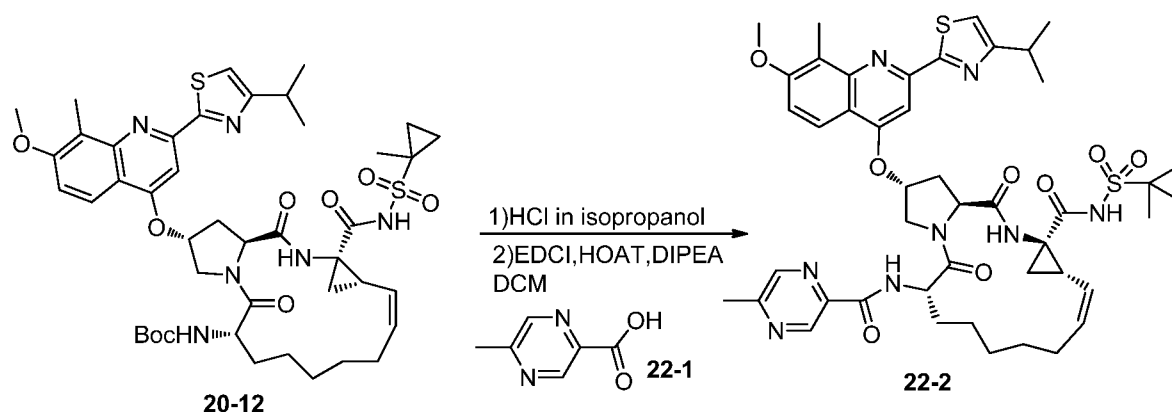
¹H NMR (600 MHz, CDCl₃): δ 10.31 (s, 1H), 8.03 (d, $J = 7.5$ Hz, 1H), 7.93 (s, 1H), 7.84 – 7.79 (m, 2H), 7.54 (s, 1H), 7.06 – 7.01 (m, 2H), 5.70 (dd, $J = 17.9, 8.7$ Hz, 1H), 5.52 (s, 1H),

5.03 – 4.98 (m, 1H), 4.76 – 4.69 (m, 2H), 4.65 – 4.60 (m, 1H), 4.13 – 4.09 (m, 1H), 3.89 (s, 3H), 3.73 (s, 3H), 3.26 – 3.19 (m, 2H), 2.75 (dd, $J = 13.8, 7.4$ Hz, 1H), 2.65 (s, 3H), 2.31 (d, $J = 8.6$ Hz, 1H), 2.07 – 2.04 (m, 1H), 1.85 (dd, $J = 15.5, 9.2$ Hz, 2H), 1.78 (dd, $J = 10.5, 5.1$ Hz, 1H), 1.66 – 1.62 (m, 1H), 1.50 (d, $J = 7.3$ Hz, 4H), 1.40 (d, $J = 6.9$ Hz, 7H), 1.26 (d, $J = 4.2$ Hz, 3H), 1.20 (s, 3H), 0.86 – 0.77 (m, 3H) ppm.

Example 22



Synthesis route:



Synthesis steps:

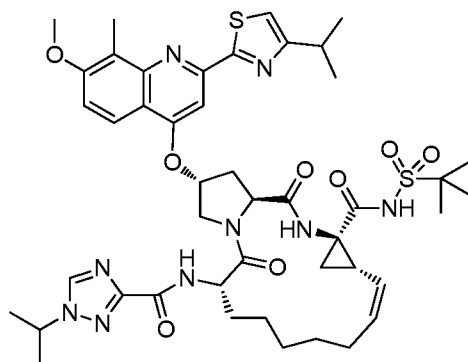
[00231] A solution of compound **20-12** (0.2 g, 0.2 mmol) in isopropanol (2 mL) was cooled to 0 °C, and a solution of HCl in isopropanol (40%, 5 mL) was added. The mixture was stirred until no more gas evolution. The mixture was filtered to afford a white solid; the solid was washed with EtOAc (5 mL). A round-bottom flask was charged with the white solid, compound **22-1** (0.1 g, 0.7 mmol), EDCI (0.2 g, 1.5 mmol) and HOAT (0.15 g, 1.1 mmol), and then DCM (10 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (0.5 mL, 3 mmol) was added slowly. The mixture was stirred at 30 °C for 6 hours. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (10 mL), dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **20-2** (0.163

g, 70%) as a white solid.

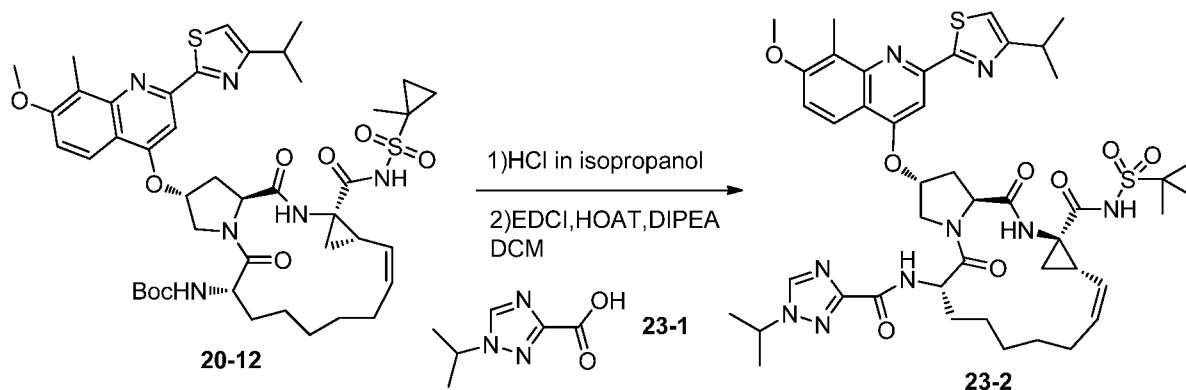
MS (ESI, pos.ion) m/z : 900.4[M+1]⁺; and

¹H NMR (600 MHz, CDCl₃): δ 10.25 (s, 1H), 9.07 (s, 1H), 8.43 (s, 1H), 8.17 (d, J = 6.8 Hz, 1H), 7.86 – 7.78 (m, 2H), 7.48 (s, 1H), 7.05 (s, 1H), 6.95 (d, J = 9.1 Hz, 1H), 5.74 (dd, J = 18.0, 8.6 Hz, 1H), 5.51 (s, 1H), 5.02 (t, J = 9.5 Hz, 1H), 4.72 – 4.65 (m, 2H), 4.51 (d, J = 11.4 Hz, 1H), 4.14 – 4.11 (m, 1H), 3.78 (s, 3H), 3.26 – 3.19 (m, 2H), 2.74 – 2.69 (m, 1H), 2.67 – 2.55 (m, 9H), 2.29 (dd, J = 17.3, 8.6 Hz, 1H), 2.07 – 2.00 (m, 2H), 1.95 – 1.89 (m, 2H), 1.78 (t, J = 10.0 Hz, 1H), 1.64 (dd, J = 9.2, 5.9 Hz, 1H), 1.50 (s, 3H), 1.41 (d, J = 6.9 Hz, 7H), 1.27 (d, J = 3.5 Hz, 2H), 1.20 (s, 3H), 0.92 – 0.75 (m, 3H) ppm.

Example 23



Synthesis route:



Synthesis steps:

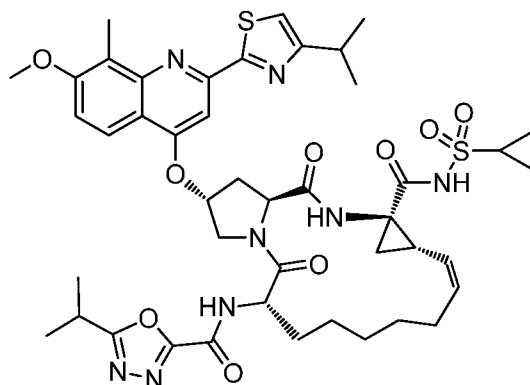
[00232] A solution of compound **20-12** (1.5 g, 1.7 mmol) in isopropanol (20 mL) was cooled to 0 °C, and a solution of HCl in isopropanol (40%, 20 mL) was added. The mixture was stirred at rt until no more gas evolution. The mixture was filtered to afford a white solid; the solid was washed with EtOAc (5 mL). A round-bottom flask was charged with the white solid, compound **23-1** (0.6 g, 3 mmol), EDCI (0.4 g, 3 mmol) and HOAT (0.3 g, 2.2 mmol), and then DCM (30 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (2 mL, 12.1 mmol) was

added slowly. The mixture was stirred at 30 °C for 4 hours. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with DCM (20 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **23-2** (0.75g, 45%) as a white solid.

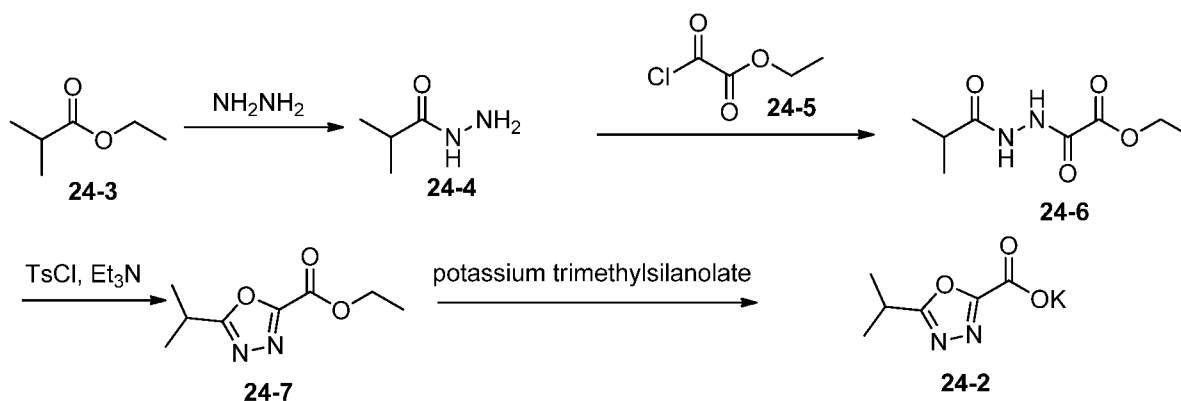
MS (ESI, pos.ion) m/z : 917.4[M+1]⁺; and

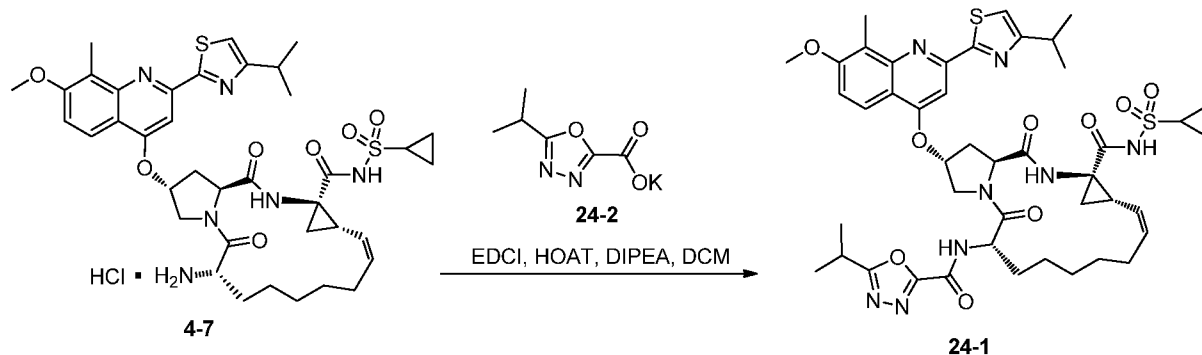
¹H NMR (400 MHz, CDCl₃): δ 10.27 (s, 1H), 8.04 (dd, J = 29.9, 23.6 Hz, 2H), 7.84 (d, J = 11.6 Hz, 2H), 7.52 (s, 1H), 7.05 (d, J = 12.8 Hz, 2H), 5.70 (d, J = 7.9 Hz, 1H), 5.51 (s, 1H), 5.01 (dd, J = 22.2, 12.9 Hz, 2H), 4.78 – 4.61 (m, 3H), 4.14 (d, J = 9.9 Hz, 1H), 3.97 (d, J = 17.5 Hz, 2H), 3.90 (s, 3H), 3.22 (s, 1H), 2.69 (d, J = 18.9 Hz, 6H), 2.32 (d, J = 7.6 Hz, 2H), 2.10 – 2.02 (m, 1H), 1.84 (s, 2H), 1.77 (d, J = 9.6 Hz, 1H), 1.69 (s, 1H), 1.53 (d, J = 6.1 Hz, 3H), 1.49 (s, 3H), 1.41 (s, 3H), 1.32 – 1.19 (m, 10H), 0.90 – 0.68 (m, 3H) ppm.

Example 24



Synthesis route:





Step 1) preparation of compound **24-4**

[00233] A mixture of compound **24-3** (20 g, 172.18 mmol) and hydrazine hydrate (20 mL, 514.5 mmol, 25.73 mol/L) in ethanol (30 mL) was refluxed for 4 hours. After the reaction was complete, the mixture was cooled to rt and concentrated *in vacuo* to afford a white solid **24-4** (10.7 g, 61%).

MS (ESI, pos.ion) m/z : 103[M+1]⁺.

Step 2) preparation of compound **24-6**

[00234] To a solution of compound **24-4** (3.0 g, 29 mmol) in DCM (40 mL) was added triethylamine (4 mL, 29 mmol) in an ice bath, and then compound **24-5** (4.0 g, 29 mmol) was added dropwise slowly. After the addition, the mixture was stirred at rt overnight. After the reaction was complete, the mixture was diluted with EtOAc (100 mL) and filtered to remove salt. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V : V) = 5 : 1 to afford compound **24-6** as a white solid (5.8 g, 99%).

MS (ESI, pos.ion) m/z : 203[M+1]⁺.

Step 3) preparation of compound **24-7**

[00235] To a solution of compound **24-6** (2.0 g, 9.9 mmol) in DCM (40 mL) were added triethylamine (1.8 mL, 13 mmol) and paratoluensulfonyl chloride (2.3 g, 12 mmol) in an ice bath. The mixture was stirred at rt for 8 hours. After the reaction was complete, the mixture was quenched with water (50 mL) and filtered. The filtrate was dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 5:1 to give compound **24-7** (1.1 g, 60%) as a white solid.

MS (ESI, pos.ion) m/z :185[M+1]⁺.

Step 4) preparation of compound **24-2**

[00236] To a solution of compound **24-7** (1.1 g, 6 mmol) in ethanol (25 mL) was added

potassium trimethylsilanolate (0.9 g, 7 mmol) with stirring. The mixture was stirred at rt overnight, there was white solid precipitated out during the reaction process. After the reaction was complete, the mixture was filtered. The filter cake was washed with a little ethanol and dried *in vacuo* to afford compound **24-2** (0.81 g, 70%) as a white solid.

^1H NMR (400 MHz, D_2O) δ 3.26 – 3.12 (m, 1H), 1.31 (d, J = 7.0 Hz, 6H) ppm.

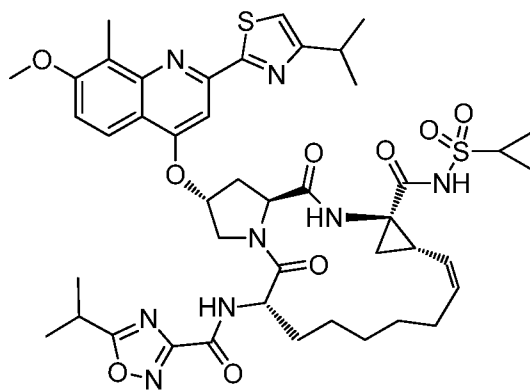
Step 5) preparation of compound **24-1**

[00237] A round-bottom flask was charged with compound **1-7** (0.5 g, 0.6 mmol), compound **24-2** (0.14 g, 0.7 mmol), EDCI (0.12 g, 0.63 mmol) and HOAT (0.1 g, 0.67 mmol), and then DCM (20 mL) was added under N_2 . The mixture was cooled to 0 °C, and DIPEA (0.3 mL, 1.8 mmol) was added slowly. The resulting mixture was stirred at 30 °C for 4 hours. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with EtOAc (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (20 mL) and dried over anhydrous Na_2SO_4 , and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **24-1** (0.14 g, 20%) as a white solid.

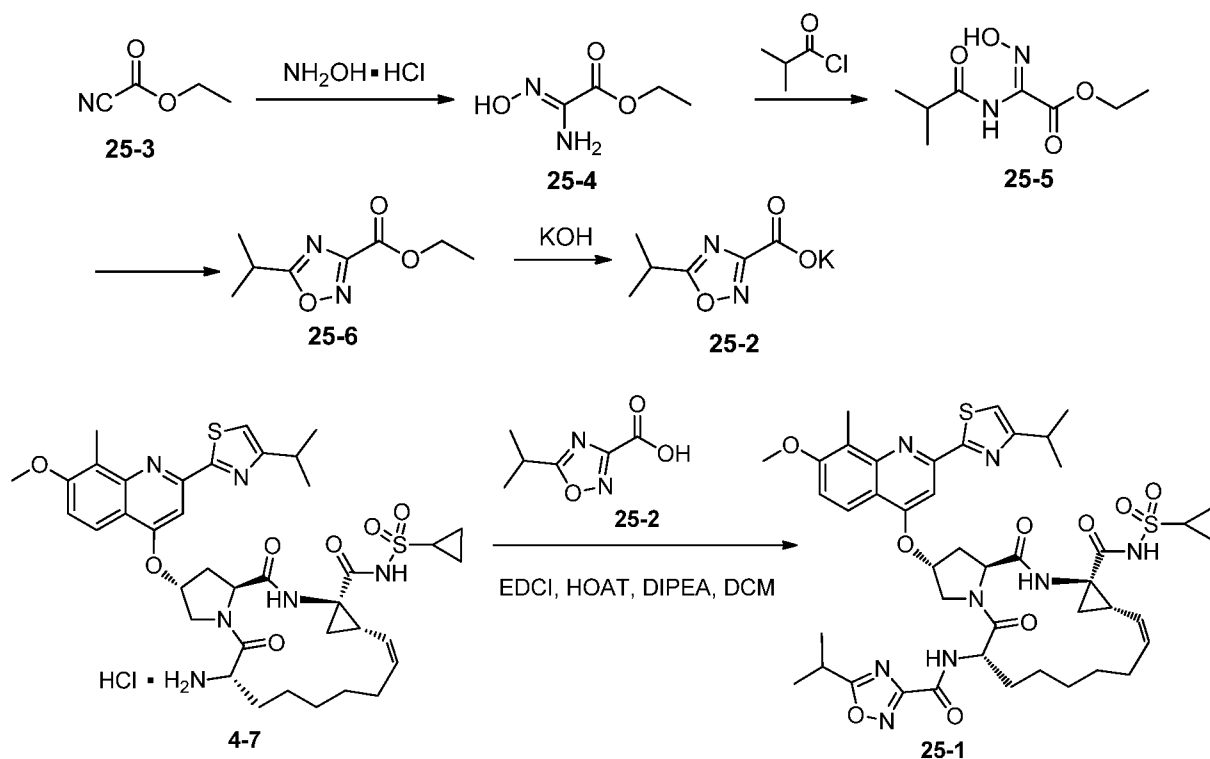
MS (ESI, pos.ion) m/z : 903 $[\text{M}+1]^+$; and

^1H NMR (600 MHz, CDCl_3) δ 10.37 (s, 1H), 8.64 (s, 1H), 8.03 (s, 1H), 7.90 (d, J = 9.0 Hz, 1H), 7.57 (s, 1H), 7.11 (d, J = 9.1 Hz, 1H), 7.04 (s, 1H), 5.80 – 5.67 (m, 1H), 5.57 (s, 1H), 5.05 – 4.96 (m, 1H), 4.86 – 4.78 (m, 1H), 4.71 – 4.57 (m, 2H), 4.22 (d, 1H), 3.90 (s, 3H), 3.27 – 3.18 (m, 1H), 3.16 – 3.05 (m, 1H), 2.94 – 2.87 (m, 1H), 2.82 – 2.74 (m, 2H), 2.68 (s, 4H), 2.31 – 2.25 (m, 1H), 2.22 – 2.15 (m, 1H), 1.87 – 1.83 (m, 2H), 1.40 (d, J = 6.9 Hz, 7H), 1.31 (dd, J = 18.4, 6.9 Hz, 11H), 1.21 – 1.03 (m, 3H), 0.97 – 0.82 (m, 3H) ppm.

Example 25



Synthesis route:



Step 1) preparation of compound **25-4**

[00238] To an EtOH (50 mL) solution in flask were added hydroxylamine hydrochloride (5.3 g, 76 mmol) and compound **25-3** (5.0 g, 50 mmol) in turn, and then K_2CO_3 (8.4 g, 61 mmol) was added in portions, and then water (25 mL) was added with stirring. After the addition, the mixture was stirred at rt for 2 hours. The reaction was monitored by TLC until the raw materials were consumed completely. The mixture was concentrated to remove EtOH. The residue was diluted with water (20 mL). The resulting mixture was extracted with DCM (30 mL $\times$ 5), the organic layers were dried over anhydrous Na_2SO_4 , and concentrated to give compound **25-4** (2.3 g, 35%) as a white solid.

Step 2) preparation of compound **25-5**

[00239] To a solution of compound **25-4** (1.0 g, 7.6 mmol) in DCM (20 mL) was added isobutyryl chloride (1.2 g, 11 mmol) in an ice bath. The mixture was stirred at rt for 4 hours. After the reaction was complete, the reaction was quenched with water (50 mL). The resulting mixture was extracted with DCM (30 mL $\times$ 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to give compound **25-5** (1.5 g, 98%) as colorless oil, which was used in next step without further purification.

^1H NMR (400 MHz, CDCl_3) δ 4.40 (q, $J = 7.1$ Hz, 2H), 2.74 (m, 1H), 1.40 (t, $J = 7.1$ Hz, 3H), 1.27 (d, $J = 7.0$ Hz, 6H) ppm.

Step 3) preparation of compound **25-6**

[00240] A solution of compound **25-5** (1.5 g, 7.4 mmol) in AcOH was stirred at 100 °C overnight. After the reaction was complete, the mixture was concentrated to remove AcOH. The residue was dissolved in EtOAc (50 mL). The resulting mixture was washed with water (30 mL) and saturated aqueous sodium chloride (30 mL) in turn, and concentrated to give compound **25-6** as pale yellow oil, which was used in next step without further purification.

MS (ESI, pos.ion) m/z : 185[M+1]⁺.

Step 4) preparation of compound **25-2**

[00241] To a solution of compound **25-6** (1.5 g, 20 mmol) in EtOH (40 mL) was added an aqueous potassium hydroxide solution (11.68 mol/L, 2 mL); there was solid precipitated out immediately, then the mixture was stirred overnight. The reaction mixture was filtered. The filter cake was washed with a little of EtOH and dried to give compound **25-2** (2.4 g, 62%) as a white solid.

¹³C NMR (150 MHz, D₂O) δ 178.82, 165.05, 163.27, 11.60 ppm.

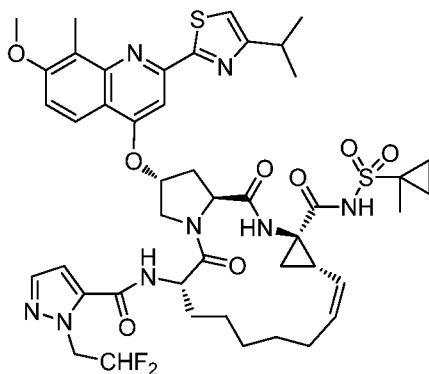
Step 5) preparation of compound **25-1**

[00242] A round-bottom flask was charged with compound **4-7** (0.5 g, 0.6 mmol), compound **25-2** (0.1 g, 0.7 mmol), EDCI (0.12 g, 0.6 mmol) and HOAT (0.1 g, 0.7 mmol), and then DCM (20 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (0.3 mL, 1.8 mmol) was added slowly. The resulting mixture was stirred at 30 °C for 4 hours. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with EtOAc (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (20 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **25-1** (0.29 g, 50%) as a white solid.

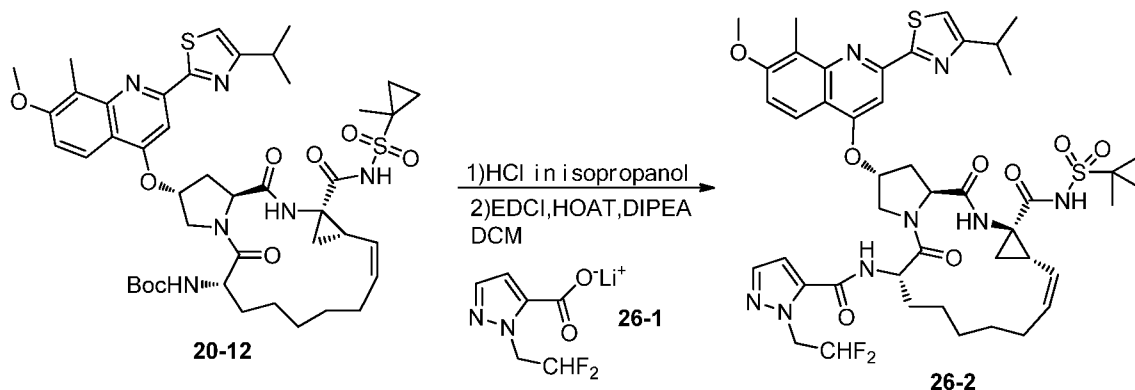
MS (ESI, pos.ion) m/z : 903[M+1]⁺; and

¹H NMR (400 MHz, CDCl₃) δ 10.25 (s, 1H), 7.98 (d, J = 9.1 Hz, 1H), 7.69 (d, J = 7.4 Hz, 1H), 7.53 (s, 1H), 7.20 (d, J = 9.6 Hz, 2H), 7.04 (s, 1H), 5.77 – 5.63 (m, 1H), 5.55 (s, 1H), 4.97 (t, J = 9.4 Hz, 1H), 4.86 (t, J = 6.9 Hz, 1H), 4.64 (t, J = 7.7 Hz, 1H), 4.51 (d, J = 11.3 Hz, 1H), 4.17 (dd, J = 11.1, 3.6 Hz, 1H), 3.94 (s, 3H), 3.77 – 3.71 (m, 1H), 3.61 – 3.41 (m, 3H), 3.31 – 3.16 (m, 2H), 2.93 – 2.83 (m, 1H), 2.70 (s, 4H), 2.34 – 2.24 (m, 1H), 1.91 – 1.84 (m, 2H), 1.62 – 1.54 (m, 2H), 1.44 – 1.38 (m, 14H), 1.19 – 1.04 (m, 3H), 0.97 – 0.87 (m, 4H) ppm.

Example 26



Synthesis route:



Synthesis steps:

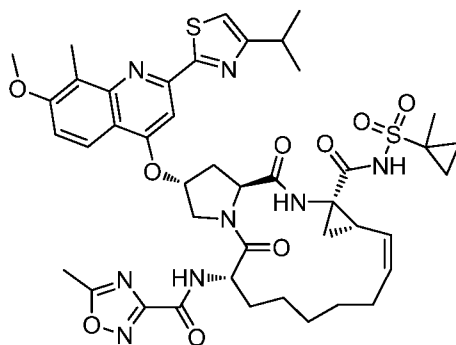
[00243] A solution of compound **20-12** (0.2 g, 0.25 mmol) in isopropanol (5 mL) was cooled to 0 °C, and a solution of HCl in isopropanol (40%, 5 mL) was added. The mixture was stirred at rt until no more gas evolution. The mixture was filtered to afford a white solid; the solid was washed with EtOAc (5 mL). A round-bottom flask was charged with the solid, compound **26-1** (0.067 g, 0.367 mmol), EDCI (0.07 g, 0.367 mmol) and HOAT (0.05 g, 0.367 mmol), and then DCM (10 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (0.4 mL, 2 mmol) was added slowly. The mixture was stirred at 30 °C for 6 hours. The mixture was quenched with water (10 mL). The resulting mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:2 to give compound **26-2** (0.160 g, 70%) as a white solid.

MS (ESI, pos.ion) *m/z*: 938.4[M+1]⁺; and

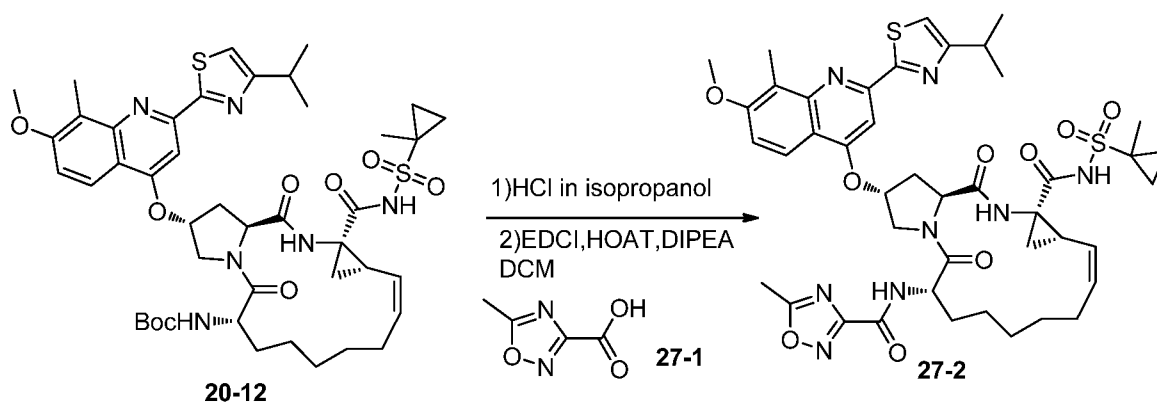
¹H NMR (600 MHz, CDCl₃) δ 10.16 (s, 1H), 7.96 (d, *J* = 8.6 Hz, 1H), 7.55 (d, *J* = 37.1 Hz, 2H), 7.41 (s, 1H), 7.20 (s, 1H), 6.79 (s, 1H), 6.62 (s, 1H), 5.73 (dd, *J* = 17.9, 8.6 Hz, 1H), 5.60 (s,

1H), 5.09 – 5.00 (m, 1H), 4.68 (dd, $J = 32.0, 27.1$ Hz, 4H), 4.20 – 4.13 (m, 1H), 3.94 (s, 2H), 3.67 – 3.35 (m, 5H), 3.31 (dd, $J = 13.6, 6.8$ Hz, 1H), 3.25 (s, 3H), 2.78 (s, 2H), 2.64 (s, 2H), 2.57 (s, 1H), 2.35 – 2.26 (m, 1H), 1.95 (dd, $J = 33.2, 15.1$ Hz, 2H), 1.81 – 1.65 (m, 2H), 1.43 (d, $J = 6.9$ Hz, 4H), 1.38 – 1.31 (m, 2H), 1.31 – 1.25 (m, 2H), 1.22 (s, 7H), 0.88 – 0.75 (m, 2H) ppm.

Example 27



Synthesis route:



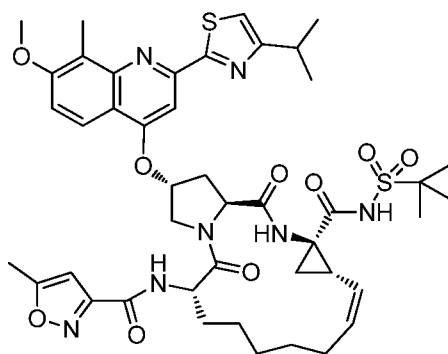
Synthesis steps:

[00244] A solution of compound **20-12** (0.2 g, 0.2 mmol) in isopropanol (2 mL) was cooled to 0 °C, and a solution of HCl in isopropanol (40%, 5 mL) was added. The mixture was stirred until no more gas evolution. The mixture was filtered to afford a white solid; the solid was washed with EtOAc (5 mL). A round-bottom flask was charged with the white solid, compound **27-1** (0.1 g, 0.7 mmol), EDCI (0.2 g, 1.5 mmol) and HOAT (0.15 g, 1.1 mmol), and then DCM (10 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (0.5 mL, 3 mmol) was added slowly. The mixture was stirred at 30 °C for 6 hours. The mixture was quenched with water (10 mL). The resulting mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **27-2** (0.120 g, 60%) as a white solid.

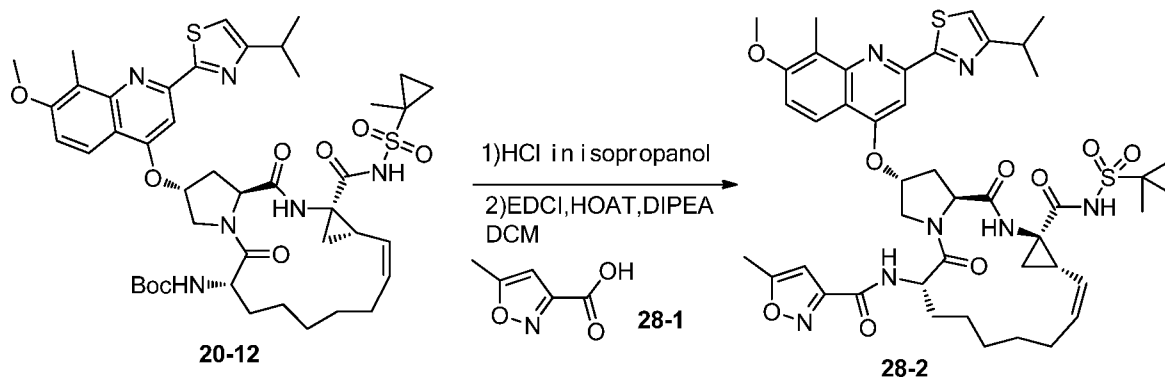
MS (ESI, pos.ion) m/z : 900.4[M+1]⁺; and

¹H NMR (600 MHz, CDCl₃): δ 10.22 (s, 1H), 7.92 (d, J = 9.1 Hz, 1H), 7.81 – 7.74 (m, 2H), 7.51 (s, 1H), 7.12 (t, J = 8.8 Hz, 1H), 7.04 (s, 1H), 5.67 (dd, J = 18.1, 8.6 Hz, 1H), 5.53 (s, 1H), 4.96 (t, J = 9.6 Hz, 1H), 4.83 – 4.78 (m, 1H), 4.70 (t, J = 7.8 Hz, 1H), 4.43 (d, J = 11.4 Hz, 1H), 4.17 – 4.12 (m, 1H), 3.88 (s, 3H), 3.24 – 3.19 (m, 1H), 2.80 (dd, J = 13.9, 7.7 Hz, 1H), 2.65 (s, 3H), 2.61 (s, 3H), 2.53 – 2.45 (m, 1H), 2.26 – 2.23 (m, 1H), 2.21 – 2.11 (m, 2H), 2.01 (d, J = 12.1 Hz, 1H), 1.95 – 1.90 (m, 1H), 1.83 (dd, J = 7.7, 6.2 Hz, 1H), 1.52 (t, J = 4.6 Hz, 1H), 1.48 (s, 4H), 1.45 (d, J = 8.7 Hz, 3H), 1.40 (d, J = 6.9 Hz, 6H), 1.28 – 1.25 (m, 3H), 0.87 – 0.77 (m, 3H) ppm.

Example 28



Synthesis route:



Synthesis steps:

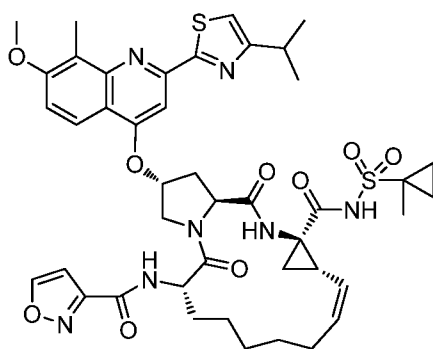
[00245] A solution of compound **20-12** (0.2 g, 0.2 mmol) in isopropanol (2 mL) was cooled to 0 °C, and a solution of HCl in isopropanol (40%, 5 mL) was added. The mixture was stirred until no more gas evolution. The mixture was filtered to afford a white solid; the solid was washed with EtOAc (5 mL). A round-bottom flask was charged with the white solid, compound **28-1** (0.1 g, 0.7 mmol), EDCI (0.2 g, 1.5 mmol) and HOAT (0.15 g, 1.1 mmol), and then DCM (10 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (0.5 mL, 3 mmol) was added

slowly. The mixture was stirred at 30 °C for 6 hours. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **28-2** (0.165 g, 80%) as a white solid.

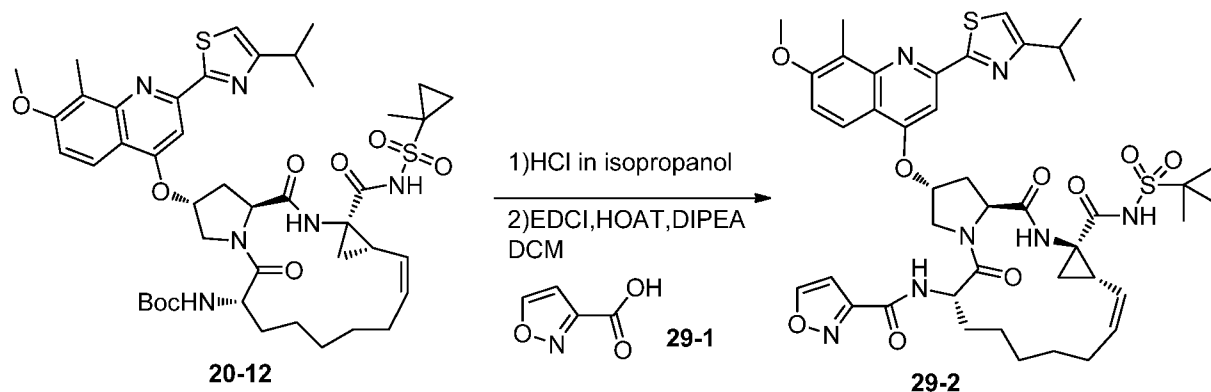
MS (ESI, pos.ion) *m/z*: 889.3[M+1]⁺; and

¹H NMR (600 MHz, CDCl₃): δ 10.30 (s, 1H), 8.09 (d, *J* = 7.4 Hz, 1H), 7.94 (s, 1H), 7.82 (d, *J* = 9.1 Hz, 1H), 7.57 (s, 1H), 7.02 (d, *J* = 12.2 Hz, 2H), 6.13 (s, 1H), 5.67 (dd, *J* = 17.6, 8.7 Hz, 1H), 5.56 (s, 1H), 4.95 (t, *J* = 9.4 Hz, 1H), 4.78 (t, *J* = 7.8 Hz, 1H), 4.71 (t, *J* = 7.8 Hz, 1H), 4.65 (d, *J* = 11.4 Hz, 1H), 4.13 (dt, *J* = 22.7, 11.4 Hz, 1H), 3.86 (s, 3H), 3.24 – 3.18 (m, 2H), 2.79 – 2.62 (m, 6H), 2.35 (s, 3H), 2.27 (dd, *J* = 16.9, 8.3 Hz, 2H), 2.11 (dd, *J* = 22.4, 10.5 Hz, 1H), 1.81 – 1.78 (m, 1H), 1.63 (s, 1H), 1.39 (d, *J* = 6.8 Hz, 7H), 1.30 – 1.21 (m, 6H), 1.19 (s, 3H), 0.86 – 0.73 (m, 3H) ppm.

Example 29



Synthesis route:



Synthesis steps:

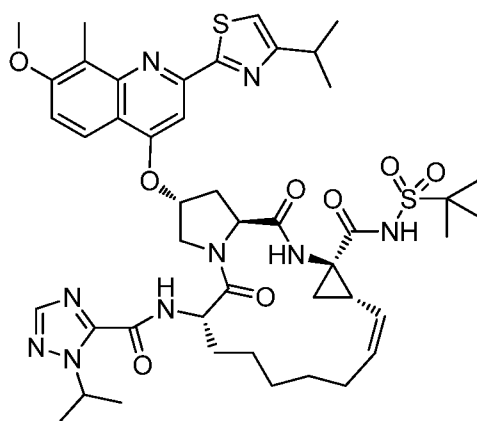
[00246] A solution of compound **20-12** (0.2 g, 0.2 mmol) in isopropanol (2 mL) was cooled to

0 °C, and a solution of HCl in isopropanol (40%, 5 mL) was added. The mixture was stirred until no more gas evolution. The mixture was filtered to afford a white solid; the solid was washed with EtOAc (5 mL). A round-bottom flask was charged with the white solid, compound **29-1** (0.1 g, 0.7 mmol), EDCI (0.2 g, 1.5 mmol) and HOAT (0.15 g, 1.1 mmol), and then DCM (10 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (0.5 mL, 3 mmol) was added slowly. The mixture was stirred at 30 °C for 6 hours. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **29-2** (0.150 g, 70%) as a white solid.

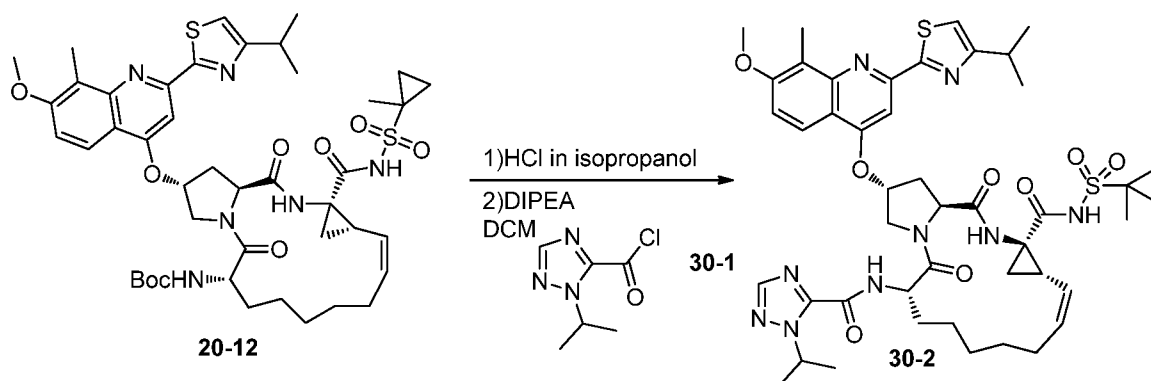
MS (ESI, pos.ion) *m/z*: 874.3[M+1]⁺; and

¹H NMR (600 MHz, CDCl₃): δ 10.30 (s, 1H), 8.40 (s, 1H), 7.95 (d, *J* = 7.4 Hz, 1H), 7.87 (d, *J* = 9.1 Hz, 1H), 7.81 (s, 1H), 7.55 (s, 1H), 7.04 (d, *J* = 9.2 Hz, 2H), 6.57 (s, 1H), 5.63 (dd, *J* = 17.8, 8.6 Hz, 1H), 5.51 (d, *J* = 27.3 Hz, 1H), 4.92 (t, *J* = 9.4 Hz, 1H), 4.76 (t, *J* = 7.3 Hz, 1H), 4.70 (t, *J* = 7.8 Hz, 1H), 4.58 (d, *J* = 11.4 Hz, 1H), 4.16 – 4.10 (m, 1H), 3.88 (s, 3H), 3.26 – 3.20 (m, 2H), 2.75 (dd, *J* = 13.6, 7.7 Hz, 1H), 2.65 (d, *J* = 18.3 Hz, 4H), 2.54 – 2.48 (m, 1H), 2.38 (s, 1H), 2.26 (dd, *J* = 17.2, 8.5 Hz, 1H), 2.05 (dd, *J* = 21.8, 10.4 Hz, 1H), 1.89 – 1.83 (m, 1H), 1.79 – 1.69 (m, 2H), 1.43 (d, *J* = 5.5 Hz, 2H), 1.39 (d, *J* = 6.9 Hz, 7H), 1.28 – 1.23 (m, 3H), 1.19 (s, 3H), 0.96 – 0.66 (m, 3H) ppm.

Example 30



Synthesis route:



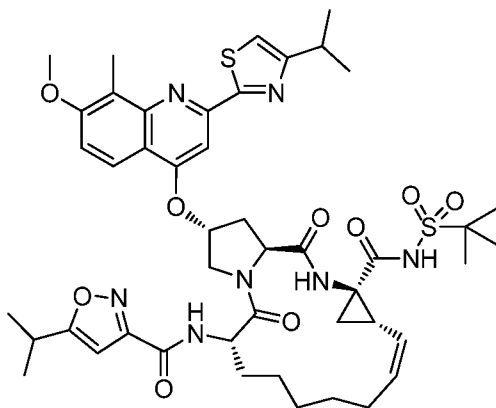
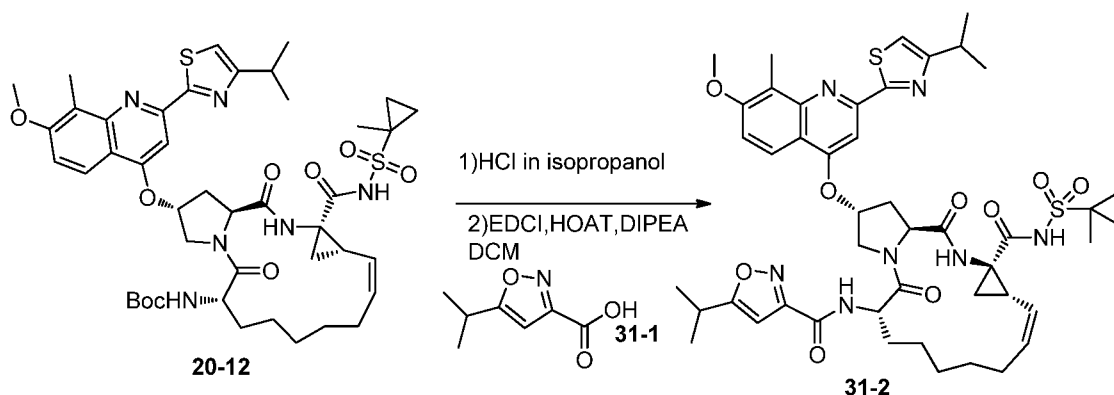
Synthesis steps:

[00247] A solution of compound **20-12** (1.5 g, 1.7 mmol) in isopropanol (20 mL) was cooled to 0 °C, and a solution of HCl in isopropanol (40%, 20 mL) was added. The mixture was stirred until no more gas evolution. The mixture was filtered to afford a white solid; the solid was washed with EtOAc (5 mL). A round-bottom flask was charged with the white solid, compound **30-1** (0.6 g, 3 mmol), EDCI (0.4 g, 3 mmol) and HOAT (0.3 g, 2.2 mmol), and then DCM (30 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (2 mL, 12.1 mmol) was added slowly. The mixture was stirred at 30 °C for 4 hours. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with DCM (20 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **30-2** (0.75g, 45%) as a white solid.

MS (ESI, pos.ion) m/z : 917.4[M+1]⁺; and

¹H NMR (400 MHz, CDCl₃): δ 10.27 (s, 1H), 8.04 (dd, J = 29.9, 23.6 Hz, 2H), 7.84 (d, J = 11.6 Hz, 2H), 7.52 (s, 1H), 7.05 (d, J = 12.8 Hz, 2H), 5.70 (d, J = 7.9 Hz, 1H), 5.51 (s, 1H), 5.01 (dd, J = 22.2, 12.9 Hz, 2H), 4.78 – 4.61 (m, 3H), 4.14 (d, J = 9.9 Hz, 1H), 3.97 (d, J = 17.5 Hz, 2H), 3.90 (s, 3H), 3.22 (s, 1H), 2.69 (d, J = 18.9 Hz, 6H), 2.32 (d, J = 7.6 Hz, 2H), 2.10 – 2.02 (m, 1H), 1.84 (s, 2H), 1.77 (d, J = 9.6 Hz, 1H), 1.69 (s, 1H), 1.53 (d, J = 6.1 Hz, 3H), 1.49 (s, 3H), 1.41 (s, 3H), 1.32 – 1.19 (m, 10H), 0.90 – 0.68 (m, 3H) ppm.

Example 31

**Synthesis route:****Synthesis steps:**

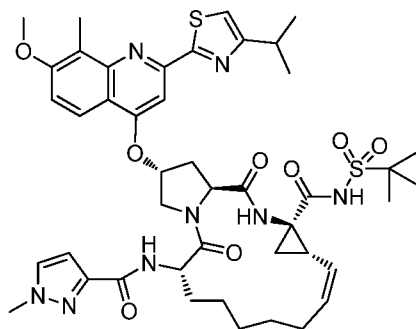
[00248] A solution of compound **20-12** (3 g, 3.7 mmol) in isopropanol (20 mL) was cooled to 0 °C, and a solution of HCl in isopropanol (40%, 20 mL) was added. The mixture was stirred until no more gas evolution. The mixture was filtered to afford a white solid; the solid was washed with EtOAc (5 mL). A round-bottom flask was charged with the white solid, compound **31-1** (1.3 g, 7.8 mmol), EDCI (1.5 g, 7.8 mmol) and HOAT (0.9 g, 6 mmol), and then DCM (30 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (3 mL, 17.1 mmol) was added slowly. The mixture was stirred at 30 °C for 6 hours. After the reaction was complete, the mixture was quenched with water (30 mL). The resulting mixture was extracted with DCM (30 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (30 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **31-2** (1.3 g, 39%) as a white solid.

MS (ESI, pos.ion) m/z : 917.3[M+1]⁺; and

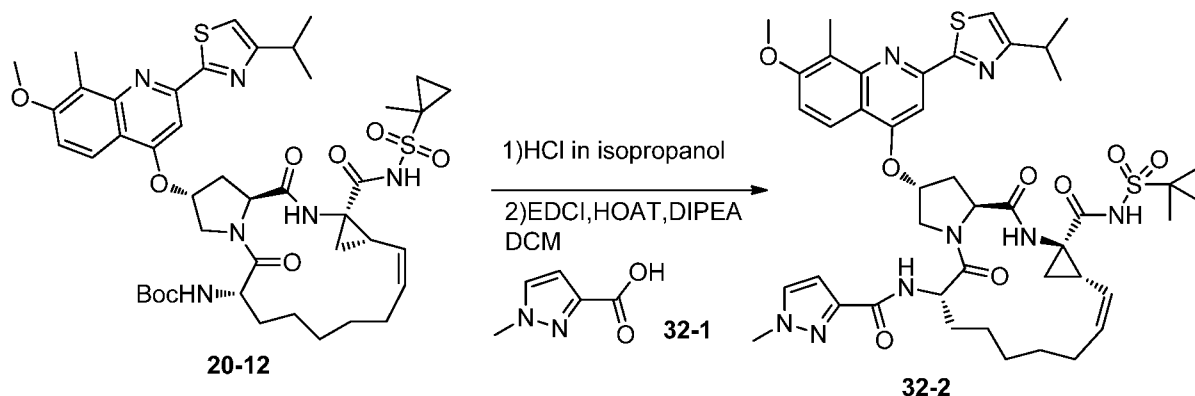
¹H NMR (400 MHz, CDCl₃): δ 10.32 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.97 (s, 1H), 7.86 (d, J = 9.1 Hz, 1H), 7.57 (s, 1H), 7.05 (d, J = 9.4 Hz, 2H), 6.14 (s, 1H), 5.68 (dd, J = 17.6, 8.7 Hz, 1H), 5.56 (s, 1H), 5.02 – 4.93 (m, 1H), 4.81 (t, J = 8.1 Hz, 1H), 4.71 (t, J = 8.1 Hz, 2H), 4.17 (dd,

$J = 11.2, 3.3$ Hz, 1H), 3.89 (s, 3H), 3.23 (dt, $J = 13.6, 6.8$ Hz, 1H), 2.99 (dq, $J = 13.7, 6.9$ Hz, 1H), 2.76 (d, $J = 7.1$ Hz, 2H), 2.69 (s, 3H), 2.29 (d, $J = 9.5$ Hz, 2H), 2.15 (dd, $J = 22.6, 11.1$ Hz, 1H), 1.79 (dd, $J = 17.2, 9.8$ Hz, 3H), 1.66 (s, 1H), 1.48 (d, $J = 10.1$ Hz, 7H), 1.40 (d, $J = 6.9$ Hz, 7H), 1.23 (dd, $J = 11.9, 7.0$ Hz, 9H), 0.86 – 0.76 (m, 2H) ppm.

Example 32



Synthesis route:



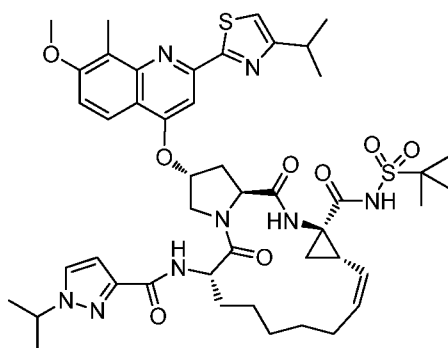
Synthesis steps:

[00249] A solution of compound **20-12** (1.35 g, 1.66 mmol) in isopropanol (15 mL) was cooled to 0 °C, and a solution of HCl in isopropanol (40%, 15 mL) was added. The mixture was stirred until no more gas evolution. The mixture was filtered to afford a white solid; the solid was washed with EtOAc (5 mL). A round-bottom flask was charged with the white solid, compound **32-1** (0.3 g, 2 mmol), EDCI (0.5 g, 4 mmol) and HOAT (0.5 g, 4 mmol), and then DCM (30 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (2.5 mL, 14 mmol) was added slowly. The mixture was stirred at 30 °C for 6 hours. After the reaction was complete, the mixture was quenched with water (30 mL). The resulting mixture was extracted with DCM (30 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (30 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **32-2** (0.72 g, 49%) as a white solid.

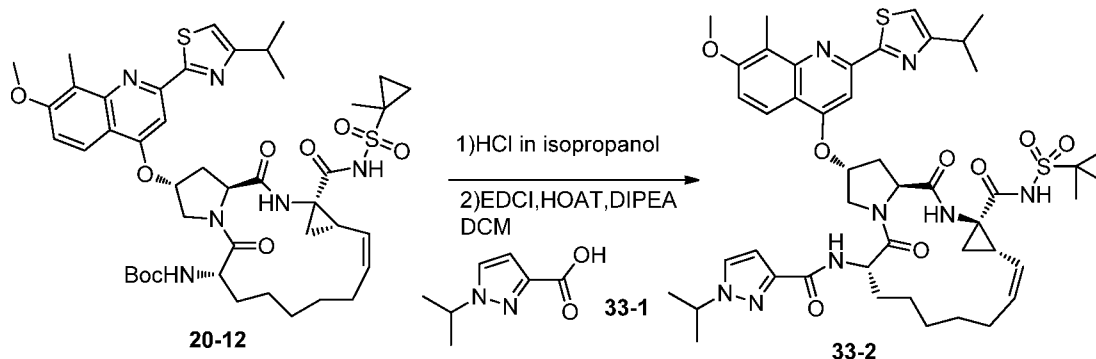
MS (ESI, pos.ion) m/z : 888.4[M+1]⁺; and

¹H NMR (400 MHz, CDCl₃): δ 10.35 (s, 1H), 8.00 (s, 1H), 7.89 (d, J = 9.1 Hz, 1H), 7.49 (s, 1H), 7.34 (d, J = 2.2 Hz, 2H), 7.03 (s, 1H), 6.98 (d, J = 9.3 Hz, 1H), 6.63 (d, J = 2.1 Hz, 1H), 5.65 (dd, J = 18.1, 8.5 Hz, 1H), 5.47 (s, 1H), 4.94 (t, J = 9.5 Hz, 1H), 4.62 (t, J = 7.5 Hz, 2H), 4.46 (d, J = 11.2 Hz, 1H), 4.13 (dd, J = 11.4, 4.2 Hz, 1H), 3.87 (s, 3H), 3.75 (s, 3H), 3.20 (dd, J = 13.0, 5.9 Hz, 1H), 2.67 (t, J = 10.7 Hz, 1H), 2.61 (s, 3H), 2.53 – 2.45 (m, 2H), 2.26 – 2.20 (m, 1H), 1.91 (dd, J = 24.3, 12.3 Hz, 2H), 1.81 – 1.72 (m, 2H), 1.68 – 1.59 (m, 2H), 1.46 (s, 3H), 1.39 (d, J = 6.9 Hz, 7H), 1.25 (d, J = 9.0 Hz, 5H), 0.94 – 0.81 (m, 1H), 0.76 (s, 2H) ppm.

Example 33



Synthesis route:



Synthesis steps:

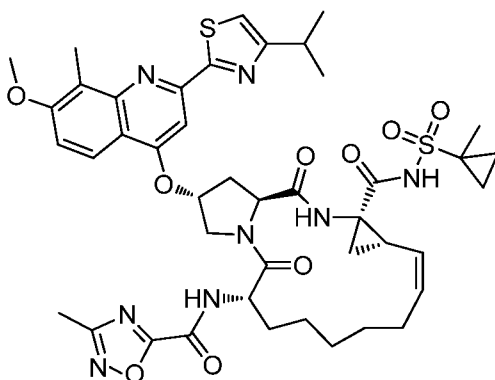
[00250] A solution of compound **20-12** (1.5 g, 1.8 mmol) in isopropanol (15 mL) was cooled to 0 °C, and a solution of HCl in isopropanol (40%, 15 mL) was added. The mixture was stirred until no more gas evolution. The mixture was filtered to afford a white solid; the solid was washed with EtOAc (5 mL). A round-bottom flask was charged with the white solid, compound **33-1** (0.3 g, 2 mmol), EDCI (0.5 g, 4 mmol) and HOAT (0.5 g, 4 mmol), and then DCM (30 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (2.5 mL, 14 mmol) was added slowly. The mixture was stirred at 30 °C for 6 hours. After the reaction was complete, the mixture was quenched with water (30 mL). The resulting mixture was extracted with DCM (30

mL) twice. The combined organic layers were washed with saturated aqueous NaCl (30 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **33-2** (0.8 g, 50%) as a white solid.

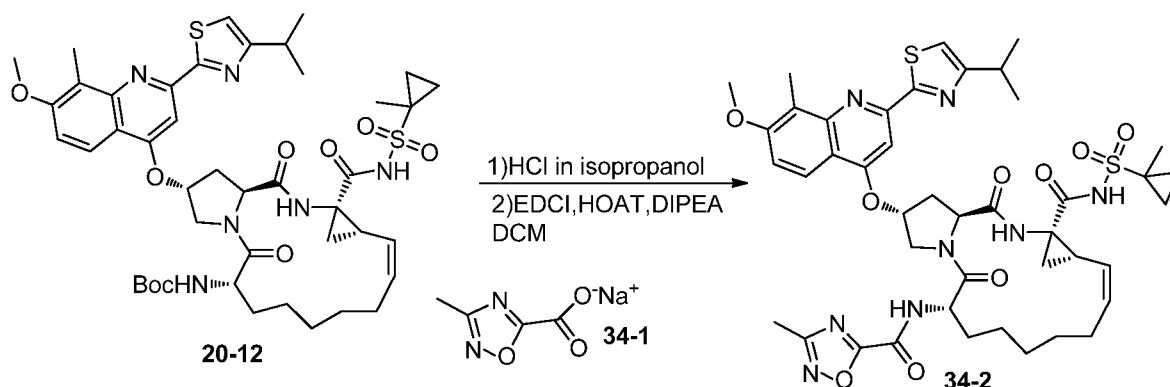
MS (ESI, pos.ion) m/z : 916.4[M+1]⁺; and

¹H NMR (400 MHz, CDCl₃) δ 10.20 (s, 1H), 7.99 (d, J = 9.0 Hz, 1H), 7.57 (s, 1H), 7.41 (d, J = 2.1 Hz, 1H), 7.28 (s, 2H), 7.11 (d, J = 9.1 Hz, 1H), 7.04 (s, 1H), 6.69 (d, J = 2.1 Hz, 1H), 5.73 (dd, J = 18.0, 8.7 Hz, 1H), 5.56 (s, 1H), 5.05 – 4.99 (m, 1H), 4.79 (t, J = 7.5 Hz, 1H), 4.66 (dd, J = 16.6, 9.3 Hz, 2H), 4.49 (dd, J = 13.4, 6.7 Hz, 1H), 4.14 (ddd, J = 18.9, 13.2, 7.2 Hz, 2H), 3.92 (s, 3H), 3.23 (d, J = 5.0 Hz, 1H), 2.69 (s, 6H), 2.58 (s, 1H), 2.34 (dd, J = 16.2, 7.5 Hz, 2H), 2.07 – 2.03 (m, 2H), 1.94 – 1.84 (m, 2H), 1.76 (t, J = 11.3 Hz, 2H), 1.54 (d, J = 6.7 Hz, 4H), 1.41 (d, J = 6.5 Hz, 4H), 1.27 (s, 6H), 1.21 (s, 1H), 0.94 – 0.76 (m, 6H) ppm.

Example 34



Synthesis route:



Synthesis steps:

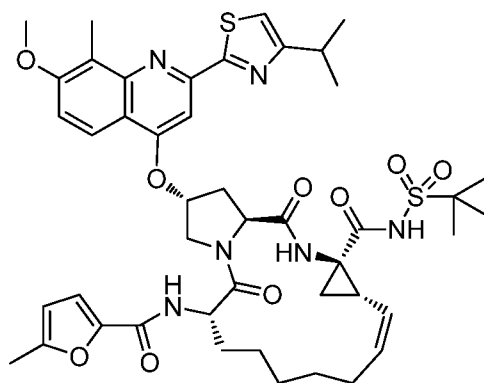
[00251] A solution of compound **20-12** (1.5 g, 1.8 mmol) in isopropanol (20 mL) was cooled to 0 °C, and a solution of HCl in isopropanol (40%, 20 mL) was added. The mixture was stirred until no more gas evolution. The mixture was filtered to afford a white solid; the solid was

washed with EtOAc (5 mL). A round-bottom flask was charged with the white solid, compound **34-1** (0.4 g, 3 mmol), EDCI (0.8 g, 4 mmol) and HOAT (0.5 g, 4 mmol), and then DCM (30 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (2.5 mL, 14 mmol) was added slowly. The mixture was stirred at 30 °C for 6 hours. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **34-2** (0.34 g, 21%) as a white solid.

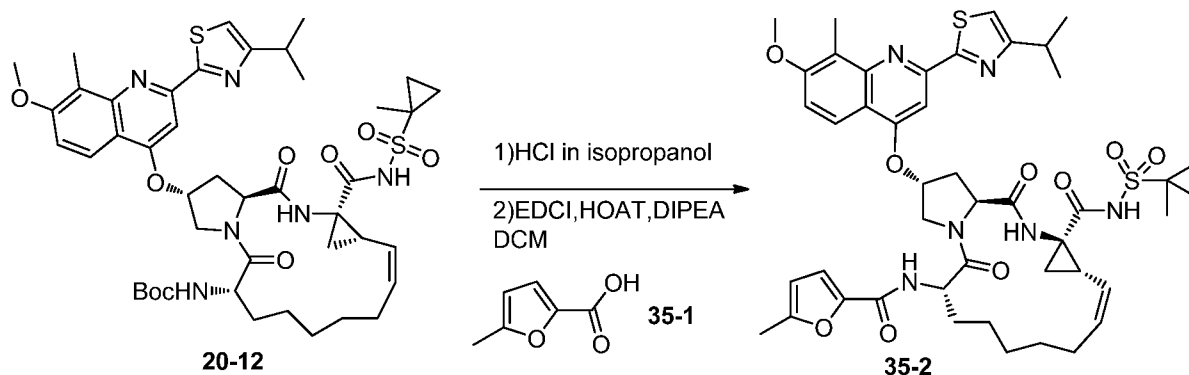
MS (ESI, pos.ion) *m/z*: 890.3[M+1]⁺; and

¹H NMR (600 MHz, CDCl₃): δ 10.36 (s, 1H), 8.29 – 8.09 (m, 2H), 7.74 (d, *J* = 5.3 Hz, 1H), 7.65 (s, 1H), 7.44 (s, 1H), 7.37 (d, *J* = 9.1 Hz, 1H), 5.84 (s, 1H), 5.67 (dd, *J* = 18.0, 8.5 Hz, 1H), 5.00 (t, *J* = 9.4 Hz, 1H), 4.83 (s, 1H), 4.73 – 4.58 (m, 2H), 4.17 (d, *J* = 10.6 Hz, 1H), 4.02 (s, 3H), 3.31 (dq, *J* = 13.3, 6.6 Hz, 1H), 2.86 (dd, *J* = 12.9, 6.0 Hz, 1H), 2.71 (dd, *J* = 20.4, 11.6 Hz, 1H), 2.58 (d, *J* = 30.1 Hz, 3H), 2.52 (d, *J* = 9.7 Hz, 1H), 2.42 (s, 3H), 2.33 (dd, *J* = 16.5, 8.1 Hz, 1H), 2.11 – 2.00 (m, 1H), 1.95 – 1.85 (m, 1H), 1.79 – 1.69 (m, 2H), 1.66 (t, *J* = 11.9 Hz, 1H), 1.58 (s, 1H), 1.50 (s, 1H), 1.48 (s, 3H), 1.41 (t, *J* = 22.4 Hz, 8H), 1.36 – 1.26 (m, 4H), 0.83 – 0.72 (m, 2H) ppm.

Example 35



Synthesis route:



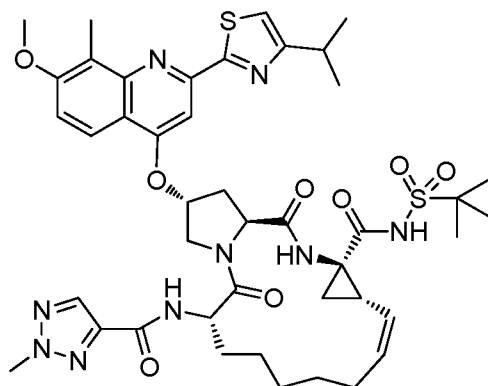
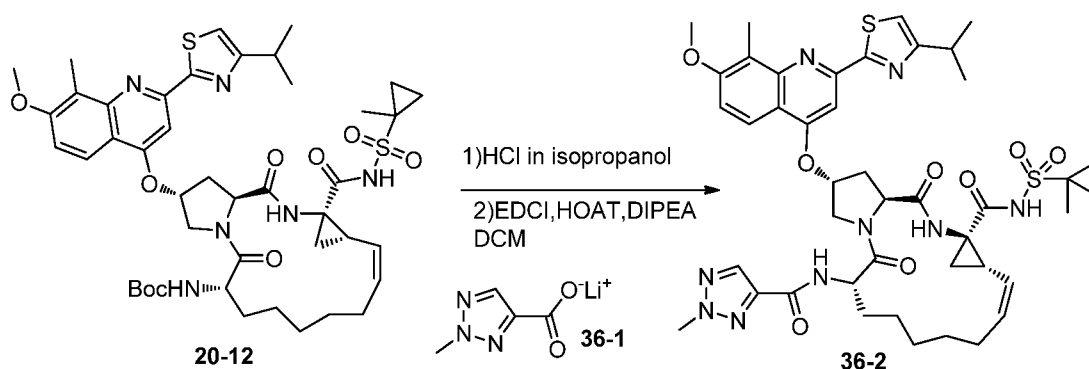
Synthesis steps:

[00252] A solution of compound **20-12** (1.5 g, 1.8 mmol) in isopropanol (20 mL) was cooled to 0 °C, and a solution of HCl in isopropanol (40%, 20 mL) was added. The mixture was stirred until no more gas evolution. The mixture was filtered to afford a white solid; the solid was washed with EtOAc (5 mL). A round-bottom flask was charged with the white solid, compound **35-1** (0.5 g, 4 mmol), EDCI (0.8 g, 4 mmol) and HOAT (0.5 g, 4 mmol), and then DCM (30 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (2.5 mL, 14 mmol) was added slowly. The mixture was stirred at 30 °C for 6 hours. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **35-2** (0.640 g, 40%) as a white solid.

MS (ESI, pos.ion) *m/z*: 888.3[M+1]⁺; and

¹H NMR (400 MHz, CDCl₃): δ 10.30 (s, 1H), 8.05 (d, *J* = 9.1 Hz, 1H), 7.84 (s, 1H), 7.58 (s, 1H), 7.26 (s, 1H), 7.18 (d, *J* = 9.3 Hz, 1H), 6.91 (d, *J* = 6.9 Hz, 1H), 6.80 (d, *J* = 2.9 Hz, 1H), 6.68 (s, 1H), 6.05 (d, *J* = 2.6 Hz, 1H), 5.72 – 5.62 (m, 2H), 5.02 (t, *J* = 9.5 Hz, 1H), 4.77 – 4.60 (m, 3H), 4.13 (t, *J* = 10.4 Hz, 1H), 3.92 (s, 3H), 3.30 (dt, *J* = 13.0, 6.5 Hz, 1H), 2.82 – 2.73 (m, 1H), 2.70 – 2.63 (m, 1H), 2.60 – 2.52 (m, 4H), 2.33 (d, *J* = 8.3 Hz, 4H), 1.97 (dd, *J* = 32.5, 10.3 Hz, 2H), 1.85 – 1.80 (m, 1H), 1.70 (t, *J* = 10.9 Hz, 2H), 1.60 (d, *J* = 5.7 Hz, 1H), 1.49 (s, 5H), 1.43 (s, 4H), 1.29 (dd, *J* = 12.9, 5.3 Hz, 4H), 1.25 – 1.18 (m, 2H), 0.79 (s, 2H) ppm.

Example 36

**Synthesis route:****Synthesis steps:**

[00253] A solution of compound **20-12** (1.5 g, 1.8 mmol) in isopropanol (20 mL) was cooled to 0 °C, and a solution of HCl in isopropanol (40%, 20 mL) was added. The mixture was stirred until no more gas evolution. The mixture was filtered to afford a white solid; the solid was washed with EtOAc (5 mL). A round-bottom flask was charged with the white solid, compound **36-1** (0.4 g, 3 mmol), EDCI (0.8 g, 4 mmol) and HOAT (0.5 g, 4 mmol), and then DCM (30 mL) was added under N₂. The mixture was cooled to 0 °C, and DIPEA (2.5 mL, 14 mmol) was added slowly. The mixture was stirred at 30 °C for 6 hours. After the reaction was complete, the mixture was quenched with water (10 mL). The resulting mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried over anhydrous Na₂SO₄, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with PE : EtOAc (V:V) = 2:1 to give compound **36-2** (0.60 g, 40%) as a white solid.

MS (ESI, pos.ion) *m/z*: 889.4[M+1]⁺; and

¹H NMR (600 MHz, CDCl₃): δ 10.21 (s, 1H), 7.98 – 7.84 (m, 2H), 7.56 (d, *J* = 19.3 Hz, 1H), 7.44 (s, 1H), 7.26 (d, *J* = 7.2 Hz, 1H), 7.08 (d, *J* = 9.5 Hz, 2H), 5.72 (dd, *J* = 17.7, 8.6 Hz, 1H), 5.55 (s, 1H), 5.02 (t, *J* = 9.4 Hz, 1H), 4.76 (d, *J* = 6.8 Hz, 1H), 4.67 (t, *J* = 7.7 Hz, 1H), 4.55 (d, *J*

= 11.1 Hz, 1H), 4.20 (s, 3H), 4.17 – 4.12 (m, 1H), 3.89 (s, 3H), 3.60 (d, $J = 40.8$ Hz, 2H), 3.27 – 3.23 (m, 1H), 2.74 (dd, $J = 13.2, 7.4$ Hz, 1H), 2.64 (s, 3H), 2.58 – 2.52 (m, 1H), 2.32 (dd, $J = 17.2, 8.6$ Hz, 1H), 2.08 – 1.99 (m, 1H), 1.97 – 1.92 (m, 1H), 1.91 – 1.87 (m, 1H), 1.79 – 1.71 (m, 2H), 1.55 (dd, $J = 9.1, 6.3$ Hz, 1H), 1.49 (s, 4H), 1.41 (d, $J = 6.8$ Hz, 4H), 1.36 – 1.26 (m, 4H), 1.21 (s, 1H), 0.96 – 0.74 (m, 3H) ppm.

Biological activities

1) Inhibition analysis of HCV NS3/4A protease

[00254] High throughput screening of HCV NS3/4A protease inhibitors was performed by using SensoLyte[®] 520 HCV protease detection kit (Anaspec) based on Fluorescence Resonance Energy Transfer (FRET) technology. The fluorescence of 5-FAM was quenched with QXL[™]520 in 5-FAM/QXL[™]520 FRET substrate peptide. 5-FAM/QXL[™]520 FRET substrate peptide contains HCV NS3/4A protease cleavage site, which can be cleaved by HCV NS3/4A protease to two independent fragments, and then the fluorescence of 5-FAM was recovered and can be detected at $E_x/E_m = 490/510$ nm.

[00255] The inhibitory effect of compound on HCV NS3/4A protease was evaluated by detecting the fluorescence signal intensity of 5-FAM. The processes were summarized as follows: the compound was dissolved in DMSO, the solution was mixed thoroughly to prepare 10 mM mother solution, which was diluted with Assay buffer containing DTT. The initial concentration tested of the compound was 1 μ M, the compound was diluted by 3-fold serially for a total of 10 concentrations, 3 μ L of the gradient diluted compound was added into a 384 well plate, the final concentration of DMSO in each well was 1%. And then 3 μ L of HCV NS3/4A recombination protease genotypes 1a (Anaspec) or HCV NS3/4Ab recombination protease genotypes 1b (Anaspec) was added into the 384 well plate, the final concentration of protease in each well was 0.25 ng/ μ L. Positive compound control group, negative control group and substrate control group were set up. The 384 well plate was placed in an incubator at 25 °C for 15 min, and the substrate solution was incubated at same temperature. After 15 min of incubation, 50-fold diluted FRET peptide substrate was added to each well, and the plate was shaken mildly for 1 min to mix well. The plate was placed in PHERAstar FS microplate reader (BMG Labtech) immediately, the fluorescence intensity of which was detected under $E_x/E_m = 490/520$ nm by using a dynamics method, the data were recorded once per 1 min over 30 min. The results were processed by using GraphPad Prism software, IC₅₀ of the compound against HCV NS3/4A

protease was calculated. The compounds have a good inhibitory effect on NS3/4A protease genotypes 1a and 1b.

2) Analysis of HCV subgenomic replicon

[00256] Detection of activity of GT1a, GT1b and GT2a replicons: HCV GT 1a H77 replicon, GT1b Con1b replicon and GT2a JFH1 replicon containing G418 resistance gene NEO and luciferase reporter gene were transfected respectively and immediately to Huh-7 cell by using an electric shock method. After the addition of G418, the cells were screened for 3 to 4 weeks, stable and transfected cell line was established. Cell line Huh7-H77 and Huh7- JFH1 was diluted to 5×10^4 /mL, 200 μ L of which was seeded to a 96 well plate. Cell line Huh7-Con1b was diluted to 1×10^5 /mL, 50 μ L of which was seeded to a 384 well plate. 16-24 h later, the compound was diluted by 3-fold serially for a total of 11 concentrations to a suitable concentration, the diluted compound was added into the 96 well plate with PODTM 810 plate assembler, the final concentration of DMSO in each well was 0.5%. The plate was incubated in a constant temperature incubator at 37 °C under 5% CO₂ for 72 h, and then to each well was added 40 μ L of luciferase assay reagent (Promega Bright-Glo), 5 min later, the plate was detected by chemiluminescence detection system (Envision). The results were processed by using GraphPad Prism software, EC₅₀ of the compound against HCV relipcon was calculated.

[00257] Detection of activity of GT3a, GT4a and GT5a chimeric replicon: HCVGT1b/GT3a-NS3, HCVGT1b/GT4a-NS3 and HCVGT1b/GT5a-NS3 chimeric replicon RNA were transfected to Huh7 cell by using an electric shock method, and then the cells were seeded to a 96 well plate containing the compound with a corresponding concentration at a density of 10000 cells per well. The compound in DMSO mother solution was diluted, and the diluted solution was added to the 96 well plate; the final concentration of DMSO was 0.5%. The cells were incubated under 5% CO₂ at 37 °C for 72 hours. Luciferase luminescence substrate Bright-Glo was added to each well, 5 min later, the signal value of luminescence was detected by chemiluminescence detection system (Envision), original data (RLU) were used for calculating inhibitory activity of the compound. The corresponding curve of the compound and the value of the inhibitory activity thereof (EC₅₀) against HCV relipcon were calculated by importing percent inhibition to GraphPad Prism software and nonlinear fitting.

[00258] The EC₅₀ values of the compound against HCV genotype 1a, 1b, 2a, 3a, 4a and 5a replicons were listed in table 2.

Table 2

Example No.	1a (nM)	1b (nM)	2a (nM)	3a (nM)	4a (nM)	5a (nM)
Example 4	0.58	1.74	-	-	-	-
Example 7	3.33	0.33	1.33	-	0.18	0.35
Example 8	1.35	0.37	2.37	-	-	-
Example 9	2.61	0.95	-	-	-	-
Example 10	8.43	4.04	-	-	-	-
Example 11	4.50	2.74	-	-	-	-
Example 13	27.2	13.8	-	-	-	-
Example 14	6.75	2.17	-	-	-	-
Example 15	5.24	1.15	-	-	-	-
Example 16	15.24	4.59	-	-	-	-
Example 17	2.37	0.78	-	-	-	-
Example 18	13.9	10.3	-	-	-	-
Example 20	-	0.51	4.57	-	0.08	0.53
Example 21	-	0.17	1.62	25.39	-	-
Example 22	-	0.35	3.80	-	-	-
Example 27	-	0.32	3.14	55.02	-	-
Example 28	-	0.29	1.36	-	-	-
Example 29	-	0.41	1.51	19.87	-	-
Example 30	-	1.19	6.51	-	-	-
Example 31	-	2.37	10.26	-	-	-
Example 32	-	-	-	18.86	-	-

[00259] The results of IC₅₀ of the compound against HCV NS3/4A protease and EC₅₀ of the compound against HCV relipcon indicates that the compounds of the invention have a better inhibitory effect on GT1a, GT1b, GT2a, GT3a, GT4a and GT5a especially on GT2a, therefore, the compounds of the invention can inhibit HCV NS3/4A protease specifically, and have a good antiviral effect.

3) Assay of liver microsomal stability

[00260] A drug solution (1.5 μ M, 30 μ L) was added into an EP tube (1.5 mL), and 150 μ L of ACN with internal standard was added immediately, and then 15 μ L of NADPH solution (6 mM) was added. After mixing well, the resulting solution was placed in refrigerator at 4°C as a 0 point

sample; each drug was prepared in duplicate. 30 μ L of 1.5 μ M drug solution was added into a 96 well plate, the different time points were marked on the wells, each drug was prepared in duplicate, the plate was preheated at 37 °C for 10 min. An NADPH solution (6 mM, 15 μ L) was added into the 60 min point well, the reaction was started and the timer was started. After the incubation, 150 μ L of ACN with internal standard was added into the wells with time marker. 15 μ L of NADPH solution (6 mM) was added into the 0 min point well. The samples were centrifuged at 4000 rpm for 10 min. The supernatant was analyzed. The ratio of sample peak area to internal standard peak area was obtained by analyzing through LC/MS/MS, the drug content in the 0 min point well was as 100%, the drug relative content of each time point was calculated. The rate constant was obtained by plotting based on “Log[drug concentration]” to “incubating time”, and then the half-life and intrinsic clearance of the drug were calculated. The results were shown as table 3:

Table 3 Stability data of the compounds in liver microsome of human, rats and dogs

Example No.	Human		Rats		Dogs	
	T _{1/2} (min)	CL _{int} (mL/min/kg)	T _{1/2} (min)	CL _{int} (mL/min/kg)	T _{1/2} (min)	CL _{int} (mL/min/kg)
Example 7	355.68	4.88	1472.00	1.68	187.86	18.38
Example 8	56.35	30.83	∞	-	55.72	61.98
Example 13	65.99	26.33	1286.61	1.93	44.52	77.61
Example 15	65.96	26.34	∞	-	11.10	311.16
Example 16	379.50	4.58	∞	-	98.46	35.08
Example 17	70.77	24.56	∞	-	37.75	91.51
Example 18	203.95	8.52	∞	-	122.00	28.32
Example 19	52.63	33.03	366.96	6.76	24.50	141.00
Example 20	49.01	35.47	6208.00	0.40	48.67	70.99
Example 21	48.58	35.78	606.10	4.10	57.48	60.11
Example 22	92.81	18.73	2636.00	0.94	31.58	109.41
Example 27	54.22	32.06	∞	-	42.56	81.18
Example 28	81.66	21.29	886.00	2.80	35.12	98.38
Example 29	58.52	29.70	∞	-	41.71	82.83

∞ : infinite time

[00261] Conclusion: The compounds of the invention in liver microsome of human, rats and dogs have a good stability.

4) PK assay of rats

[00262] 250-300 g male SD rats were grouped to two groups, each group had 3 rats. The two groups were administered with test compound by intravenous injection and gavage respectively. Blood samples were collected at 8 to 9 time points within 24 hours, and the standard curve was established based on the concentrations of the samples in a suitable range; the concentration of test compound in plasma samples was detected by using AB SCIEX API4000 or Agilent 6430 LC-MS/MS in a MRM mode, and performing quantitative analysis. Pharmacokinetic parameters were calculated according to drug concentration -time curve using a noncompartmental method by WinNonLin 6.3 software.

[00263] Conclusion: The compounds disclosed herein have obvious advantages in exposure and half-life compared with the compound reported already.

[00264] It will be evident to one skilled in the art that the present disclosure is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing examples, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

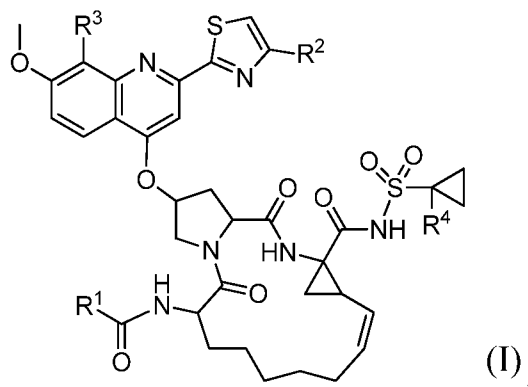
[00265] Reference throughout this specification to “an embodiment,” “some embodiments,” “one embodiment,” “another example,” “an example,” “a specific examples,” or “some examples,” means that a particular feature, structure, material, or characteristic described in connection with the embodiment or example is included in at least one embodiment or example of the present disclosure. Thus, the appearances of the phrases such as “in some embodiments,” “in one embodiment,” “in an embodiment,” “in another example,” “in an example,” “in a specific examples,” or “in some examples,” in various places throughout this specification are not necessarily referring to the same embodiment or example of the present disclosure. Furthermore, the particular features, structures, materials or characteristics may be combined in any suitable manner in one or more embodiments or examples.

[00266] Although explanatory embodiments have been shown and described, it would be appreciated by those skilled in the art that the above embodiments cannot be construed to limit the present disclosure, and changes, alternatives, and modifications can be made in the embodiments without departing from spirit, principles and scope of the present disclosure. The

scope of the invention is limited by the claims and equivalent thereof.

What is claimed is:

1. A compound having Formula (I) or a stereoisomer, a tautomer, an enantiomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



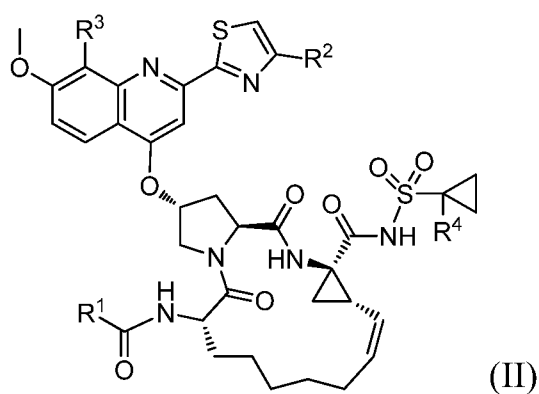
wherein R¹ is C₆₋₁₀ aryl or C₁₋₉ heteroaryl;

each of R² and R³ is independently H, F, Cl, Br, I, amino, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₂₋₁₀ heterocyclyl, C₆₋₁₀ aryl or C₁₋₉ heteroaryl; and

R⁴ is H, deuterium or C₁₋₆ alkyl, and

wherein each the C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₂₋₁₀ heterocyclyl, C₆₋₁₀ aryl, C₁₋₉ heteroaryl and amino is independently and optionally substituted with 1, 2, 3 or 4 substituents independently selected from deuterium, hydroxy, amino, F, Cl, Br, I, cyano, nitro, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ alkylamino, C₃₋₁₀ cycloalkyl, C₂₋₁₀ heterocyclyl, C₆₋₁₀ aryl and C₁₋₉ heteroaryl.

2. The compound of claim 1 having Formula (II), or a stereoisomer, a tautomer, an enantiomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof



3. The compound of claim 1 or 2, wherein R¹ is phenyl or 5-6 membered heteroaryl; and wherein each of the phenyl and 5-6 membered heteroaryl is independently and optionally

substituted with 1, 2, 3 or 4 substituents independently selected from deuterium, hydroxy, amino, F, Cl, Br, I, cyano, nitro, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₁₋₃ alkylamino, C₃₋₁₀ cycloalkyl, C₂₋₁₀ heterocyclyl and C₆₋₁₀ aryl.

4. The compound of claim 1 or 2, wherein R¹ is phenyl, furyl, thienyl, thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, oxadiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyridyl, quinolyl, indolyl or acridinyl; and wherein each R¹ is independently and optionally substituted with 1, 2, 3 or 4 substituents independently selected from deuterium, hydroxy, amino, F, Cl, Br, I, cyano, nitro, trifluoromethyl, difluoroethyl, trifluoromethoxy, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *i*-butyl, *t*-butyl, vinyl, ethynyl, methoxy, ethoxy, cyclopropyl, cyclobutyl, cyclopentyl and phenyl.

5. The compound of claim 1 or 2, wherein each of R² and R³ is independently H, F, Cl, Br, I, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *i*-butyl, trifluoromethyl, trifluoromethoxy, *t*-butyl, vinyl, propenyl, ethynyl, propinyl, methoxy, ethoxy, cyclopropyl, cyclobutyl, cyclopentyl, phenyl, methylamino or ethylamino.

6. The compound of claim 1 or 2, wherein R⁴ is H, deuterium, methyl, deuterated methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl or *t*-butyl.

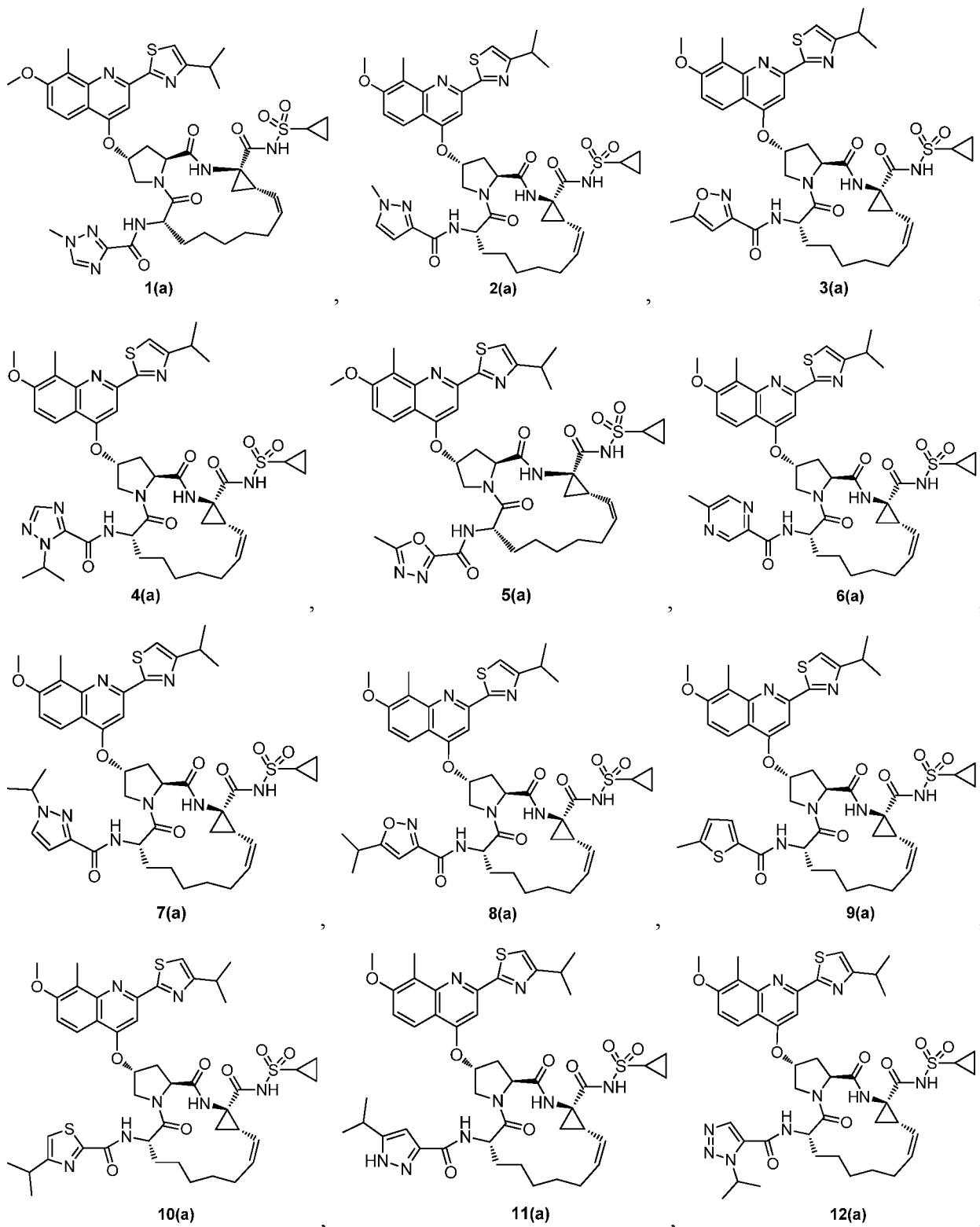
7. The compound of claim 1 or 2, wherein R¹ is 5-6 membered heteroaryl; and wherein the 5-6 membered heteroaryl is independently and optionally substituted with 1, 2, 3 or 4 substituents independently selected from deuterium, hydroxy, amino, F, Cl, Br, I, cyano, nitro, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy and C₁₋₃ alkylamino;

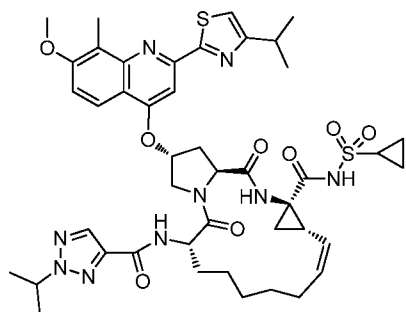
R² is C₁₋₆ alkyl;

R³ is C₁₋₃ alkyl; and

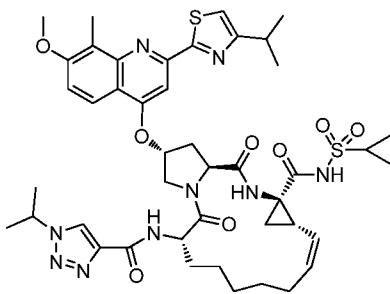
R⁴ is H or C₁₋₃ alkyl.

8. The compound of claim 1 or 2 having one of the following structures or a stereoisomer, a tautomer, an enantiomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof:

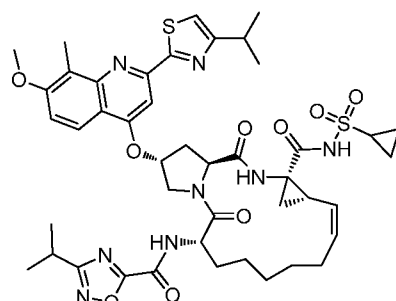




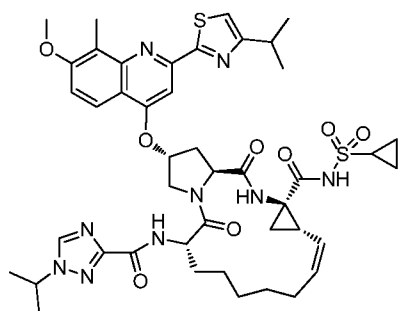
13(a)



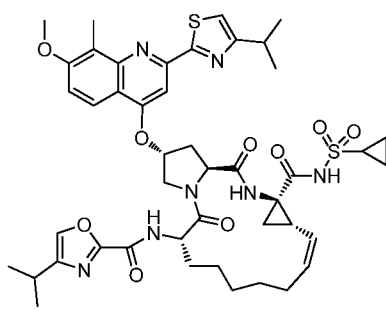
14(a)



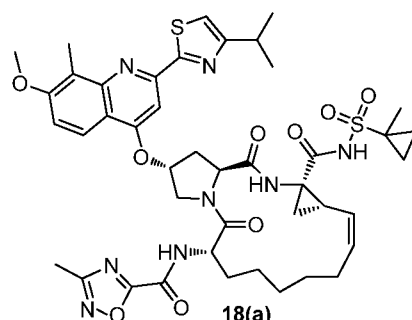
15(a)



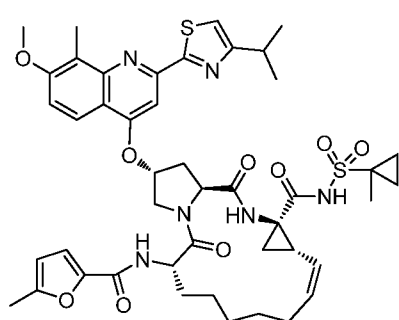
16(a)



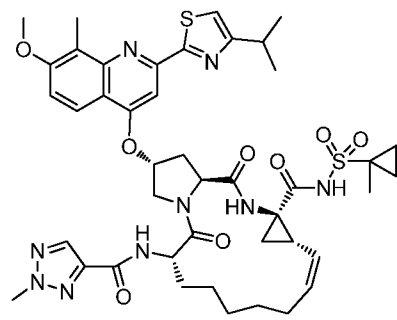
17(a)



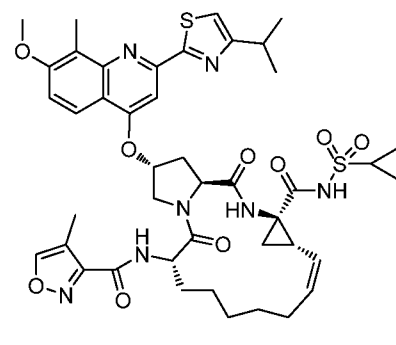
18(a)



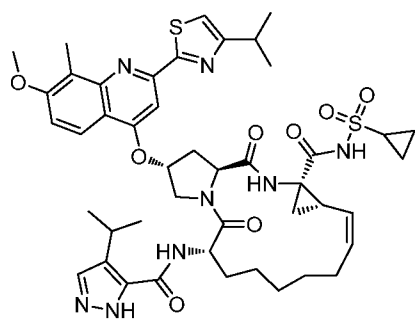
19(a)



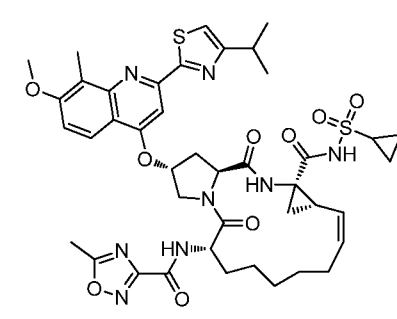
20(a)



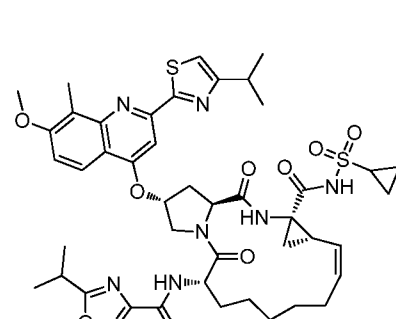
21(a)



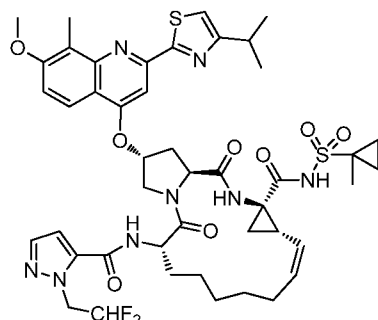
22(a)



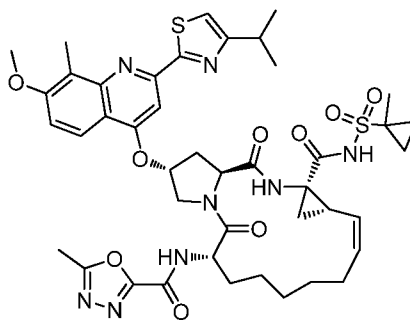
23(a)



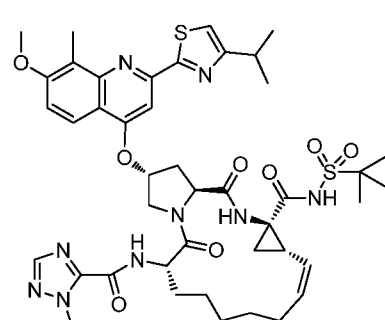
24(a)



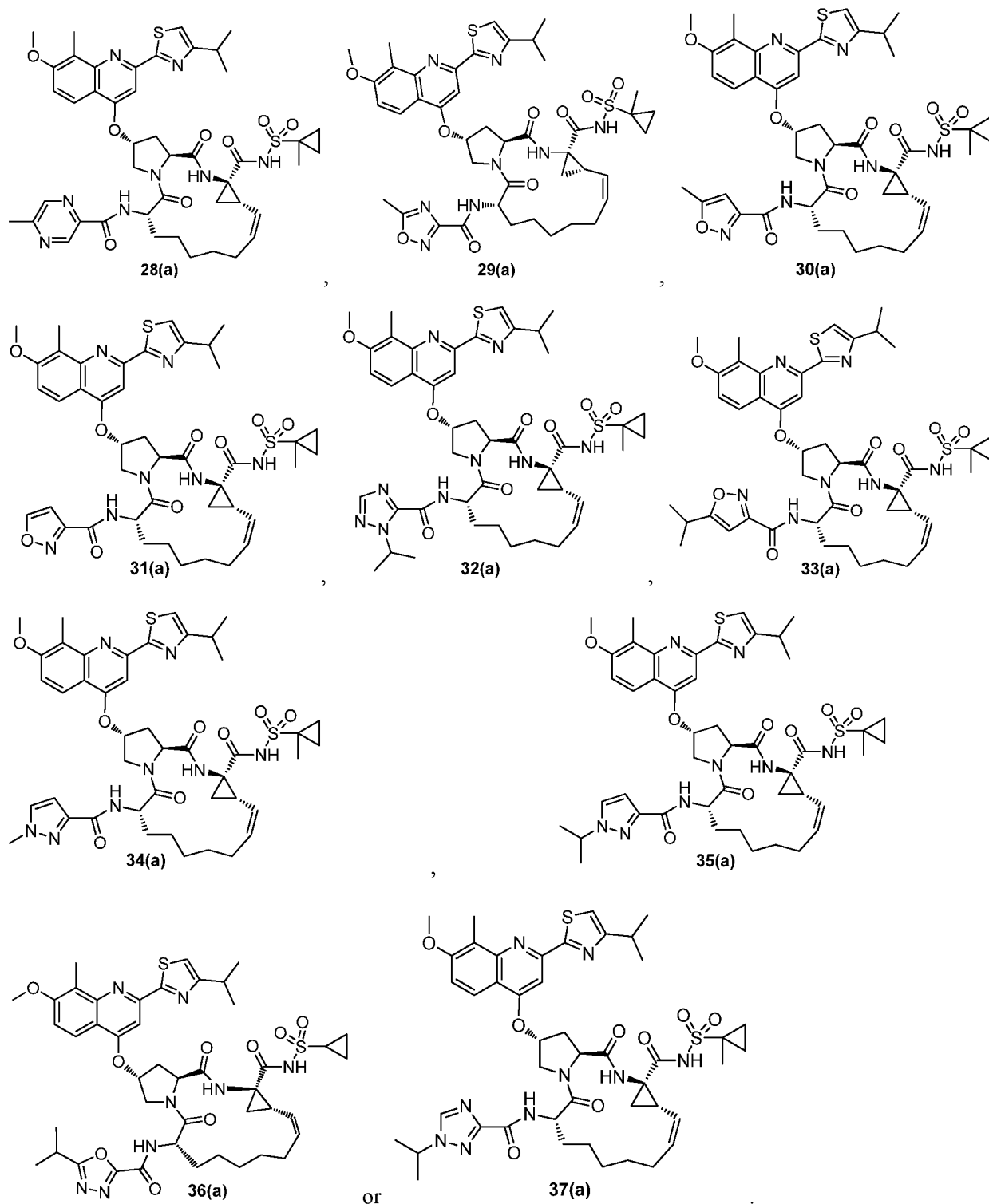
25(a)



26(a)



27(a)



9. A pharmaceutical composition comprising the compound of any one of claims 1 to 8 and a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof.

10. The pharmaceutical composition of claim 9 further comprising an anti-HCV agent, wherein the anti-HCV agent is interferon, ribavirin, IL-2, IL-6, IL-12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA,

imiquimod, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, rimantadine, bavituximab, CIVACIRTM, boceprevir, telaprevir, erlotinib, daclatasvir, simeprevir, asunaprevir, vaniprevir, faldaprevir, paritaprevir, danoprevir, sovalprevir, grazoprevir, vedroprevir, BZF-961, GS-9256, narlaprevir, ANA975, ombitasvir, EDP239, PPI-668, velpatasvir, samatasvir, elbasvir, MK-8325, GSK-2336805, PPI-461, BI-2013335, ciluprevir, ACH-1095, VX-985, IDX-375, VX-500, VX-813, PHX-1766, PHX-2054, IDX-136, IDX-316, modithromycin, VBY-376, TMC-649128, mericitabine, sofosbuvir, INX-189, IDX-184, IDX102, R-1479, UNX-08189, PSI-6130, PSI-938, PSI-879, nesbuvir, HCV-371, VCH-916, lomibuvir, MK-3281, dasabuvir, ABT-072, filibuvir, deleobuvir, tegobuvir, A-837093, JKT-109, GI-59728, GL-60667, AZD-2795, TMC647055, MK-3682, GS-9669, odalasvir, furaprevir, setrobuvir, alisporivir, BIT-225, AV-4025, ACH-3422, MK-2748, MK-8325, JNJ-47910382, ABP-560, TD-6450, TVB-2640, ID-12, PPI-383, A-848837, RG-7795, BC-2125 or a combination thereof; wherein the interferon is interferon α -2b, pegylated interferon α , interferon α -2a, pegylated interferon α -2a, consensus interferon- α , interferon γ or a combination thereof.

11. The pharmaceutical composition of any one of claims 9 to 10 further comprising at least one HCV inhibitor.

12. The pharmaceutical composition of claim 11, wherein the HCV inhibitor inhibits HCV replication process and/or a function of an HCV viral protein, and wherein the HCV replication process is a whole viral cycle consisting of HCV entry, uncoating, translation, replication, assembly and egress; and wherein the HCV viral protein comprises a metalloproteinase, non-structural protein NS2, NS3, NS4A, NS4B, NS5A or NS5B, an internal ribosome entry site (IRES), or inosine-5'-monophosphate dehydrogenase (IMPDH) required in HCV viral replication.

13. Use of the compound of any one of claims 1 to 8 or the pharmaceutical composition of any one of claims 9 to 12 in the manufacture of a medicament for inhibiting HCV replication process and/or a function of an HCV viral protein, wherein the HCV replication process is a whole viral cycle consisting of HCV entry, uncoating, translation, replication, assembly and egress; and wherein the HCV viral protein comprises a metalloproteinase, non-structural protein NS2, NS3, NS4A, NS4B, NS5A or NS5B, an internal ribosome entry site (IRES) and inosine-5'-monophosphate dehydrogenase (IMPDH) required in HCV viral replication.

14. Use of the compound of any one of claims 1 to 8 or the pharmaceutical composition of any one of claims 9 to 12 in the manufacture of a medicament for preventing, managing, treating or lessening the severity of HCV infection or a HCV disorder.

15. The compound of any one of claims 1 to 8 or the pharmaceutical composition of any one of claims 9 to 12 for use in inhibiting HCV replication process and/or a function of an HCV viral protein, wherein the HCV replication process is a whole viral cycle consisting of HCV entry, uncoating, translation, replication, assembly and egress; and wherein the HCV viral protein comprises a metalloproteinase, non-structural protein NS2, NS3, NS4A, NS4B, NS5A or NS5B, an internal ribosome entry site (IRES) and inosine-5'-monophosphate dehydrogenase (IMPDH) required in HCV viral replication.

16. The compound of any one of claims 1 to 8 or the pharmaceutical composition of any one of claims 9 to 12 for use in preventing, managing, treating or lessening the severity of HCV infection or a HCV disorder.

17. A method of inhibiting HCV replication process and/or a function of a HCV viral protein in a subject comprising administering to the subject the compound of any one of claims 1 to 8 or the pharmaceutical composition of any one of claims 9 to 12, wherein the HCV replication process is a whole viral cycle consisting of HCV entry, uncoating, translation, replication, assembly and egress; and wherein the HCV viral protein comprises a metalloproteinase, non-structural protein NS2, NS3, NS4A, NS4B, NS5A or NS5B, an internal ribosome entry site (IRES) and inosine-5'-monophosphate dehydrogenase (IMPDH) required in HCV viral replication.

18. A method of preventing, managing, treating or lessening the severity of HCV infection or a HCV disorder in a patient comprising administering the patient a therapeutically effective amount of the compound of any one of claims 1 to 8 or the pharmaceutical composition of any one of claims 9 to 12.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2016/073156

A. CLASSIFICATION OF SUBJECT MATTER

C07D 519/00(2006.01)i; A61K 31/395(2006.01)i; A61P 31/14(2006.01)i; A61P 1/16(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D, C07K, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CPRSABS; CNKI; CNTXT; DWPI; SIPOABS; EPTXT; USTXT; WOTXT; JPTXT; ELSEVIER, CA and search terms: formulas (I) and (II), formulas 1(a)-37(a), HCV, hepatitis C virus, NS3, inhibitor, etc.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010088394 A1 (GLAXOSMITHKLINE LLC) 05 August 2010 (2010-08-05) see the abstract, claims 36-58, examples 1-36 and description, page 28, line 13 to page 29, line 7	1-16
X	KAZMIERSKI, W. M. et al. "Discovery of Novel Urea-Based Hepatitis C Protease Inhibitors with High Potency against Protease-Inhibitor-Resistant Mutants" <i>J. Med. Chem.</i> , Vol. 55, No. 7, 03 April 2012 (2012-04-03), see the abstract, table 1	1-16



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance

“E” earlier application or patent but published on or after the international filing date

“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

“O” document referring to an oral disclosure, use, exhibition or other means

“P” document published prior to the international filing date but later than the priority date claimed

“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

“&” document member of the same patent family

Date of the actual completion of the international search

15 April 2016

Date of mailing of the international search report

13 May 2016

Name and mailing address of the ISA/CN

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2016/073156

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **17 and 18**
because they relate to subject matter not required to be searched by this Authority, namely:
[1] PCT Rule 39.1(iv)- Method for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2016/073156

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)		Publication date (day/month/year)
WO	2010088394	A1	05 August 2010	EP	2393493 A1	14 December 2011
				JP	2012516351 A	19 July 2012
				EP	2393493 A4	17 July 2013
				US	2010196321 A1	05 August 2010